DRUGDEX® Evaluations

DULOXETINE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  - Antidepressant
  - Central Nervous System Agent
  - Neuropathic Pain Agent
  - Serotonin/Norepinephrine Reuptake Inhibitor

2) Dosing Information
- **a)** Duloxetine Hydrochloride
  - **1)** Adult
    - **a)** Diabetic peripheral neuropathy - Pain
      - **1)** 60 mg ORALLY once daily (Prod Info CYMBALTA(R) delayed-rele
    - **b)** Fibromyalgia
      - **1)** initial, 30 mg ORALLY once daily for 1 week; increase to recomm CYMBALTA(R) delayed-release oral capsules, 2008)
    - **c)** Generalized anxiety disorder
      - **1)** 60 mg ORALLY once daily, may start at 30 mg ORALLY once dai depending on tolerability (Prod Info CYMBALTA(R) delayed-release
      - **2)** may increase by increments of 30 mg once daily to a MAX of 120 additional benefit in clinical trials (Prod Info CYMBALTA(R) delayed-r
    - **d)** Major depressive disorder
      - **1)** initial (acute), 20 mg ORALLY twice daily up to 60 mg/day (once d release oral capsules, 2008)
      - **2)** maintenance, 60 mg ORALLY once daily (Prod Info CYMBALTA(
    - **e)** Urinary incontinence
      - **1)** 40 mg ORALLY twice daily (clinical trial dosing) (Weinstein et al, 2
  - **2)** Pediatric
    - **a)** safety and efficacy in pediatric patients have not been established (Pro

3) Contraindications
- **a)** Duloxetine Hydrochloride
  - **1)** concomitant use of MAOIs (Prod Info Cymbalta(R) Delayed-release oral ca
  - **2)** narrow-angle glaucoma, uncontrolled; increased risk of mydriasis (Prod Inf

4) Serious Adverse Effects
- **a)** Duloxetine Hydrochloride
  - **1)** Bleeding, Abnormal
  - **2)** Depression, worsening
  - **3)** Hepatotoxicity
  - **4)** Serotonin syndrome
  - **5)** Suicidal thoughts
  - **6)** Withdrawal sign or symptom

5) Clinical Applications
- **a)** Duloxetine Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Diabetic peripheral neuropathy - Pain
    - **b)** Fibromyalgia
    - **c)** Generalized anxiety disorder
    - **d)** Major depressive disorder
  - **2)** Non-FDA Approved Indications
    - **a)** Urinary incontinence

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

B) Synonyms

Duloxetine
Duloxetine HCl
Duloxetine Hydrochloride

C) Physicochemical Properties

1) Duloxetine Hydrochloride

a) Molecular Weight

1) 333.88 (Prod Info CYMBALTA(R) delayed-release oral capsules,

b) Solubility

1) Slightly soluble in water (Prod Info CYMBALTA(R) delayed-releas

1.2 Storage and Stability

A) Duloxetine Hydrochloride

1) Preparation

a) Oral route

1) Duloxetine hydrochloride (HCl) capsules should be swallowed wh
food or mixed with liquids. Duloxetine HCl may be given with food or
release oral capsules, 2008).

B) Duloxetine Hydrochloride

1) Oral route

a) Capsule, Delayed Release

1) Store at controlled room temperature, 25 degrees Celsius (77 deg
degrees Celsius (59 and 86 degrees Fahrenheit) (Prod Info CYMBAL

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

1.3.1 Normal Dosage

1.3.1.A Duloxetine Hydrochloride

1.3.1.A.1 Oral route

Diabetic peripheral neuropathy - Pain

Fibromyalgia

Generalized anxiety disorder

Major depressive disorder

- Contraindications
- Precautions
- Adverse Reactions
- Teratogenicity / Effects in Pregnancy / Breastfeeding
- Drug Interactions

– Clinical Applications

- Monitoring Parameters
- Patient Instructions
- Place In Therapy
- Mechanism of Action / Pharmacology
- Therapeutic Uses
- Comparative Efficacy / Evaluation With Other Therapies

References

(back to top)

Urinary incontinence

1.3.1.A.1.a Diabetic peripheral neuropathy - Pain

1) The recommended dose of duloxetine for the treatment of ne 60 milligrams (mg) once daily. There is no evidence that doses h lower starting dose may be considered for patients in whom tole oral capsules, 2008).

2) Therapy Withdrawal

a) Abrupt discontinuation of duloxetine has lead to sympton irritability, and nightmare. Gradual reduction of the dose, rat symptoms occur following a decrease in dose, resuming the smaller decreases (Prod Info CYMBALTA(R) delayed-releas

1.3.1.A.1.b Fibromyalgia

1) The recommended dose for the management of fibromyalgia mg once daily for 1 week and increase to 60 mg/day based on tc The duration of maintenance therapy should be based on clinica clinical trials (Prod Info CYMBALTA(R) delayed-release oral cap maintained at 6 months of therapy (Russell et al, 2008). Howeve in clinical trials, even among those who did not respond to the 6(adverse events (Prod Info CYMBALTA(R) delayed-release oral c

2) Therapy Withdrawal

a) Abrupt discontinuation of duloxetine has lead to sympton irritability, and nightmare. Gradual reduction of the dose, rat symptoms occur following a decrease in dose, resuming the smaller decreases (Prod Info CYMBALTA(R) delayed-releas

1.3.1.A.1.c Generalized anxiety disorder

1) The recommended dose of duloxetine for the treatment of ge without regard to meals. If tolerability is a concern, patients may mg once daily. There is no evidence that doses greater than 60 r my be increased by increments of 30 mg once daily to a maximu delayed-release oral capsules, 2008).

2) Therapy Withdrawal

a) Abrupt discontinuation of duloxetine has lead to sympton irritability, and nightmare. Gradual reduction of the dose, rat symptoms occur following a decrease in dose, resuming the smaller decreases (Prod Info CYMBALTA(R) delayed-releas

1.3.1.A.1.d Major depressive disorder

1) Initial (acute) Therapy

a) The recommended initial dose of duloxetine hydrochlorid milligrams (mg) orally twice daily. The dose may be increase tolerability is a concern, patients may be started at 30 mg or is no evidence that doses greater than 60 mg/day confer an oral capsules, 2008).

2) Maintenance Therapy

a) The recommended maintenance dose of duloxetine hydr is 60 milligrams orally once daily. Maintenance treatment wi Reassess the dose and the need for maintenance therapy ir release oral capsules, 2008).

3) Therapy Withdrawal

a) Abrupt discontinuation of duloxetine has lead to sympton irritability, and nightmare. Gradual reduction of the dose, rat symptoms occur following a decrease in dose, resuming the smaller decreases (Prod Info CYMBALTA(R) delayed-releas

1.3.1.A.1.e Urinary incontinence

1) In clinical trials, duloxetine 40 milligrams orally twice daily wa incontinence episodes in clinical trials among women with stress Dmochowski et al, 2003) and mixed urinary incontinence (Bent e

1.3.2 Dosage in Renal Failure

A) Duloxetine Hydrochloride

1) In renally impaired patients, duloxetine should be initiated at a lower d recommended for patients with end-stage renal disease (requiring dialysis

milliliters/minute) (Prod Info CYMBALTA(R) delayed-release oral capsules

1.3.3 Dosage in Hepatic Insufficiency

A) Duloxetine Hydrochloride

1) Duloxetine is not recommended for use in patients with any hepatic ins capsules, 2008).

1.3.4 Dosage in Geriatric Patients

A) Duloxetine Hydrochloride

1) No dosage adjustment is recommended for elderly patients. Caution is CYMBALTA(R) delayed-release oral capsules, 2008).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Duloxetine Hydrochloride

1) The safety and efficacy in pediatric patients have not been established 2008).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Duloxetine Hydrochloride

a) Initial Response

1) Depression, oral: within 2 weeks (Hirschfeld et al, 2005).

a) Patients treated with duloxetine experienced significant impro (HAMD-17) compared to placebo-treated patients by the second week trials, which compared duloxetine 60 mg orally once daily (depressive disorder, rapid improvements in the individual sympto and psychic anxiety were demonstrated by the end of the first we

b) Peak Response

1) Platelet serotonin uptake inhibition, oral: 4 to 6 hours (Kasahara e

a) Represents time to maximal or near-maximal inhibition in plat pharmacodynamic parameter may correlate with CNS activity (Is for clinical monitoring has not been determined.

B) Duration

1) Duloxetine Hydrochloride

a) Multiple Dose

1) Platelet serotonin uptake inhibition, oral: at least 7 days (Kasahara

a) Represents duration of inhibition after the last dose of a regim levels of duloxetine were no longer detectable.

2.2 Drug Concentration Levels

A) Duloxetine Hydrochloride

1) Therapeutic Drug Concentration

a) DEPRESSION, not established.

1) Studies attempting to define plasma levels that are associated wit

2) Significant inhibition of serotonin uptake in platelets from healthy s concentrations exceeding 5 ng/mL (Ishigooka, 1997). This pharmaco 1997; Kasahara et al, 1996), although its usefulness for clinical monit

2) Peak Concentration

a) Oral: 13 ng/mL (20-mg dose) (Johnson et al, 1995).

1) Following single oral doses of 20 mg, a mean peak duloxetine pla desmethyl metabolite (active) were less than 2 ng/mL (Johnson et al,

3) Time to Peak Concentration

a) Oral: 6 to 10 hours (Prod Info CYMBALTA(R) delayed-release oral cap

1) Maximal plasma concentrations (Cmax) of duloxetine occur 6 hou
presence of food (Prod Info CYMBALTA(R) delayed-release oral cap
2) Values represent times to peak levels over the range of 10 to 40 r
higher doses. Duloxetine exhibits linear pharmacokinetics (Sharma e
3) Steady-State: Steady-state has been reached in 3 to 5 days with 2
in healthy subjects; with the latter regimen, the mean peak plasma le
1995).
4) During oral administration of 20 and 30 mg twice daily in healthy s
approximately 15 ng/mL and 20 ng/mL, respectively, in one study (Sh

4) Area Under the Curve
a) After a single 60-milligram dose of duloxetine, patients with end stage
Cmax and AUC values approximately 100% greater than those of patients
glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate, the major circul
approximately 7- to 9-fold higher and would be expected to increase furth
release oral capsules, 2008).
b) After a single 20-milligram dose of duloxetine, 6 cirrhotic patients with
fold increase in AUC compared to non-cirrhotic patients (Prod Info CYMB

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Duloxetine Hydrochloride
1) Bioavailability
a) Oral: 30% to 80% (Bymaster et al, 2005).
1) The absolute oral bioavailability of a 60-mg dose averaged 5(
b) There is a median 2-hour lag until absorption begins (Prod Info C
c) With an evening dose, there is a 3-hour delay in absorption and a
dose (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008)
2) Effects of Food
a) slows absorption
b) Food does not affect Cmax but delays time to peak concentration
(Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).

2.3.2 Distribution

A) Distribution Sites
1) Duloxetine Hydrochloride
a) Protein Binding
1) greater than 90%, primarily to albumin and alpha-1-acid glyc
capsules, 2008).
b) Other Distribution Sites
1) Saliva, 0% (Johnson et al, 1995).
B) Distribution Kinetics
1) Duloxetine Hydrochloride
a) Volume of Distribution
1) 1640 L (Prod Info CYMBALTA(R) delayed-release oral capsu

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
1) Duloxetine Hydrochloride
a) LIVER, extensive (Sharma et al, 2000; Artigas, 1995).
1) The major metabolic pathways involve oxidation of the naphtl
cytochrome P450 (CYP) isozymes, CYP1A2 and CYP2D6 (Prod
B) Metabolites
1) Duloxetine Hydrochloride

a) 4-hydroxy duloxetine glucuronide (inactive) (Prod Info CYMBALTA Lantz et al, 2003).
1) Approximately 47% of a given dose is conjugated to 4-hydrox since the inhibition constant (Ki) values for serotonin and norepir compound duloxetine (Bymaster et al, 2005).
b) 5-hydroxy-6-methoxy duloxetine sulfate (inactive) (Prod Info CYM 2005; Lantz et al, 2003).
1) Approximately 22% of a given dose is conjugated to 5-hydrox activity since the inhibition constant (Ki) values for serotonin and parent compound duloxetine (Bymaster et al, 2005).

2.3.4 Excretion

A) Kidney
1) Duloxetine Hydrochloride
a) Renal Excretion (%)
1) 70% (Prod Info CYMBALTA(R) delayed-release oral capsules
a) Excreted mainly as metabolites; only trace amounts (less CYMBALTA(R) delayed-release oral capsules, 2008).
B) Feces
1) Duloxetine Hydrochloride
a) 20% (Prod Info CYMBALTA(R) delayed-release oral capsules, 20
1) Approximately 20% of duloxetine is excreted in the feces (Prc is unclear from available data if this represents unabsorbed drug
C) Total Body Clearance
1) Duloxetine Hydrochloride
a) 114 L/hr (Sharma et al, 2000).
1) Value after oral doses in healthy subjects.
2) Cirrhotic (Child-Pugh Class B) patients (n=6) had a clearance a 20-milligram dose of duloxetine (Prod Info CYMBALTA(R) dela

2.3.5 Elimination Half-life

A) Parent Compound
1) Duloxetine Hydrochloride
a) Elimination Half-Life
1) 12 hours (range: 8 to 17 hours) (Prod Info CYMBALTA(R) del
a) Duloxetine pharmacokinetics are dose proportional over release oral capsules, 2008).
b) The elimination half-life of duloxetine in 6 cirrhotic patien a significantly longer half-life (47.8 hours vs 13.5 hours, p <

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Duloxetine Hydrochloride
a) Oral (Capsule, Delayed Release)
Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal th young adults in short-term studies of major depressive disorder (MDI of duloxetine hydrochloride or any other antidepressant in a child, ad need. Short-term studies did not show an increase in the risk of suici beyond age 24; there was a reduction in risk with antidepressants co certain other psychiatric disorders are themselves associated with inc started on antidepressant therapy should be monitored appropriately unusual changes in behavior. Families and caregivers should be adv the prescriber. Duloxetine hydrochloride is not approved for use in pe

capsules, 2009).

3.1 Contraindications

A) Duloxetine Hydrochloride

1) concomitant use of MAOIs (Prod Info Cymbalta(R) Delayed-release oral ca
2) narrow-angle glaucoma, uncontrolled; increased risk of mydriasis (Prod Inf

3.2 Precautions

A) Duloxetine Hydrochloride

1) suicidal ideation and behavior or worsening depression; increased risk, par
first few months of therapy or following changes in dosage (Prod Info Cymbalt
2) abnormal bleeding has been reported, including life-threatening hemorrhag
2009)
3) abrupt withdrawal; serious discontinuation symptoms have been reported (
4) alcohol, substantial use; increased risk of liver injury (Prod Info Cymbalta(F
5) bipolar disorder; increased risk of precipitation of a mixed/manic episode (F
6) concomitant use of thioridazine or serotonergic drugs (serotonin precursors
inhibitors); use is not recommended (Prod Info Cymbalta(R) Delayed-release c
7) concomitant use of potent CYP1A2 inhibitors (fluvoxamine, cimetidine, quin
be avoided (Prod Info Cymbalta(R) Delayed-release oral capsules, 2009)
8) concomitant use of CNS-acting drugs, 5-hydroxytryptamine receptor agonis
warfarin), tricyclic antidepressants (nortriptyline, amitriptyline, imipramine), phe
flecainide); use cautiously (Prod Info Cymbalta(R) Delayed-release oral capsu
9) conditions that slow gastric emptying, such as diabetes; may affect stability
capsules, 2009)
10) diabetes; may worsen glycemic control (Prod Info Cymbalta(R) Delayed-r
11) hepatic impairment; use is not recommended (Prod Info Cymbalta(R) Dela
12) hepatotoxicity, including hepatitis, jaundice, and elevated transaminase le
release oral capsules, 2009)
13) liver disease, chronic; may aggravate condition (Prod Info Cymbalta(R) D
14) mania, history; risk of activation of mania/hypomania (Prod Info Cymbalta
15) narrow-angle glaucoma, controlled; increased risk of mydriasis (Prod Info
16) renal impairment, severe and end stage renal disease (creatinine clearan
Cymbalta(R) Delayed-release oral capsules, 2009)
17) seizures, history (Prod Info CYMBALTA(R) delayed-release oral capsules
18) serotonin syndrome has been reported, including cases that are life-threa
monitoring recommended (Prod Info CYMBALTA(R) delayed-release oral caps
19) use of duloxetine within 14 days of MAOI discontinuation (Prod Info CYMB
20) use of an MAOI within 5 days after duloxetine discontinuation (Prod Info C
21) urinary retention requiring hospitalization and/or catheterization has been
capsules, 2008)
22) volume-depleted, elderly, or concurrent diuretic therapy; hyponatremia, sy
(SIADH) has occurred with duloxetine; discontinue if symptoms develop (Prod
23) report suspected adverse reaction to Eli Lilly and Company at 1-800-LillyR
(Prod Info CYMBALTA(R) delayed-release oral capsules, 2008)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Duloxetine Hydrochloride

Increased blood pressure

Orthostatic hypotension

Palpitations

Syncope

3.3.1.A.1 Increased blood pressure

a) In clinical trials of all indications, duloxetine hydrochloride treatme systolic and up to 2.3 mmHg in diastolic blood pressures compared w therapy initiation and periodically during treatment (Prod Info CYMBA

b) Small increases in systolic/diastolic blood pressure and decrease twice-daily dosing in recumbent healthy subjects; no significant effect position (Sharma et al, 2000a).

3.3.1.A.2 Orthostatic hypotension

a) Orthostatic hypotension and syncope have been associated with t first week of therapy, but can occur at any time and is especially seer who are on concomitant medications that induce orthostatic hypotens (fluvoxamine, cimetidine, quinolone antimicrobials (ciprofloxacin, eno capsules, 2008).

3.3.1.A.3 Palpitations

a) Incidence: 1% to 2% (Prod Info CYMBALTA(R) delayed-release o

b) In pooled clinical trials of major depressive disorder and generaliz of patients receiving duloxetine hydrochloride (n=2995) compared wit also reported in 1% or greater of patients receiving duloxetine hydroc indications of duloxetine (Prod Info CYMBALTA(R) delayed-release c

c) In placebo-controlled trials, palpitations were reported in 2% of fib compared with 2% of patients receiving placebo (n=535) (Prod Info C

3.3.1.A.4 Syncope

a) Orthostatic hypotension and syncope have been associated with t first week of therapy, but can occur at any time and is especially seer who are on concomitant medications that induce orthostatic hypotens (fluvoxamine, cimetidine, quinolone antimicrobials (ciprofloxacin, eno capsules, 2008).

3.3.2 Dermatologic Effects

3.3.2.A Duloxetine Hydrochloride

Diaphoresis

Flushing

Pruritus

Rash

3.3.2.A.1 Diaphoresis

a) Incidence: 6% to 8% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 2% of the
delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, hyperh
receiving duloxetine hydrochloride at 60 mg twice daily, 6% of the 22
daily, compared 2% of the 223 subjects receiving placebo (Prod Info
d) In fibromyalgia placebo-controlled trials, hyperhidrosis was report
compared with 1% of patients receiving placebo (n=535) (Prod Info C
e) In clinical trials of all approved indications, hyperhidrosis was repo
with 2% of patients receiving placebo (n=3048), and was one of the r
CYMBALTA(R) delayed-release oral capsules, 2008).

3.3.2.A.2 Flushing

a) Incidence: 2% to 3% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with less than
CYMBALTA(R) delayed-release oral capsules, 2008).
c) In fibromyalgia placebo-controlled trials, hot flush was reported in
compared with 2% of patients receiving placebo (n=535) (Prod Info C

3.3.2.A.3 Pruritus

a) Incidence: 3% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In fibromyalgia placebo-controlled trials, pruritus was reported in 3
compared with 2% of patients receiving placebo (n=535) (Prod Info C

3.3.2.A.4 Rash

a) Incidence: 4% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In fibromyalgia placebo-controlled trials, rash was reported in 4%
compared with 2% of patients receiving placebo (n=535) (Prod Info C

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Duloxetine Hydrochloride

Blood glucose abnormal

Hyponatremia

Syndrome of inappropriate antidiuretic hormone secretion

Weight loss

3.3.3.A.1 Blood glucose abnormal

a) Based on pooled data from three 12-week, double-blind, randomiz
week, open-label extension phase (n=867), duloxetine therapy was a
(FPG) among patients treated for diabetic peripheral neuropathy (DP
randomized to receive placebo (n=339) or duloxetine 60 mg once or
patients were then re-randomized in a 2:1 ratio during the extension p
investigator-driven routine care (n=287), such as gabapentin, venlafa
history of DPN, and more than 88% had type 2 diabetes mellitus. The
(mg/dL) (10.1 millimoles/liter (mmol/L)) and 7.8%, respectively. Dulox
with placebo during the acute phase (9 mg/dL (0.5 mmol/L) vs -2 mg/
routine care during the extension phase (12 mg/dL (0.67 mmol/L) vs
changes in HbA1C associated with duloxetine was significantly differ

vs 0.19%; p less than 0.001) (Hardy et al, 2007).

3.3.3.A.2 Hyponatremia

a) Summary

1) Hyponatremia has been associated with duloxetine therapy. S reported and were reversible upon duloxetine discontinuation. In syndrome of inappropriate antidiuretic hormone secretion (SIADI patients are at greater risk of hyponatremia. Discontinuation of d symptomatic hyponatremia (Prod Info CYMBALTA(R) delayed-re

b) Hyponatremia developed in 5 depressed patients after approxima duloxetine. The 5 patients (35 to 70 years old) had a history of recurr severe acute episode. Duloxetine was initiated at 30 mg/day followec was subsequently increased to 90 mg/day or 120 mg/day, after 3 to 4 medications were lorazepam and zopiclone. Serum osmolality, and s week after the dose increase, patients developed fatigue, lethargy, ar in all patients. Duloxetine was discontinued in 4 patients and the dose on water restriction (less than 1200 mL/day), and the intake of sodiur salt tablets in 2 patients. Symptoms of hyponatremia and serum sodi hyponatremia such as advanced age, thiazide diuretics, polypharmac insufficiency, hypothyroidism, tumors, respiratory disease, or acute c Lindstaedt, 2007).

c) In a case report, a 48-year-old woman developed syndrome of ina hyponatremia and seizures when administered duloxetine. The patier upon psychiatric evaluation was diagnosed with minor depression an days later, she developed 2 generalized seizures, was afebrile, coma analysis revealed serum sodium level of 103 mEq/L, and a BUN of 6 diagnosed with SIADH (urinary sodium 118 mEq/L, serum osmolality The patient was inadvertently rechallenged with duloxetine on days 3 levels 120 mEq/L on day 3, and 98 mEq/L on day 4) and she had 1 a 2 days the patient regained consciousness and was uneventfully disc

3.3.3.A.3 Syndrome of inappropriate antidiuretic hormone secretion

a) Hyponatremia has been associated with duloxetine therapy. Seru and were reversible upon duloxetine discontinuation. In many cases inappropriate antidiuretic hormone secretion (SIADH). The elderly, pa greater risk of hyponatremia. Discontinuation of duloxetine therapy sh hyponatremia (Prod Info CYMBALTA(R) delayed-release oral capsul

b) In a case report, a 48-year-old woman developed syndrome of ina hyponatremia and seizures when administered duloxetine. The patier upon psychiatric evaluation was diagnosed with minor depression an she developed 2 generalized seizures, was afebrile, comatose, and h revealed serum sodium level of 103 mEq/L, and a BUN of 6 mg/dL. D SIADH (urinary sodium 118 mEq/L, serum osmolality 215 mOsm/kg H inadvertently rechallenged with duloxetine on days 3 and 4, which rep on day 3, and 98 mEq/L on day 4) and she had 1 additional seizure. patient regained consciousness and was uneventfully discharged 7 d

3.3.3.A.4 Weight loss

a) Incidence: 2% (Prod Info CYMBALTA(R) delayed-release oral cap

b) In major depressive disorder and generalized anxiety disorder pla patients receiving duloxetine hydrochloride compared with less than with duloxetine hydrochloride for up to 10 weeks in clinical trials show placebo-treated patients showed a weight gain of approximately 0.2 k 2008).

c) In diabetic peripheral neuropathy placebo-controlled clinical trials, weeks experienced a mean weight loss of approximately 1.1 kg, com placebo-treated patients (Prod Info CYMBALTA(R) delayed-release c

d) In fibromyalgia placebo-controlled trials, patients receiving duloxe weight loss of approximately 0.4 kg compared with a mean weight ga Info CYMBALTA(R) delayed-release oral capsules, 2008).

3.3.4 Gastrointestinal Effects

3.3.4.A Duloxetine Hydrochloride

Constipation

Decrease in appetite

Diarrhea

Indigestion

Loose stool

Nausea

Taste sense altered

Vomiting

Xerostomia

3.3.4.A.1 Constipation

a) Incidence: 5% to 15% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 4% of the
delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, constip
hydrochloride at 60 mg twice daily, 11% of the 228 patients at 60 mg
with 3% of the 223 subjects receiving placebo (Prod Info CYMBALTA
d) In fibromyalgia placebo-controlled trials, constipation was reporte
compared with 4% of patients receiving placebo (n=535) (Prod Info C
e) In clinical trials of all approved indications, constipation was repor
with 4% of patients receiving placebo (n=3048), and was one of the r
CYMBALTA(R) delayed-release oral capsules, 2008).

3.3.4.A.2 Decrease in appetite

a) In major depressive disorder and generalized anxiety disorder pla
occurred in 7% of the 2995 patients receiving duloxetine hydrochloric
(Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
b) In diabetic peripheral neuropathy placebo-controlled trials, decrea
patients receiving duloxetine hydrochloride at 60 mg twice daily, 7% c
20 mg daily, compared with less than 2% of the 223 subjects receivin
capsules, 2008).
c) In fibromyalgia placebo-controlled trials, decreased appetite (inclu
duloxetine hydrochloride (n=876) compared with 2% of patients recei
release oral capsules, 2008).
d) In clinical trials of all approved indications, decreased appetite (in
duloxetine (n=4843) compared with 2% of patients receiving placebo
adverse reactions (Prod Info CYMBALTA(R) delayed-release oral cap

3.3.4.A.3 Diarrhea

a) Incidence: 7% to 13% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 7% of the
delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, diarrhe
hydrochloride at 60 mg twice daily, 11% of the 228 patients at 60 mg
with 6% of the 223 subjects receiving placebo (Prod Info CYMBALTA
d) In fibromyalgia placebo-controlled trials, diarrhea was reported in
compared with 8% of patients receiving placebo (n=535) (Prod Info C
e) In clinical trials of all approved indications, diarrhea was reported
7% of patients receiving placebo (n=3048) (Prod Info CYMBALTA(R)

3.3.4.A.4 Indigestion

a) Incidence: 4% to 5% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, dyspep
hydrochloride at 60 mg twice daily, 4% of the 228 patients at 60 mg c
less than 3% of the 223 subjects receiving placebo (Prod Info CYMB

c) In fibromyalgia placebo-controlled trials, dyspepsia was reported i
compared with 3% of patients receiving placebo (n=535) (Prod Info C

3.3.4.A.5 Loose stool

a) Incidence: 2% to 3% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, loose s
hydrochloride at 60 mg twice daily, 3% of the 228 patients at 60 mg c
1% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c

3.3.4.A.6 Nausea

a) Incidence: 14% to 30% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 9% of the
delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, nausea
hydrochloride at 60 mg twice daily, 22% of the 228 patients at 60 mg
with 9% of the 223 subjects receiving placebo. Nausea led to discont
0.4% placebo-treated individuals (Prod Info CYMBALTA(R) delayed-r
d) In placebo-controlled trials, nausea was reported in 29% of fibrom
compared with 11% of patients receiving placebo (n=535) (Prod Info
e) In clinical trials of all approved indications, nausea was reported ir
9% of patients receiving placebo (n=3048), and was one of the most
(R) delayed-release oral capsules, 2008).

3.3.4.A.7 Taste sense altered

a) Incidence: 3% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In fibromyalgia placebo-controlled trials, dysgeusia was reported i
compared with 1% of patients receiving placebo (n=535) (Prod Info C

3.3.4.A.8 Vomiting

a) Incidence: 5% to 6% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 2% of the
delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, vomitin
hydrochloride at 60 mg twice daily, 5% of the 228 patients at 60 mg c
4% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c

3.3.4.A.9 Xerostomia

a) Incidence: 5% to 18% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 6% of the
delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, dry mo
hydrochloride at 60 mg twice daily, 7% of the 228 patients at 60 mg c
4% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c
d) In fibromyalgia placebo-controlled trials, dry mouth was reported i
compared with 5% of patients receiving placebo (n=535) (Prod Info C
e) In clinical trials of all approved indications, dry mouth was reporte
with 6% of patients receiving placebo (n=3048), and was one of the n
CYMBALTA(R) delayed-release oral capsules, 2008).

3.3.5 Hematologic Effects

3.3.5.A Duloxetine Hydrochloride

3.3.5.A.1 Bleeding, Abnormal

a) In case reports and epidemiological studies, drugs which interfere
reuptake inhibitors (SNRIs)) have been associated with an increased
including ecchymoses, hematomas, epistaxes, petechiae, gastrointes
reported with SSRI and SNRI use. Because the risk of bleeding may
coagulation (eg, NSAIDs, aspirin, warfarin), use caution when these a
Additionally, patients receiving concurrent warfarin therapy should be
Info CYMBALTA(R) delayed-release oral capsules, 2008).

3.3.6 Hepatic Effects

3.3.6.A Duloxetine Hydrochloride

3.3.6.A.1 Hepatotoxicity

a) The risk for elevated serum transaminase levels increases with th
transaminase levels has been approximately 2 months and has resul
of patients. In the cohort of controlled trials in any indication, alanine
limit of normal were observed in 1.1% (85/7632) of patients receiving
placebo group. During placebo-controlled, fixed-dose trials, dose resp
elevations greater than 5 times the upper limit of normal and ALT ele
observed (Prod Info CYMBALTA(R) delayed-release oral capsules, 2
b) During the postmarketing use of duloxetine, hepatomegaly and tra
limit of normal with or without jaundice have been reported. Additiona
occurred. Patients with chronic liver disease or cirrhosis have experie
Due to the potential for aggravation of preexisting liver disease or the
concurrently, duloxetine should not be given to patients consuming s
chronic liver disease (Prod Info CYMBALTA(R) delayed-release oral

3.3.8 Musculoskeletal Effects

3.3.8.A Duloxetine Hydrochloride

Asthenia

Cramp

Musculoskeletal pain

Myalgia

Spasm

3.3.8.A.1 Asthenia

a) Incidence: 2% to 8% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, asthen
hydrochloride at 60 mg twice daily, 4% of the 228 patients at 60 mg c
1% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c

3.3.8.A.2 Cramp

a) Incidence: 4% to 5% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, muscle
hydrochloride at 60 mg twice daily, 4% of the 228 patients at 60 mg c
3% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c

3.3.8.A.3 Musculoskeletal pain

a) Incidence: 5% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In fibromyalgia placebo-controlled trials, musculoskeletal pain was
(n=876) compared with 4% of patients receiving placebo (n=535) (Pr

3.3.8.A.4 Myalgia

a) Incidence: 1% to 4% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, myalgi
hydrochloride at 60 mg twice daily, 1% of the 228 patients at 60 mg c
less than 1% of the 223 subjects receiving placebo (Prod Info CYMB

3.3.8.A.5 Spasm

a) Incidence: 4% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In fibromyalgia placebo-controlled trials, muscle spasm was repor
(n=876) compared with 3% of patients receiving placebo (n=535) (Pr

3.3.9 Neurologic Effects

3.3.9.A Duloxetine Hydrochloride

Dizziness

Headache

Insomnia

Restless legs syndrome

Seizure

Somnolence

Tremor

Vertigo

3.3.9.A.1 Dizziness

a) Incidence: 6% to 17% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 6% of the
delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, dizzine
hydrochloride at 60 mg twice daily, 14% of the 228 patients at 60 mg
with 6% of the 223 subjects receiving placebo. Dizziness led to disco
and 0.4% placebo-treated patients (Prod Info CYMBALTA(R) delayed
d) In fibromyalgia placebo-controlled trials, dizziness was reported ir
compared with 7% of patients receiving placebo (n=535) (Prod Info C
e) In clinical trials of all approved indications, dizziness was reported
with 6% of patients receiving placebo (n=3048) (Prod Info CYMBALT

3.3.9.A.2 Headache

a) Incidence: 13% to 20% (Prod Info CYMBALTA(R) delayed-release
b) In diabetic peripheral neuropathy placebo-controlled trials, headac
hydrochloride at 60 mg twice daily, 13% of the 228 patients at 60 mg
with 10% of the 223 subjects receiving placebo (Prod Info CYMBALT
c) In fibromyalgia placebo-controlled trials, headache was reported i
compared with 12% of patients receiving placebo (n=535) (Prod Info
d) In clinical trials of all approved indications, headache was reported
with 15% of patients receiving placebo (n=3048) (Prod Info CYMBAL

3.3.9.A.3 Insomnia

a) Incidence: 8% to 16% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
early morning awakening, and initial insomnia) occurred in 10% of the
with 6% of the 1955 subjects receiving placebo (Prod Info CYMBALT
c) In diabetic peripheral neuropathy placebo-controlled trials, insomn
hydrochloride at 60 mg twice daily, 8% of the 228 patients at 60 mg c
7% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c
d) In fibromyalgia placebo-controlled trials, insomnia (including midd
reported in 16% of patients receiving duloxetine hydrochloride (n=876
(Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
e) In clinical trials of all approved indications, insomnia was reported
with 7% of patients receiving placebo (n=3048) (Prod Info CYMBALT

3.3.9.A.4 Restless legs syndrome

a) In a prospective, naturalistic study of patients (median age, 46 yea
271 (9%) subjects experienced new-onset restless leg syndrome (RL
treatment. Antidepressants included fluoxetine, paroxetine, citaloprar
and mirtazapine. Mirtazapine led to a marked decline of RLS in 28%
other antidepressants showed RLS symptoms (newly occurred or det
occurred early in treatment (median of 2.5 days, range 1 to 23 days)

3.3.9.A.5 Seizure

a) Incidence: 0.03% (Prod Info CYMBALTA(R) delayed-release oral
b) In placebo-controlled clinical trials, seizures occurred in 0.03% (3/
hydrochloride compared with 0.01% (1/6770) of patients receiving pla
surveillance reports (Prod Info CYMBALTA(R) delayed-release oral c
c) In a case report, a 48-year-old woman developed syndrome of ina
hyponatremia and seizures when administered duloxetine. The patier
upon psychiatric evaluation was diagnosed with minor depression an
she developed 2 generalized seizures, was afebrile, comatose, and h
revealed serum sodium level of 103 mEq/L, and a BUN of 6 mg/dL. D
SIADH (urinary sodium 118 mEq/L, serum osmolality 215 mOsm/kg h
inadvertently rechallenged with duloxetine on days 3 and 4, which rep
on day 3, and 98 mEq/L on day 4) and she had one additional seizur
patient regained consciousness and was uneventfully discharged 7 d

3.3.9.A.6 Somnolence

a) Incidence: 7% to 21% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
sedation) occurred in 10% of the 2995 patients receiving duloxetine h
placebo (Prod Info CYMBALTA(R) delayed-release oral capsules, 20
c) In diabetic peripheral neuropathy placebo-controlled trials, somno
hydrochloride at 60 mg twice daily, 15% of the 228 patients at 60 mg
with 5% of the 223 subjects receiving placebo. Somnolence led to dis
patients and none in the placebo-treated group (Prod Info CYMBALT
d) In fibromyalgia placebo-controlled trials, somnolence (including hy
receiving duloxetine hydrochloride (n=876) compared with 3% of pati
delayed-release oral capsules, 2008).
e) In clinical trials of all approved indications, somnolence (including
receiving duloxetine (n=4843) compared with 3% of patients receiving
reported adverse reactions (Prod Info CYMBALTA(R) delayed-releas

3.3.9.A.7 Tremor

a) Incidence: up to 5% (Prod Info CYMBALTA(R) delayed-release or
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with less than
CYMBALTA(R) delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, tremor
hydrochloride at 60 mg twice daily, 1% of the 228 patients at 60 mg c
0% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c
d) In fibromyalgia placebo-controlled trials, tremor was reported in 4
compared with 1% of patients receiving placebo (n=535) (Prod Info C

3.3.9.A.8 Vertigo

a) Incidence: 1% or greater (Prod Info CYMBALTA(R) delayed-relea
b) Vertigo has been reported in 1% or greater of patients receiving d
indications (n=27,229) (Prod Info CYMBALTA(R) delayed-release ora

3.3.10 Ophthalmic Effects

3.3.10.A Duloxetine Hydrochloride

Blurred vision

Mydriasis

3.3.10.A.1 Blurred vision

a) Incidence: 1% or greater (Prod Info CYMBALTA(R) delayed-relea
b) In major depressive disorder and generalized anxiety disorder pla
patients receiving duloxetine hydrochloride compared with 2% of the
delayed-release oral capsules, 2008).
c) In placebo-controlled trials, blurred vision was reported in 2% of fi
compared with 1% of patients receiving placebo (n=535) (Prod Info C
d) Blurred vision has been reported in 1% or greater of patients (n=2
all indications (Prod Info CYMBALTA(R) delayed-release oral capsule

3.3.10.A.2 Mydriasis

a) In clinical trials, duloxetine hydrochloride has been associated witl uncontrolled narrow-angle glaucoma and should be used cautiously i delayed-release oral capsules, 2008).

3.3.12 Psychiatric Effects

3.3.12.A Duloxetine Hydrochloride

Agitation

Anxiety

Bipolar disorder, Rapid cycling induction

Depression, worsening

Dream disorder

Posttraumatic stress disorder, exacerbation of symptoms

Suicidal thoughts

3.3.12.A.1 Agitation

a) Incidence: 5% to 6% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla nervousness, restlessness, tension, and psychomotor agitation) occu hydrochloride compared with 3% of the 1955 subjects receiving place 2009).
c) In placebo-controlled trials, agitation (including feeling jittery, nerv was reported in 6% of fibromyalgia patients receiving duloxetine hydr placebo (n=535) (Prod Info CYMBALTA(R) delayed-release oral caps

3.3.12.A.2 Anxiety

a) Incidence: 3% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In major depressive disorder and generalized anxiety disorder pla patients receiving duloxetine hydrochloride compared with 2% of the delayed-release oral capsules, 2009).

3.3.12.A.3 Bipolar disorder, Rapid cycling induction

a) A 17-year-old female (weight 45 kg) with bipolar disorder experier starting duloxetine. Significant medical history included a depressive medications were oral sodium valproate 400 mg/day and oral olanzap became depressed without reason, with signs of sadness, frequent c and would not do any work. She was started on oral duloxetine 20 m excessively, was euphoric, had assertions of high intelligence and ab aggressive and abusive behavior. It was subsequently noticed that ab euphoria and depression. Duloxetine was stopped, the dose of sodiu olanzapine was maintained at 10 mg/day. At week 4 follow-up, her m depressive symptoms (Desarkar et al, 2007).

3.3.12.A.4 Depression, worsening

a) Clinical worsening of depression has been reported in patients rec months of treatment and during dose adjustments. It may persist unti antidepressants for any indication should be monitored for signs of cl capsules, 2009).

3.3.12.A.5 Dream disorder

a) Incidence: 2% to 3% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla occurred in 2% of the 2995 patients receiving duloxetine hydrochloric (Prod Info CYMBALTA(R) delayed-release oral capsules, 2009).
c) In placebo-controlled trials, abnormal dreams (including nightmare duloxetine hydrochloride (n=876) compared with 1% of patients recei

release oral capsules, 2009).

3.3.12.A.6 Posttraumatic stress disorder, exacerbation of symptom

a) In a case report, a 53-year-old Vietnam veteran with post- traumat depression experienced severe exacerbation of PTSD symptoms. Th propranolol, and risperidone. Within 1 week of beginning duloxetine 6 Vietnam, nightmares, emotional numbing, increased startle response Decreasing his duloxetine dose to 30 mg per day lessened the PTSD did the symptoms return to baseline (Deneys & Ahearn, 2006).

3.3.12.A.7 Suicidal thoughts

a) Adult and pediatric patients being treated with antidepressants for anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggres hypomania, or mania may be at risk of suicidal ideation and behavior with other psychiatric and nonpsychiatric disorders. If these symptom necessary to discontinue medications when symptoms are severe, su symptoms. Patients and their caregivers should be provided with the patients especially during the initial few months of therapy or at times oral capsules, 2009).

b) A causal role for antidepressants in inducing suicidality has been antidepressants in a child or adolescent must balance this risk with th controlled trials of nine antidepressants (citalopram, fluoxetine, fluvox nefazodone, and venlafaxine extended-release) including over 4400 obsessive compulsive disorder (OCD), or other psychiatric disorders, few months of therapy was demonstrated in patients receiving antide suicidality was most consistently observed in the trials that included p trials in other psychiatric indications, such as obsessive compulsive d

1) In a pooled analyses of placebo-controlled trials in adults with trials (median duration of 2 months) of 11 antidepressant drugs i among the drugs studied. However, for almost all drugs studied, patients. The risk difference (drug versus placebo in the number additional cases in patients less than 18 years of age, 5 addition to 64 years, and 6 fewer cases in patients 65 years and older. No the adult trials; however, the number of suicides was insufficient use (ie, beyond several months) in pediatric patients is not know maintenance trials in adults with depression to substantiate a del (Prod Info LEXAPRO(R) Oral solution, Oral tablets, 2009; Anon,

3.3.13 Renal Effects

3.3.13.A Duloxetine Hydrochloride

Delay when starting to pass urine

Increased frequency of urination

Urinary retention

3.3.13.A.1 Delay when starting to pass urine

a) Urinary hesitation has been associated with the use of selective s Info CYMBALTA(R) delayed-release oral capsules, 2008).

3.3.13.A.2 Increased frequency of urination

a) Incidence: 1% to 5% (Prod Info CYMBALTA(R) delayed-release o

b) In diabetic peripheral neuropathy placebo-controlled trials, pollaki hydrochloride at 60 mg twice daily, 1% of the 228 patients at 60 mg d of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) dela

3.3.13.A.3 Urinary retention

a) Urethral retention has been associated with the use of selective s During postmarketing surveillance of duloxetine, cases of urinary rete reported (Prod Info CYMBALTA(R) delayed-release oral capsules, 20

3.3.14 Reproductive Effects

3.3.14.A Duloxetine Hydrochloride

Abnormal ejaculation

Erectile dysfunction

Late ejaculation

Orgasm disorder

Reduced libido

3.3.14.A.1 Abnormal ejaculation

a) Incidence: 2% to 4% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla
failure and ejaculation dysfunction) occurred in 2% of the male patien
1% of the male patients receiving placebo (Prod Info CYMBALTA(R)
c) In fibromyalgia placebo-controlled trials, ejaculation disorder (inclu
reported in 4% of male patients receiving duloxetine hydrochloride (n
(n=26) (Prod Info CYMBALTA(R) delayed-release oral capsules, 200

3.3.14.A.2 Erectile dysfunction

a) Incidence: 1% to 5% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla
male patients receiving duloxetine hydrochloride compared with 1% o
(R) delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, erectile
duloxetine hydrochloride at 60 mg twice daily, 1% of the 228 patients
compared with 0% of the 223 subjects receiving placebo (Prod Info C

3.3.14.A.3 Late ejaculation

a) Incidence: 3% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In major depressive disorder and generalized anxiety disorder pla
male patients receiving duloxetine hydrochloride compared with less
CYMBALTA(R) delayed-release oral capsules, 2008).

3.3.14.A.4 Orgasm disorder

a) Incidence: 3% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In major depressive disorder and generalized anxiety disorder pla
occurred in 3% of the 2995 patients receiving duloxetine hydrochloric
placebo (Prod Info CYMBALTA(R) delayed-release oral capsules, 20
c) In fibromyalgia placebo-controlled trials, abnormal orgasm (includi
duloxetine hydrochloride (n=876) compared with less than 1% of pati
delayed-release oral capsules, 2008).

3.3.14.A.5 Reduced libido

a) Incidence: 2% to 4% (Prod Info CYMBALTA(R) delayed-release o
b) In major depressive disorder and generalized anxiety disorder pla
occurred in 4% of the 2995 patients receiving duloxetine hydrochloric
(Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
c) In fibromyalgia placebo-controlled trials, decreased libido (includir
duloxetine hydrochloride (n=876) compared with less than 1% of pati
delayed-release oral capsules, 2008).

3.3.15 Respiratory Effects

3.3.15.A Duloxetine Hydrochloride

Cough

Nasopharyngitis

Pain in throat

Upper respiratory infection

3.3.15.A.1 Cough

a) Incidence: 3% to 6% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, cough
hydrochloride at 60 mg twice daily, 3% of the 228 patients at 60 mg c
of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) dela
c) In fibromyalgia placebo-controlled trials, cough was reported in 4%
compared with 3% of patients receiving placebo (n=535) (Prod Info C

3.3.15.A.2 Nasopharyngitis

a) Incidence: 7% to 9% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, nasopl
duloxetine hydrochloride at 60 mg twice daily, 7% of the 228 patients
compared with 5% of the 223 subjects receiving placebo (Prod Info C

3.3.15.A.3 Pain in throat

a) Incidence: 1% to 6% (Prod Info CYMBALTA(R) delayed-release o
b) In diabetic peripheral neuropathy placebo-controlled trials, pharyn
duloxetine hydrochloride at 60 mg twice daily, 1% of the 228 patients
compared 1% of the 223 subjects receiving placebo (Prod Info CYME
c) In fibromyalgia placebo-controlled trials, pharyngolaryngeal pain w
hydrochloride (n=876) compared with 3% of patients receiving placeb
capsules, 2008).

3.3.15.A.4 Upper respiratory infection

a) Incidence: 7% (Prod Info CYMBALTA(R) delayed-release oral cap
b) In fibromyalgia placebo-controlled trials, upper respiratory tract inf
hydrochloride (n=876) compared with 6% of patients receiving placeb
capsules, 2008).

3.3.16 Other

3.3.16.A Duloxetine Hydrochloride

Fatigue

Fever

Serotonin syndrome

Withdrawal sign or symptom

3.3.16.A.1 Fatigue

a) Incidence: 2% to 15% (Prod Info CYMBALTA(R) delayed-release
b) In major depressive disorder and generalized anxiety disorder pla
10% of the 2995 patients receiving duloxetine hydrochloride compare
CYMBALTA(R) delayed-release oral capsules, 2008).
c) In diabetic peripheral neuropathy placebo-controlled trials, fatigue
hydrochloride at 60 mg twice daily, 10% of the 228 patients at 60 mg
with 5% of the 223 subjects receiving placebo. Fatigue led to disconti
none in the placebo-treated group (Prod Info CYMBALTA(R) delayed
d) In fibromyalgia placebo-controlled trials, fatigue (including astheni
hydrochloride (n=876) compared with 8% of patients receiving placeb
capsules, 2008).
e) In clinical trials of all approved indications, fatigue was reported in
6% of patients receiving placebo (n=3048) (Prod Info CYMBALTA(R)

3.3.16.A.2 Fever

a) Incidence: 1% to 3% (Prod Info CYMBALTA(R) delayed-release o

b) In diabetic peripheral neuropathy placebo-controlled trials, pyrexia hydrochloride at 60 mg twice daily, 1% of the 228 patients at 60 mg c 1% of the 223 subjects receiving placebo (Prod Info CYMBALTA(R) c

3.3.16.A.3 Serotonin syndrome

a) Serotonin syndrome, including life-threatening cases, or neurolept reported with the use of duloxetine alone. Signs and symptoms of ser hallucination, coma), autonomic instability (eg, tachycardia, labile blo hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, r resemble NMS with symptoms including hyperthermia, muscle rigidity signs, and mental status changes. Serotonin syndrome occurs most c including triptans, with drugs that impair metabolism of serotonin, incl antagonists (Prod Info Cymbalta(R) Delayed-release oral capsules, 2

3.3.16.A.4 Withdrawal sign or symptom

a) Incidence: 1% or greater (Prod Info CYMBALTA(R) delayed-relea
b) In clinical trials, abrupt discontinuation of duloxetine resulted in 1% dizziness, nausea, headache, fatigue, paresthesia, vomiting, irritabilit vertigo compared with patients discontinuing placebo. During marketi (SNRIs), reports of dysphoric mood, irritability, agitation, dizziness, se headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, limiting, however some have been severe. All patients should be mor should be gradually tapered. If intolerable symptoms occur, treatmen instituting a more gradual decrease in dose (Prod Info CYMBALTA(R
c) In a pooled analysis of 9 clinical trials divided into three categories duloxetine n=490, placebo n=380), 2 long-term placebo-controlled (3 open-label study (52 weeks; duloxetine n=553), discontinuation-emer therapy was abruptly stopped. Patients experiencing at least one DE 22.9% placebo), 9.1% (versus 2% placebo) and 50% (open-label), re common DEAE was dizziness reported in 12.4% (vs. 0.8% placebo), respectively, followed by nausea (5.9% (vs 0.3% placebo), 0.8% (vs 0.8% placebo), 0.8% (vs 0% placebo), and 7.2% (open-label)). Patier moderate in severity, and incidence and severity was not affected by DEAEs resolved by study end with 68.2%, 47.1% and 63.7% resolvin placebo-controlled, and long-term open-label studies, respectively. Th less than 2 weeks prior to discontinuation of duloxetine therapy (Pera
d) Small increases in heart rate and sleep disturbances (insomnia, a discontinuation of multiple-dose administration in healthy subjects (SI relatively high (20 to 40 mg twice daily). Withdrawal data following on patients are unavailable.

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

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

a) Either studies in animals have revealed adverse effects on the fetus (te studies in women or studies in women and animals are not available. Dru potential risk to the fetus.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) Due to the lack of adequate, well-controlled studies in pregnant women only if the potential benefit outweighs the potential risk to the fetus. Becau SSRI- and SNRI-exposed neonates late in the third trimester, the potentia should be taken into account. Tapering duloxetine may be considered in p CYMBALTA(R) delayed-release oral capsules, 2008).

4) Literature Reports

a) Neonates exposed to serotonin and norepinephrine reuptake inhibitors complications necessitating extended hospitalization, respiratory support, upon delivery. Respiratory distress, cyanosis, apnea, seizures, temperatu hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying of a toxic effect of the drug or a drug discontinuation syndrome. In some c syndrome (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008
b) There are no adequate and well-controlled studies with duloxetine in p studies of rats and rabbits treated with oral duloxetine up to 45 mg/kg/day recommended human dose [MRHD; 60 mg/day] on a mg/m(2) basis for ra decreased. When pregnant rats were treated with duloxetine 30 mg/kg/da

weights decreased, and the incidence of stillborn pups and pup mortality i
mg/kg/day (2 times the MRHD). Maternal exposure to 30 mg/kg/day also
and decreased habituation of locomotor activity) (Prod Info CYMBALTA(F

B) Breastfeeding

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

a) Available evidence and/or expert consensus is inconclusive or is inade
breastfeeding. Weigh the potential benefits of drug treatment against pote

2) Clinical Management

a) Duloxetine is excreted in human breast milk at approximately 0.14% o
adverse effects in the nursing infant from exposure to the drug are unkno
(Prod Info CYMBALTA(R) delayed-release oral capsules, 2008; Lobo et a
outweigh the potential risk to the infant and duloxetine is administered to
closely for adverse effects (Lobo et al, 2008)

3) Literature Reports

a) Duloxetine was found in human breast milk during a study of 6 lactatin
weeks postpartum), who received duloxetine 40 mg twice daily for 3.5 da
mcg/day (range, 4 to 15 mcg/day). The estimated daily infant dose was 2
approximately 0.14% (maximum 0.25%) of the maternal dose. The mean
0.25 (95% CI, 0.18 to 0.35). Excretion of duloxetine metabolites into brea

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Abciximab

Aceclofenac

Acemetacin

Acenocoumarol

Acetophenazine

Alclofenac

Almotriptan

Amineptine

Amitriptyline

Amitriptylinoxide

Amoxapine

Anagrelide

Ancrod

Anisindione

Antithrombin III Human

Ardeparin

Aspirin

Benoxaprofen

Bivalirudin

Bromfenac

Bufexamac

Carprofen

Celecoxib

Certoparin

Chlorpromazine

Cifenline

Cilostazol

Ciprofloxacin

Citalopram

Clomipramine

Clonixin

Clopidogrel

Cyclobenzaprine

Dalteparin

Danaparoid

Defibrotide

Dermatan Sulfate

Desipramine

Desirudin

Desvenlafaxine

Dexketoprofen

Dibenzepin

Diclofenac

Dicumarol

Diflunisal

Dipyridamole

Dipyrone

Dixyrazine

Dothiepin

Doxepin

Droxicam

Eletriptan

Encainide

Enoxacin

Enoxaparin

Epoprostenol

Eptifibatide

Escitalopram

Ethopropazine

Etodolac

Etofenamate

Etoricoxib

Felbinac

Fenbufen

Fenoprofen

Fentiazac

Flecainide

Floctafenine

Flufenamic Acid

Fluoxetine

Fluphenazine

Flurbiprofen

Fluvoxamine

Fondaparinux

Frovatriptan

Heparin

Ibuprofen

Iloprost

Imipramine

Indecainide

Indomethacin

Indoprofen

Isocarboxazid

Isoxicam

Ketoprofen

Ketorolac

Lamifiban

Lexipafant

Linezolid

Lithium

Lofepramine

Lorcainide

Lornoxicam

Meclofenamate

Mefenamic Acid

Melitracen

Meloxicam

Mesoridazine

Methdilazine

Methotrimeprazine

Metopimazine

Milnacipran

Morniflumate

Nabumetone

Nadroparin

Naproxen

Naratriptan

Niflumic Acid

Nimesulide

Nortriptyline

Opipramol

Oxaprozin

Parecoxib

Parnaparin

Paroxetine

Pentosan Polysulfate Sodium

Perazine

Periciazine

Perphenazine

Phenindione

Phenprocoumon

Phenylbutazone

Pipotiazine

Pirazolac

Piroxicam

Pirprofen

Procarbazine

Prochlorperazine

Promazine

Promethazine

Propafenone

Propiomazine

Propyphenazone

Proquazone

Protriptyline

Quinidine

Rasagiline

Rasagiline

Recainam

Reviparin

Rizatriptan

Rofecoxib

Selegiline

Sertraline

Sibrafiban

St John's Wort

Sulfinpyrazone

Sulindac

Sulodexide

Sumatriptan

Suprofen

Tamoxifen

Tapentadol

Tenidap

Tenoxicam

Thiethylperazine

Thiopropazate

Thioproperazine

Thioridazine

Tianeptine

Tiaprofenic Acid

Ticlopidine

Tinzaparin

Tirofiban

Tolmetin

Tramadol

Tranylcypromine

Trifluoperazine

Triflupromazine

Trimeprazine

Trimipramine

Tryptophan

Valdecoxib

Venlafaxine

Warfarin

Xemilofiban

Zolmitriptan

Zomepirac

3.5.1.A Abciximab

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repo
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.B Aceclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu

threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.C Acemetacin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.D Acenocoumarol

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into

measured and the patient was not genotyped for CYP2D6 or CYP1A2 duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.E Acetophenazine

1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.F Alclofenac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.G Almotriptan

1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: A life-threatening condition known as serotonin syndrome m combination with a serotonin and norepinephrine reuptake inhibitor (SNRI include restlessness, hallucinations, loss of coordination, fast heart beat, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should b that either the triptan or the SNRI may be prescribed by a different physic are prescribed this combination and monitor them closely for symptoms o dose increases (Prod Info CYMBALTA(R) delayed-release oral capsules,
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as almotripta (SNRI), such as duloxetine, may result in a life-threatening condition calle commonly used intermittently and that either the triptan or the SNRI may b together, discuss the risks of serotonin syndrome with the patient and mo hyperthermia, hyperreflexia, incoordination), especially during treatment i release oral capsules, 2008).
7) Probable Mechanism: additive pharmacologic effects resulting in exce

3.5.1.H Amineptine

1) Interaction Effect: increased tricyclic antidepressant serum concentrati confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre increasing the risk of adverse events. Duloxetine is a moderately potent i substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetin with duloxetine and a TCA is unavoidable, plasma concentrations of the t made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.I Amitriptyline

1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.J Amitriptylinoxide
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.K Amoxapine
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.L Anagrelide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repor
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.M Ancrod
1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study c
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i

bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.N Anisindione
1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study o
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.

0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained o
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patient
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting factc
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-intc
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.O Antithrombin III Human

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintа
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study c
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are given
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increase
Using national pharmacy and hospitalization records, Netherlands res
abnormal bleeding and compared them with 5818 control subjects als
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained o
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patient
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting factc
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox

titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-intc
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.P Ardeparin

1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study c
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects als
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et

b) A case report describes a 44-year-old female patient maintained c
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting factc
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day 1
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic

c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-intc
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.Q Aspirin

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repor
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).

7) Probable Mechanism: unknown

3.5.1.R Benoxaprofen

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu

7) Probable Mechanism: unknown

3.5.1.S Bivalirudin

1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et

b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic

c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.T Bromfenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake

associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.U Bufexamac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.V Carprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.W Celecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.X Certoparin
1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports

a) A population-based, case-controlled study of new coumarin users selective serotonin reuptake inhibitors (SSRIs) resulted in an increas Using national pharmacy and hospitalization records, Netherlands re abnormal bleeding and compared them with 5818 control subjects al was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5 0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained c after 55 days of concomitant duloxetine treatment. Warfarin was initia medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1 mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30 day 58, only the warfarin was discontinued, and by day 85 the patien mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10 the INR was again elevated at 6.4, vitamin K-dependent clotting facto normal. Duloxetine was then discontinued, and 4 days later the INR r to 54%. INR was 0.9 by day 105, and warfarin was restarted on day 1 maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm, probable. The authors suggest that duloxetine may have an effect on warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol mechanical, prosthetic mitral-valve substitution experienced a persist mg/day. Ten hours after taking duloxetine, the patient was taken to th blood pressure had increased to 190/110 mmHg and her INR had dra administered intravenously for the headache and hypertension, dulox titrated to 12 mg/wk. Twenty-one days later, the INR returned to base Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st family interviews discounted the possibility of acenocoumarol self-into measured and the patient was not genotyped for CYP2D6 or CYP1A2 duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.Y Chlorpromazine

1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.Z Cifenline

1) Interaction Effect: increased class IC antiarrhythmic serum concentrati torsades de pointes, cardiac arrest)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6. Give antiarrhythmic agents as well as considering that they are CYP2D6 substr whenever duloxetine is coadministered with this class of antiarrhythmic ag 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati cause elevated plasma concentrations of the antiarrhythmic (Prod Info CY class IC antiarrhythmic serum concentrations and ECG for signs of potent hypotension); adjust dose accordingly. Alternatively, consider selecting an pharmacokinetics of class IC antiarrhythmic agents.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of cl

3.5.1.AA Cilostazol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake been associated with an increased risk of bleeding. Bleeding events repor petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de

3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.AB Ciprofloxacin
1) Interaction Effect: increased duloxetine bioavailability and risk of adver
2) Summary: Since duloxetine is a substrate for cytochrome P450 isoforn
expected to occur in the presence of coadministration with ciprofloxacin, a
and about 2.5-fold, respectively, when duloxetine was administered with fl
(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the concomitant use of ciproflo
exposure and serum levels (Prod Info CYMBALTA(R) delayed-release ora
events and adjust duloxetine dose as necessary.
7) Probable Mechanism: inhibition of CYP1A2-mediated duloxetine metal

3.5.1.AC Citalopram
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup
citalopram, a selective serotonin reuptake inhibitor, is not recommended c
CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of citalopram and duloxetir
serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsu
7) Probable Mechanism: potentiation of serotonergic activity in the CNS b

3.5.1.AD Clomipramine
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.AE Clonixin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.AF Clopidogrel
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repor

petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.AG Cyclobenzaprine

1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Concomitant use of cyclobenzaprine and duloxetine resulte
Other possibly contributing drugs in this case were bupropion and opiates
concomitant use of cyclobenzaprine and duloxetine is warranted, monitor
abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, pe
(including tachycardia, mydriasis, diaphoresis, and the presence of bowel
agitation and delirium). Discuss the risks and symptoms of serotonin syn
serotonin syndrome develops, discontinue the offending drugs, and provi
necessary (Boyer & Shannon, 2005).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: A case of serotonin syndrome was reported wit
therefore, concomitant use is discouraged. Other possibly contributing dr
hydromorphone) (Keegan et al, 2006). If cyclobenzaprine and duloxetine
syndrome such as neuromuscular abnormalities (including hyper-reflexia,
shivering), autonomic hyperactivity (including tachycardia, mydriasis, diap
mental status changes (including agitation and delirium). Serotonin syndr
discontinue the offending agents and provide supportive care, correction
Shannon, 2005).
7) Probable Mechanism: additive serotonergic effects
8) Literature Reports
a) A 53-year-old male on duloxetine experienced serotonin syndrom
patient had a history of chronic pain and depression. His previous me
oxycodone for several weeks, bupropion 300 mg/day for more than 6
for an unstated time. On the second day after an uneventful surgical
hallucinations shortly after starting cyclobenzaprine 10 mg 3 times da
tachycardia, marked agitation, pronounced tremors, spontaneous sus
Laboratory analysis revealed hypernatremia (154 mEq/L), lactic acido
(peaked at 265 units/L). Severe agitation required administration of p
treated with hydration, a beta-blocker, and cyproheptadine 8 mg via r
and duloxetine were discontinued. Improvement occurred over the fo
without any complications. Other possibly contributing drugs towards
or hydromorphone) (Keegan et al, 2006).

3.5.1.AH Dalteparin

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al

was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.AI Danaparoid

1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
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0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th

blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.AJ Defibrotide

1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study o
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands res
abnormal bleeding and compared them with 5818 control subjects als
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
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0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et

b) A case report describes a 44-year-old female patient maintained o
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic

c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.AK Dermatan Sulfate

1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study o
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe

dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
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after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.AL Desipramine
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent in
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.AM Desirudin
1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study o
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.AN Desvenlafaxine
1) Interaction Effect: increased risk of serotonin syndrome (hypertension,
2) Summary: Both desvenlafaxine and duloxetine are selective serotonin
of desvenlafaxine and duloxetine is not recommended as it may result in s
CYMBALTA(R) delayed-release oral capsules, 2008). Symptoms of serot
coordination, fast heart beat, rapid changes in blood pressure, increased
diarrhea. Discuss the risks of serotonin syndrome with patients who are p
closely for symptoms of serotonin syndrome, especially during therapy ini
extended-release tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of desvenlafaxine and dulo
recommended (Prod Info CYMBALTA(R) delayed-release oral capsules, 2
serotonin syndrome with the patient and monitor closely for symptoms of
incoordination), especially during treatment initiation and dose increases (
7) Probable Mechanism: additive serotonergic effect

3.5.1.AO Dexketoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.AP Dibenzepin

1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)

2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh

7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.AQ Diclofenac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu

7) Probable Mechanism: unknown

3.5.1.AR Dicumarol

1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study c
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et

b) A case report describes a 44-year-old female patient maintained c
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting factc
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on

warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.AS Diflunisal

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.AT Dipyridamole

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repo
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.AU Dipyrone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.AV Dixyrazine

1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.AW Dothiepin

1) Interaction Effect: increased tricyclic antidepressant serum concentrati

confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.AX Doxepin
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.AY Droxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.AZ Eletriptan
1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: A life-threatening condition known as serotonin syndrome m
combination with a serotonin and norepinephrine reuptake inhibitor (SNRI
include restlessness, hallucinations, loss of coordination, fast heart beat, r
overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should b
that either the triptan or the SNRI may be prescribed by a different physici
are prescribed this combination and monitor them closely for symptoms o
dose increases (Prod Info CYMBALTA(R) delayed-release oral capsules,
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as eletriptan,
such as duloxetine, may result in a life-threatening condition called seroto
intermittently and that either the triptan or the SNRI may be prescribed by
discuss the risks of serotonin syndrome with the patient and monitor close
hyperthermia, hyperreflexia, incoordination), especially during treatment in
release oral capsules, 2008).
7) Probable Mechanism: additive pharmacologic effects resulting in exces

3.5.1.BA Encainide
1) Interaction Effect: increased class IC antiarrhythmic serum concentrati
torsades de pointes, cardiac arrest)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6. Give

antiarrhythmic agents as well as considering that they are CYP2D6 substr
whenever duloxetine is coadministered with this class of antiarrhythmic ag
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
cause elevated plasma concentrations of the antiarrhythmic (Prod Info CY
class IC antiarrhythmic serum concentrations and ECG for signs of potent
hypotension); adjust dose accordingly. Alternatively, consider selecting ar
pharmacokinetics of class IC antiarrhythmic agents.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of cl

3.5.1.BB Enoxacin
1) Interaction Effect: increased duloxetine bioavailability and risk of adver
2) Summary: Since duloxetine is a substrate for cytochrome P450 isoforr
expected to occur in the presence of coadministration with enoxacin, a CY
and about 2.5-fold, respectively, when duloxetine was administered with fl
(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the concomitant use of duloxet
exposure and serum levels (Prod Info CYMBALTA(R) delayed-release ora
events and adjust duloxetine dose as necessary.
7) Probable Mechanism: inhibition of CYP1A2-mediated duloxetine metal

3.5.1.BC Enoxaparin
1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study c
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects als
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained c
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patient
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting factc
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day 1
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist

mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.BD Epoprostenol

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repor
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.BE Eptifibatide

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repor
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.BF Escitalopram

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

3.5.1.BG Ethopropazine

1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.BH Etodolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BI Etofenamate
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BJ Etoricoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BK Felbinac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BL Fenbufen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BM Fenoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BN Fentiazac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BO Flecainide
1) Interaction Effect: increased class IC antiarrhythmic serum concentrati
torsades de pointes, cardiac arrest)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6. Give
antiarrhythmic agents as well as considering that they are CYP2D6 substr
whenever duloxetine is coadministered with this class of antiarrhythmic ag
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
cause elevated plasma concentrations of the antiarrhythmic (Prod Info CY
class IC antiarrhythmic serum concentrations and ECG for signs of potent
hypotension); adjust dose accordingly. Alternatively, consider selecting ar
pharmacokinetics of class IC antiarrhythmic agents.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of cl

3.5.1.BP Floctafenine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BQ Flufenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BR Fluoxetine
1) Interaction Effect: increased duloxetine and fluoxetine serum concentr
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup
fluoxetine, an SSRI, is not recommended due to the potential for serotonir
fluoxetine is likely to increase the bioavailability of either drug, increasing
are both substrates for, and moderately potent inhibitors of CYP2D6. Coa

(the potent CYP2D6 inhibitor paroxetine 20 mg once daily) resulted in a 6
Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concomitant use of duloxetine and fluoxetin
serotonin syndrome. Additionally, concomitant use has resulted in increas
CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: fluoxetine inhibition of CYP2D6-mediated dulox

3.5.1.BS Fluphenazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.BT Flurbiprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BU Fluvoxamine
1) Interaction Effect: increased duloxetine bioavailability and an increase
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup
CYP1A2 and CYP2D6 isozymes. The concomitant use of duloxetine with
for serotonin syndrome. In addition, coadministration of fluvoxamine 100 r
14 CYP2D6 poor metabolizer subjects resulted in a 6-fold increase in dulo
given duloxetine 60 mg together with fluvoxamine 100 mg, duloxetine AU
3-fold, respectively (Prod Info CYMBALTA(R) delayed-release oral capsul
3) Severity: major
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: The concomitant use of duloxetine and fluvoxam
of serotonin syndrome. Additionally, concomitant use has resulted in signi
Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: inhibition of CYP1A2-mediated duloxetine metal

3.5.1.BV Fondaparinux
1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.BW Frovatriptan
1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: A life-threatening condition known as serotonin syndrome m
combination with a serotonin and norepinephrine reuptake inhibitor (SNRI
include restlessness, hallucinations, loss of coordination, fast heart beat,
overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should b
that either the triptan or the SNRI may be prescribed by a different physici
are prescribed this combination and monitor them closely for symptoms o
dose increases (Prod Info CYMBALTA(R) delayed-release oral capsules,
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as frovatripta
(SNRI), such as duloxetine, may result in a life-threatening condition calle
commonly used intermittently and that either the triptan or the SNRI may l
together, discuss the risks of serotonin syndrome with the patient and mo
hyperthermia, hyperreflexia, incoordination), especially during treatment in
release oral capsules, 2008).
7) Probable Mechanism: additive pharmacologic effects resulting in exce

3.5.1.BX Heparin
1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.BY Ibuprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.BZ Iloprost
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repo
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.CA Imipramine
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre

increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the t
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.CB Indecainide
1) Interaction Effect: increased class IC antiarrhythmic serum concentrati
torsades de pointes, cardiac arrest)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6. Give
antiarrhythmic agents as well as considering that they are CYP2D6 substr
whenever duloxetine is coadministered with this class of antiarrhythmic ag
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
cause elevated plasma concentrations of the antiarrhythmic (Prod Info CY
class IC antiarrhythmic serum concentrations and ECG for signs of potent
hypotension); adjust dose accordingly. Alternatively, consider selecting ar
pharmacokinetics of class IC antiarrhythmic agents.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of cl

3.5.1.CC Indomethacin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CD Indoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CE Isocarboxazid
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h
2) Summary: Duloxetine exerts inhibitory effects on both norepinephrine
overlapping therapy with duloxetine and an MAOI, such as isocarboxazid,
serotonergic state characterized by symptoms such as agitation and restl
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have be
inhibitors and MAOIs. Concomitant administration of duloxetine and isoca
elapse after discontinuing isocarboxazid before initiating therapy with dulo
discontinuing duloxetine before initiating therapy with isocarboxazid (Prod
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Concurrent use of duloxetine and isocarboxazid isocarboxazid before initiating duloxetine. Wait at least 5 days after discor (Prod Info Cymbalta(R) Delayed-release oral capsules, 2009).
7) Probable Mechanism: additive serotonergic effects

3.5.1.CF Isoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CG Ketoprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CH Ketorolac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CI Lamifiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake been associated with an increased risk of bleeding. Bleeding events repo petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.CJ Lexipafant
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake been associated with an increased risk of bleeding. Bleeding events repo petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g

bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.CK Linezolid
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h
2) Summary: Linezolid is a reversible, nonselective inhibitor of monoamir tablets, oral suspension, 2008). Concurrent administration or overlapping toxicity or serotonin syndrome, a hyperserotonergic state characterized by mental status, hyperreflexia, diaphoresis, shivering, and tremor. There ha with concomitant use of linezolid and serotonergic agents, including one c concomitant therapy with linezolid and serotonergic agents be clinically ne serotonin syndrome (hyperreflexia, incoordination, hyperpyrexia, or impair oral suspension, 2008). Serotonin syndrome can be life-threatening. If ser and provide supportive care and other therapy as necessary (Boyer & Sha
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Unless carefully monitored for serotonin syndror duloxetine (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension monitor closely for symptoms of serotonin syndrome such as neuromuscu rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hypera diarrhea), and mental status changes (including agitation and delirium). S syndrome develops, discontinue the offending agents and provide suppor 2005).
7) Probable Mechanism: inhibition of monoamine oxidase-mediated sero
8) Literature Reports
a) Serotonin syndrome was induced in a 55-year-old woman maintai following the addition of intravenous linezolid 600 mg every 12 hours an inpatient oncology center for pain management and treatment of a vancomycin-resistant enterococcus in wound cultures, linezolid was a first dose of linezolid, the patient demonstrated mental status change movements. Additional symptoms occurring over the following hours nonsensical speech, involuntary movements of the extremities, contir were noncontributory; a low-grade fever (38 degrees Celsius) was pr throughout the day, returning to baseline mental and physical status l later the patient chose to resume duloxetine at a 30-mg/day dose. Du hospital stay. A week later, the patient died from malignancy-associat

3.5.1.CL Lithium
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup concurrently with agents affecting the serotonergic neurotransmitter syste serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsu symptoms of serotonin syndrome such as neuromuscular abnormalities (i peripheral hypertonicity, and shivering), autonomic hyperactivity (including bowel sounds and diarrhea), and mental status changes (including agitati syndrome with patients who are prescribed this combination. If serotonin s provide supportive care, correction of vital signs, or other therapy, as nece
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution if duloxetine is coadministered with syndrome (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008 symptoms of serotonin syndrome such as neuromuscular abnormalities (i peripheral hypertonicity, and shivering), autonomic hyperactivity (including sounds, and diarrhea), and mental status changes (including agitation and serotonin syndrome develops, discontinue the offending agents and provi as necessary (Boyer & Shannon, 2005).
7) Probable Mechanism: additive serotonergic effects

3.5.1.CM Lofepramine
1) Interaction Effect: increased tricyclic antidepressant serum concentrati confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre increasing the risk of adverse events. Duloxetine is a moderately potent ir substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine with duloxetine and a TCA is unavoidable, plasma concentrations of the tr made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.CN Lorcainide
1) Interaction Effect: increased class IC antiarrhythmic serum concentrati torsades de pointes, cardiac arrest)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6. Give antiarrhythmic agents as well as considering that they are CYP2D6 substr whenever duloxetine is coadministered with this class of antiarrhythmic ag 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati cause elevated plasma concentrations of the antiarrhythmic (Prod Info CY class IC antiarrhythmic serum concentrations and ECG for signs of potent hypotension); adjust dose accordingly. Alternatively, consider selecting ar pharmacokinetics of class IC antiarrhythmic agents.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of cl

3.5.1.CO Lornoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CP Meclofenamate
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CQ Mefenamic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CR Melitracen
1) Interaction Effect: increased tricyclic antidepressant serum concentrati

confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre increasing the risk of adverse events. Duloxetine is a moderately potent ir substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine with duloxetine and a TCA is unavoidable, plasma concentrations of the t made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.CS Meloxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CT Mesoridazine
1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.CU Methdilazine
1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.CV Methotrimeprazine
1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).

7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.CW Metopimazine

1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.CX Milnacipran

1) Interaction Effect: increased risk of serotonin syndrome (hypertension,
2) Summary: Concurrent use of milnacipran and an SSRI or a serotonin r hypertension, coronary artery vasoconstriction or serotonin syndrome, wh may include restlessness, hallucinations, loss of coordination, fast heart b temperature, overreactive reflexes, nausea, vomiting, and diarrhea (Prod
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of milnacipran and an SSRI or result in hypertension and coronary artery vasoconstriction through the ac discuss the risks of serotonin syndrome with the patient and monitor close hyperthermia, hyperreflexia, incoordination), especially during treatment ir tablets, 2009).
7) Probable Mechanism: additive serotonergic effect

3.5.1.CY Morniflumate

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.CZ Nabumetone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DA Nadroparin

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events reported h life-threatening hemorrhages. A population-based, case-controlled study with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin coadministration of serotonin and norepinephrine reuptake inhibitors with

release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.DB Naproxen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DC Naratriptan
1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: A life-threatening condition known as serotonin syndrome m
combination with a serotonin and norepinephrine reuptake inhibitor (SNRI
include restlessness, hallucinations, loss of coordination, fast heart beat,
overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should b
that either the triptan or the SNRI may be prescribed by a different physici
are prescribed this combination and monitor them closely for symptoms o
dose increases (Prod Info CYMBALTA(R) delayed-release oral capsules,
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as naratripta
(SNRI), such as duloxetine, may result in a life-threatening condition calle

commonly used intermittently and that either the triptan or the SNRI may l
together, discuss the risks of serotonin syndrome with the patient and mo
hyperthermia, hyperreflexia, incoordination), especially during treatment i
release oral capsules, 2008).
7) Probable Mechanism: additive pharmacologic effects resulting in exce

3.5.1.DD Niflumic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DE Nimesulide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DF Nortriptyline
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the t
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.DG Opipramol
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the t
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.DH Oxaprozin
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta

that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DI Parecoxib

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DJ Parnaparin

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base

Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.DK Paroxetine

1) Interaction Effect: increased duloxetine serum concentrations and an i
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup
paroxetine, an SSRI, is not recommended due to the potential for seroton
potent CYP2D6 inhibitor, at a dose of 20 mg once daily with duloxetine 40
concentration (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 paroxeti
serotonin syndrome. Additionally, concomitant use has resulted in signific
(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: paroxetine inhibition of CYP2D6-mediated dulox

3.5.1.DL Pentosan Polysulfate Sodium

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports

a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects als
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et

b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic

c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.DM Perazine

1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.DN Periciazine

1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.DO Perphenazine

1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.DP Phenindione

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events reported h life-threatening hemorrhages. A population-based, case-controlled study with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin coadministration of serotonin and norepinephrine reuptake inhibitors with release oral capsules, 2008). Conversely, one case report described a pe dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver Patients who are taking warfarin should be monitored closely for altered a duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports

a) A population-based, case-controlled study of new coumarin users selective serotonin reuptake inhibitors (SSRIs) resulted in an increas Using national pharmacy and hospitalization records, Netherlands re abnormal bleeding and compared them with 5818 control subjects als was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr

(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained o
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patient
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting factc
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-intc
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.DQ Phenprocoumon

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintа
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study c
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted i
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.5
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained o
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patient
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting factc
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra

administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-intc
measured and the patient was not genotyped for CYP2D6 or CYP1A2
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.DR Phenylbutazone

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DS Pipotiazine

1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.DT Pirazolac

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DU Piroxicam

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DV Pirprofen

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.DW Procarbazine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h
2) Summary: Duloxetine exerts inhibitory effects on both norepinephrine
overlapping therapy with duloxetine and an MAOI, such as procarbazine,
serotonergic state characterized by symptoms such as agitation and restl
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have be
inhibitors and MAOIs. Concomitant administration of duloxetine and proca
elapse after discontinuing procarbazine before initiating therapy with dulo
discontinuing duloxetine before initiating therapy with procarbazine (Prod
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of duloxetine and procarbazine
procarbazine before initiating duloxetine. Wait at least 5 days after discon
(Prod Info Cymbalta(R) Delayed-release oral capsules, 2009).
7) Probable Mechanism: additive serotonergic effects

3.5.1.DX Prochlorperazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.DY Promazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.DZ Promethazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.EA Propafenone
1) Interaction Effect: increased class IC antiarrhythmic serum concentrati

torsades de pointes, cardiac arrest)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6. Give antiarrhythmic agents as well as considering that they are CYP2D6 substr whenever duloxetine is coadministered with this class of antiarrhythmic ag 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati cause elevated plasma concentrations of the antiarrhythmic (Prod Info CY class IC antiarrhythmic serum concentrations and ECG for signs of potent hypotension); adjust dose accordingly. Alternatively, consider selecting ar pharmacokinetics of class IC antiarrhythmic agents.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of cl

3.5.1.EB Propiomazine
1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.EC Propyphenazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.ED Proquazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.EE Protriptyline
1) Interaction Effect: increased tricyclic antidepressant serum concentrati confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre increasing the risk of adverse events. Duloxetine is a moderately potent ir substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine with duloxetine and a TCA is unavoidable, plasma concentrations of the tr

made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.EF Quinidine

1) Interaction Effect: increased duloxetine serum concentrations and risk
2) Summary: The coadministration of duloxetine (a substrate of CYP2D6
increase the bioavailability of duloxetine, increasing the risk of serious adv
with another potent CYP2D6 inhibitor (paroxetine 20 mg once daily) resul
(Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
quinidine may cause elevated duloxetine plasma concentrations (Prod Inf
7) Probable Mechanism: quinidine inhibition of CYP2D6-mediated duloxe

3.5.1.EG Rasagiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h
2) Summary: Duloxetine exerts inhibitory effects on both norepinephrine
overlapping therapy with duloxetine and an MAOI, such as rasagiline, ma
serotonergic state characterized by symptoms such as agitation and restl
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have be
inhibitors and MAOIs. Concomitant administration of duloxetine and rasag
elapse after discontinuing rasagiline before initiating therapy with duloxeti
duloxetine before initiating therapy with rasagiline (Prod Info Cymbalta(R)
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of duloxetine and rasagiline is c
rasagiline before initiating duloxetine. Wait at least 5 days after discontinu
Info Cymbalta(R) Delayed-release oral capsules, 2009).
7) Probable Mechanism: additive serotonergic effects

3.5.1.EH Rasagiline

1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h
2) Summary: Concomitant use of rasagiline and duloxetine, a selective s
avoided. Concurrent administration or overlapping therapy with SSRIs an
sometimes fatal reactions. Signs and symptoms included hyperthermia, ri
fluctuations, and mental status changes progressing to extreme agitation,
SNRIs and non-selective MAOIs. At least 14 days should elapse after dis
Info AZILECT(R) oral tablets, 2006). Similarly, at least 5 days should elap
rasagiline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of duloxetine and rasagiline is n
rasagiline before initiating therapy with duloxetine, or wait at least 5 days
rasagiline (Prod Info AZILECT(R) oral tablets, 2006; Prod Info CYMBALT
7) Probable Mechanism: inhibition of monamine oxidase-mediated seroto

3.5.1.EI Recainam

1) Interaction Effect: increased class IC antiarrhythmic serum concentrati
torsades de pointes, cardiac arrest)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6. Give
antiarrhythmic agents as well as considering that they are CYP2D6 substr
whenever duloxetine is coadministered with this class of antiarrhythmic ag
2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
cause elevated plasma concentrations of the antiarrhythmic (Prod Info CY
class IC antiarrhythmic serum concentrations and ECG for signs of potent
hypotension); adjust dose accordingly. Alternatively, consider selecting ar
pharmacokinetics of class IC antiarrhythmic agents.
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of cl

3.5.1.EJ Reviparin

1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d

7) Probable Mechanism: unknown

8) Literature Reports

a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp e

b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR r
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic

c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.EK Rizatriptan

1) Interaction Effect: increased risk of serotonin syndrome

2) Summary: A life-threatening condition known as serotonin syndrome m
combination with a serotonin and norepinephrine reuptake inhibitor (SNRI
include restlessness, hallucinations, loss of coordination, fast heart beat,
overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should b
that either the triptan or the SNRI may be prescribed by a different physici
are prescribed this combination and monitor them closely for symptoms o
dose increases (Prod Info CYMBALTA(R) delayed-release oral capsules,

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of a triptan, such as rizatriptan
such as duloxetine, may result in a life-threatening condition called seroto
intermittently and that either the triptan or the SNRI may be prescribed by
discuss the risks of serotonin syndrome with the patient and monitor close
hyperthermia, hyperreflexia, incoordination), especially during treatment i

release oral capsules, 2008).
7) Probable Mechanism: additive pharmacologic effects resulting in exce

3.5.1.EL Rofecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.EM Selegiline
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h
2) Summary: Duloxetine exerts inhibitory effects on both norepinephrine overlapping therapy with duloxetine and an MAOI, such as selegiline, may serotonergic state characterized by symptoms such as agitation and restl diaphoresis, shivering, and tremor. Serious, even fatal, reactions have be inhibitors and MAOIs. Concomitant administration of duloxetine and seleg elapse after discontinuing selegiline before initiating therapy with duloxeti duloxetine before initiating therapy with selegiline (Prod Info Cymbalta(R)
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of duloxetine and selegiline is c selegiline before initiating duloxetine. Wait at least 5 days after discontinu Cymbalta(R) Delayed-release oral capsules, 2009).
7) Probable Mechanism: additive serotonergic effects

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

3.5.1.EO Sibrafiban
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake been associated with an increased risk of bleeding. Bleeding events repo petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.EP St John's Wort
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup affect the serotonergic neurotransmitter systems, may result in an increas delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution if duloxetine is coadministered with

serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsu
7) Probable Mechanism: additive serotonergic effects

3.5.1.EQ Sulfinpyrazone
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repo
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.ER Sulindac
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.ES Sulodexide
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repo
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.ET Sumatriptan
1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: A life-threatening condition known as serotonin syndrome m
combination with a serotonin and norepinephrine reuptake inhibitor (SNRI
include restlessness, hallucinations, loss of coordination, fast heart beat,
overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should b
that either the triptan or the SNRI may be prescribed by a different physic
are prescribed this combination and monitor them closely for symptoms o
dose increases (Prod Info CYMBALTA(R) delayed-release oral capsules,
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of a triptan, such as sumatripta
(SNRI), such as duloxetine, may result in a life-threatening condition calle
commonly used intermittently and that either the triptan or the SNRI may l
together, discuss the risks of serotonin syndrome with the patient and mo
hyperthermia, hyperreflexia, incoordination), especially during treatment i
release oral capsules, 2008).
7) Probable Mechanism: additive pharmacologic effects resulting in exce

3.5.1.EU Suprofen
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu

threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.EV Tamoxifen

1) Interaction Effect: decreased plasma concentrations of the active meta
2) Summary: Duloxetine is a moderate CYP2D6 inhibitor (Prod Info CYM is a prodrug metabolized to active metabolites by CYP450 enzymes. Con tamoxifen efficacy by inhibiting the formation of endoxifen, an active meta interactions may result in variations in endoxifen concentrations, which ma efficacy (Desta et al, 2004). Tamoxifen use in the presence of CYP2D6 in may substantially reduce the plasma concentrations of endoxifen and may However, one small case control study found that pharmacokinetic alterat tumor recurrence in breast cancer patients (Lehmann et al, 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tamoxifen and paroxetine, a concentrations of 4-hydroxy-N-desmethyl tamoxifen, an active metabolite moderate CYP2D6 inhibitor (Prod Info CYMBALTA(R) delayed-release or with coadministration may be necessary.
7) Probable Mechanism: inhibition of CYP2D6-mediated tamoxifen metab
8) Literature Reports
a) The use of CYP2D6 inhibitors should be avoided in breast cancer reduced plasma concentrations of the antiestrogenic tamoxifen metal postmenopausal breast cancer patients receiving tamoxifen were ger medication history. Adjusted analysis showed that decreased metabo (hazard ratio 1.74; 95% confidence interval (CI), 1.1 to 2.74; p=0.017 p=0.027), and shorter time to recurrence (hazard ratio 1.91; 95% CI, (n=115). The greatest risk of breast cancer relapse was found in the 7.55; p=0.007) (Goetz et al, 2007). Decreased metabolizers had eithe inhibitor together with tamoxifen (regardless of genotype), and extens receiving a CYP2D6 inhibitor (Goetz et al, 2008).
b) Plasma concentrations of 4-hydroxy-N-desmethyl tamoxifen (endo CYP2D6 metabolic pathway. Studies have shown that concomitant u resulted in reduced plasma concentrations of endoxifen (Johnson et a CYP2D6 inhibitor (Prod Info CYMBALTA(R) delayed-release oral cap
c) Concomitant use of paroxetine, a potent inhibitor of CYP2D6, and the antiestrogenic metabolite (endoxifen), results in substantially redu diagnosed breast cancer patients taking tamoxifen 20 mg/day were g CYP3A5, and sulfotransferase (SULT) 1A1 genes. After 1 and 4 mon and endoxifen were measured. After 4 months of tamoxifen, plasma those with a CYP2D6 homozygous variant genotype (20 nM; 95% CI 33.3 to 52.9) than those with a homozygous wild-type genotype (78 n endoxifen concentration for subjects with a homozygous wild-type ge than those not taking such inhibitors (38.6 nM versus 91.4 nM, 95% C venlafaxine, a weak inhibitor of CYP2D6, resulted in slightly reduced paroxetine, a potent inhibitor of CYP2D6, resulted in substantial redu tamoxifen and metabolites were not altered significantly by genetic va
d) A case control study (n=28) designed to evaluate the effect of CY tamoxifen for estrogen receptor-positive breast cancer found no signi exposure (3 months or greater) to CYP2D6, 2C9, or 3A4 inhibitors or (patients without recurrent breast cancer) were matched by cancer st exposure. Selective serotonin reuptake inhibitors, including paroxetin for the metabolism of tamoxifen to the potent antiestrogen 4-hydroxy norepinephrine reuptake inhibitors are also inhibitors of CYP2D6, sim

3.5.1.EW Tapentadol

1) Interaction Effect: increased risk of serotonin syndrome (hypertension,
2) Summary: Concurrent use of duloxetine and tapentadol may result in s of serotonin syndrome may include restlessness, hallucinations, loss of co increased body temperature, overreactive reflexes, nausea, vomiting, and 2008).

3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of duloxetine and tapentadol n
syndrome. If these agents are used together, monitor the patient closely f
hyperthermia, hyperreflexia, incoordination), especially during treatment i
release oral tablets, 2008).
7) Probable Mechanism: additive serotonergic effect

3.5.1.EX Tenidap
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.EY Tenoxicam
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.EZ Thiethylperazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.FA Thiopropazate
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.FB Thioproperazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther

likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.FC Thioridazine
1) Interaction Effect: increased thioridazine serum concentrations and ris
2) Summary: Given thioridazine's tendency to prolong the QTc-interval in
serious or fatal ventricular arrhythmias precludes the safe concomitant us
potent inhibitor of CYP2D6 (for which thioridazine is a substrate) and ther
likely to produce elevated thioridazine plasma concentrations with attenda
CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of duloxetine and thioridazine
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated thiori

3.5.1.FD Tianeptine
1) Interaction Effect: increased tricyclic antidepressant serum concentrati
confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre
increasing the risk of adverse events. Duloxetine is a moderately potent ir
substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad
baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine
with duloxetine and a TCA is unavoidable, plasma concentrations of the tr
made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule
TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.FE Tiaprofenic Acid
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.FF Ticlopidine
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repor
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.FG Tinzaparin
1) Interaction Effect: increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.FH Tirofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repo
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.FI Tolmetin

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events have inclu
threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm
increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.FJ Tramadol
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup
concurrently with agents affecting the serotonergic neurotransmitter syste
serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsu
symptoms of serotonin syndrome such as neuromuscular abnormalities (i
peripheral hypertonicity, and shivering), autonomic hyperactivity (including
bowel sounds and diarrhea), and mental status changes (including agitati
syndrome with patients who are prescribed this combination. If serotonin s
provide supportive care, correction of vital signs, or other therapy, as nece
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution if duloxetine is coadministered with
syndrome (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008
symptoms of serotonin syndrome such as neuromuscular abnormalities (i
peripheral hypertonicity, and shivering), autonomic hyperactivity (including
sounds, and diarrhea), and mental status changes (including agitation and
serotonin syndrome develops, discontinue the offending agents and provi
as necessary (Boyer & Shannon, 2005).
7) Probable Mechanism: additive serotonergic effects

3.5.1.FK Tranylcypromine
1) Interaction Effect: CNS toxicity or serotonin syndrome (hypertension, h
2) Summary: Duloxetine exerts inhibitory effects on both norepinephrine
overlapping therapy with duloxetine and an MAOI, such as tranylcypromin
serotonergic state characterized by symptoms such as agitation and restl
diaphoresis, shivering, and tremor. Serious, even fatal, reactions have be
inhibitors and MAOIs. Concomitant administration of duloxetine and tranyl
should elapse after discontinuing tranylcypromine before initiating therapy
discontinuing duloxetine before initiating therapy with tranylcypromine (Pr
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of duloxetine and tranylcypromi
tranylcypromine before initiating duloxetine. Wait at least 5 days after disc
tranylcypromine (Prod Info Cymbalta(R) Delayed-release oral capsules, 2
7) Probable Mechanism: additive serotonergic effects

3.5.1.FL Trifluoperazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati
elevated phenothiazine plasma concentrations. Monitor for increased phe
release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.FM Triflupromazine
1) Interaction Effect: increased phenothiazine serum concentrations and
orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther
likely to increase bioavailability of the phenothiazine agent, increasing the
delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.FN Trimeprazine
1) Interaction Effect: increased phenothiazine serum concentrations and orthostatic hypotension, hyperthermia, extrapyramidal effects)
2) Summary: Duloxetine is a moderately potent inhibitor of CYP2D6; ther likely to increase bioavailability of the phenothiazine agent, increasing the delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing duloxetine to pati elevated phenothiazine plasma concentrations. Monitor for increased phe release oral capsules, 2008).
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated phen

3.5.1.FO Trimipramine
1) Interaction Effect: increased tricyclic antidepressant serum concentrati confusion, cardiac arrhythmias)
2) Summary: The coadministration of duloxetine with a tricyclic antidepre increasing the risk of adverse events. Duloxetine is a moderately potent ir substrate desipramine 50 mg and duloxetine 60 mg twice daily were coad baseline (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the combined use of duloxetine with duloxetine and a TCA is unavoidable, plasma concentrations of the tr made accordingly (Prod Info CYMBALTA(R) delayed-release oral capsule TCA toxicity (anticholinergic effects, sedation, confusion, and cardiac arrh
7) Probable Mechanism: duloxetine inhibition of CYP2D6-mediated tricyc

3.5.1.FP Tryptophan
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup serotonergic agents such as tryptophan (serotonin precursor) is not recon CYMBALTA(R) delayed-release oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of duloxetine and tryptoph serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsu
7) Probable Mechanism: potentiation of serotonergic activity in the CNS b

3.5.1.FQ Valdecoxib
1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu
7) Probable Mechanism: unknown

3.5.1.FR Venlafaxine
1) Interaction Effect: an increased risk of serotonin syndrome
2) Summary: Duloxetine is a selective serotonin and norepinephrine reup venlafaxine, also a selective serotonin and norepinephrine reuptake inhibi syndrome (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008
3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of duloxetine and venlafax
serotonin syndrome (Prod Info CYMBALTA(R) delayed-release oral capsu
7) Probable Mechanism: additive serotonergic effects

3.5.1.FS Warfarin

1) Interaction Effect: increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
associated with an increased risk of bleeding. Bleeding events reported h
life-threatening hemorrhages. A population-based, case-controlled study
with concomitant selective serotonin reuptake inhibitors (SSRIs) resulted
bleeding (Schalekamp et al, 2008). Altered anticoagulant effects (includin
coadministration of serotonin and norepinephrine reuptake inhibitors with
release oral capsules, 2008). Conversely, one case report described a pe
dose in a patient maintained on acenocoumarol (Monastero et al, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When duloxetine and an anticoagulant are giver
Patients who are taking warfarin should be monitored closely for altered a
duloxetine therapy is initiated or discontinued (Prod Info CYMBALTA(R) d
7) Probable Mechanism: unknown
8) Literature Reports
a) A population-based, case-controlled study of new coumarin users
selective serotonin reuptake inhibitors (SSRIs) resulted in an increas
Using national pharmacy and hospitalization records, Netherlands re
abnormal bleeding and compared them with 5818 control subjects al
was 220 days (range, 1 to 4690 days). Patients on SSRIs showed gr
(adjusted odds ratio (OR) 1.7, 95% confidence interval (CI), 1.1 to 2.
0.8, 95% CI, 0.4 to 1.5) was not significantly different (Schalekamp et
b) A case report describes a 44-year-old female patient maintained
after 55 days of concomitant duloxetine treatment. Warfarin was initia
medication regimen included atorvastatin 10 mg, warfarin 7.5 mg to 1
mg, and albuterol extended-release 4 mg twice a day. Duloxetine 30
day 58, only the warfarin was discontinued, and by day 85 the patien
mcg/mL (therapeutic range 2 to 8 mcg/mL). Intravenous vitamin K 10
the INR was again elevated at 6.4, vitamin K-dependent clotting facto
normal. Duloxetine was then discontinued, and 4 days later the INR
to 54%. INR was 0.9 by day 105, and warfarin was restarted on day
maintained on 7.5 to 10 mg/day. According to the Naranjo algorithm,
probable. The authors suggest that duloxetine may have an effect on
warfarin from its protein-binding sites, or may have unique metabolic
c) A 63-year-old woman successfully maintained on acenocoumarol
mechanical, prosthetic mitral-valve substitution experienced a persist
mg/day. Ten hours after taking duloxetine, the patient was taken to th
blood pressure had increased to 190/110 mmHg and her INR had dra
administered intravenously for the headache and hypertension, dulox
titrated to 12 mg/wk. Twenty-one days later, the INR returned to base
Follow-up examinations on days 28, 56, 84, 168, and 252 revealed st
family interviews discounted the possibility of acenocoumarol self-into
measured and the patient was not genotyped for CYP2D6 or CYP1A
duloxetine was deemed as probable based on the Naranjo Adverse D

3.5.1.FT Xemilofiban

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for mainta
that the combined use of selective serotonin and norepinephrine reuptake
been associated with an increased risk of bleeding. Bleeding events repo
petechiae, and life-threatening hemorrhages (Prod Info CYMBALTA(R) de
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and an antiplatelet agent are g
bleeding (Prod Info CYMBALTA(R) delayed-release oral capsules, 2008).
7) Probable Mechanism: unknown

3.5.1.FU Zolmitriptan

1) Interaction Effect: increased risk of serotonin syndrome

2) Summary: A life-threatening condition known as serotonin syndrome n combination with a serotonin and norepinephrine reuptake inhibitor (SNRI include restlessness, hallucinations, loss of coordination, fast heart beat, overreactive reflexes, nausea, vomiting, and diarrhea. Clinicians should b that either the triptan or the SNRI may be prescribed by a different physic are prescribed this combination and monitor them closely for symptoms o dose increases (Prod Info CYMBALTA(R) delayed-release oral capsules,

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of a triptan, such as zolmiptrta (SNRI), such as duloxetine, may result in a life-threatening condition calle commonly used intermittently and that either the triptan or the SNRI may l together, discuss the risks of serotonin syndrome with the patient and mo hyperthermia, hyperreflexia, incoordination), especially during treatment i release oral capsules, 2008).

7) Probable Mechanism: additive pharmacologic effects resulting in exce

3.5.1.FV Zomepirac

1) Interaction Effect: an increased risk of bleeding

2) Summary: The release of serotonin by platelets is important for mainta that the combined use of selective serotonin and norepinephrine reuptake associated with an increased risk of bleeding. Bleeding events have inclu threatening hemorrhages (Prod Info CYMBALTA(R) oral delayed-release

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: When duloxetine and a nonsteroidal antiinflamm increased bleeding (Prod Info CYMBALTA(R) oral delayed-release capsu

7) Probable Mechanism: unknown

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) Duloxetine Hydrochloride

1) Therapeutic

a) Physical Findings

1) In patients with diabetic peripheral neuropathic pain, assess pain

2) Monitor fibromyalgia patients for reduction or improvement in pain

3) In patients with generalized anxiety disorder, monitor for improver

4) In patients with major depressive disorder, monitor reduction or im

2) Toxic

a) Laboratory Parameters

1) Consider monitor liver function prior to initiating therapy and perio fatal, has been reported in patients receiving duloxetine. Case preser abdominal pain, hepatomegaly, and elevation of transaminases to m jaundice). Discontinue duloxetine therapy in patients who develop jau dysfunction. Do not resume duloxetine therapy unless causal associa

CYMBALTA(R) delayed-release oral capsules, 2008).
2) Consider monitoring for signs of hyponatremia. There have been r
110 micromoles/liter; however, levels reversed following duloxetine th
diuretics, or volume-depleted patients may be at greater risk. Conside
symptomatic hyponatremia (Prod Info CYMBALTA(R) delayed-releas

b) Physical Findings
1) Monitor blood pressure and pulse in patients prior to initiating trea
delayed-release oral capsules, 2008).
2) Consider monitoring ocular pressure in patients with controlled na
3) Monitor patients for withdrawal symptoms (e.g. dysphoric mood, ir
abrupt discontinuation of therapy (Prod Info CYMBALTA(R) delayed-
4) Monitor for worsening of depression, suicidality, or unusual chang
dose increases or decreases. Such monitoring should include at leas
members or caregivers during the initial 4 weeks of treatment, then vi
and then as clinically indicated beyond 12 weeks. Families and careg
daily observation) of patients and communication with the prescriber
Anon, 2004).
5) Consider monitoring for signs and symptoms of hyponatremia (he
confusion, weakness, and unsteadiness). There have been reports o
micromoles/liter; however, levels reversed following duloxetine therap
diuretics, or volume-depleted patients may be at greater risk. Conside
symptomatic hyponatremia (Prod Info CYMBALTA(R) delayed-releas

4.2 Patient Instructions

A) Duloxetine (By mouth)

Duloxetine

Treats depression, generalized anxiety disorder, nerve pain caused by diabete
a selective serotonin and norepinephrine reuptake inhibitor (SSNRI).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to duloxe
Eldepryl®, Marplan®, Nardil®, or Parnate® within the past 14 days. You shoul
glaucoma, liver disease, or severe kidney disease.

How to Use This Medicine:
Delayed Release Capsule
Your doctor will tell you how much of this medicine to use and how often.
find out what works best for you. Do not use more medicine or use it more
You may take this medicine with or without food.
Swallow the delayed-release capsule whole. Do not sprinkle contents of th
not crush, break, open, or chew the capsule.
You may need to use this medicine for several weeks before you begin to
not improving, and talk to your doctor.
This medicine should come with a Medication Guide. Read and follow the
have any questions. Ask your pharmacist for the Medication Guide if you
to show that you understand this information.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you ca
the medicine and skip the missed dose. Do not use extra medicine to mak

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

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over
Do not take cimetidine (Tagamet®), thioridazine (Mellaril®), or medicine t
Cipro®, Penetrex®) while you are being treated with this medicine, unless
Make sure your doctor knows if you are using St. John's Wort, lithium (Litl
medicines to treat depression (such as amitriptyline, desipramine, fluoxeti
Effexor®, Lexapro™, Luvox®, Norpramin®, Paxil®, Zoloft®), medicine to
Relpax®), medicine to treat an infection (such as linezolid, Levaquin®, Te
prochlorperazine, Compazine®, Phenergan®, Thorazine®, Trilafon®), me

propafenone, quinidine, Rythmol®, Tambocor®), pain or arthritis medicine
Celebrex®, Vioxx®), or a blood thinner (such as warfarin, Coumadin®).
Tell your doctor if you are using any medicines that make you sleepy. The
pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine. Drinking alcohol w
If you regularly drink 3 or more alcoholic drinks every day, tell your doctor

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant, trying to become pregn
disease, high blood pressure, narrow-angle glaucoma, diabetes, any dige
the blood). Also tell your doctor if you have a history of seizures or mania.
For some children, teenagers, and young adults, this medicine can increa
right away if you or your child start to feel more depressed and have thou
behaviors that trouble you or your child, especially if they are new or get v
have trouble sleeping, get upset easily, have a big increase in energy, or
sudden or strong feelings, such as feeling nervous, angry, restless, violen
your family has bipolar disorder (manic-depressive) or has tried to commit
Make sure your doctor knows if you have ever abused drugs or alcohol.
This medicine may make you dizzy or drowsy. Avoid driving, using machi
not alert. You may also feel lightheaded when getting up from a lying or si
bothering you or keeping you from doing your daily activities, tell your doc
Your doctor will need to check your progress at regular visits while you ar
Do not stop using this medicine suddenly without asking your doctor. You
completely.
After you stop using the medicine, call your doctor if you have mood or be
seizures, tingling pain, or ringing in your ears.

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
breathing.
Aggression, anxiety, anger, or hostility.
Dark-colored urine or pale stools.
Extreme sleepiness or drowsiness.
Fast or uneven heartbeat, or dizziness.
Feeling confused, nervous, restless, or clumsy.
Lightheadedness or fainting.
Muscle spasms, twitching, or stiffness.
Nausea, vomiting, loss of appetite, or pain in your stomach.
Panic attacks, tremors, or feeling irritable.
Severe nausea or diarrhea.
Unexplained fever, sweating, or shivering.
Unusual behavior, or thoughts about hurting yourself.
Unusual bleeding or bruising.
Unusual tiredness or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:

Blurred vision.
Cough, sore throat, or runny or stuffy nose.
Dry mouth, constipation, upset stomach, or mild nausea or diarrhea.
Feeling tired, or having trouble sleeping.
Headache.
Increased sweating.
Problems with sex, or loss of interest in sex.
Problems with urination.
Skin rash.
Weight loss.

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

4.3 Place In Therapy

A) Duloxetine Hydrochloride

1) Depression

a) Duloxetine hydrochloride is indicated for the acute and maintenance tr
and venlafaxine, duloxetine is a serotonin/norepinephrine reuptake inhibit
capsules, 2008). These agents are claimed to be at least as effective as t

selective serotonin reuptake inhibitors (SSRIs). The primary role of SNRIs who have responded poorly to other agents (eg, tricyclics or SSRIs).

b) At present, duloxetine is not recommended over other available SNRIs

2) Diabetic Peripheral Neuropathic Pain

a) Duloxetine is indicated for the treatment of neuropathic pain associate release oral capsules, 2008). At doses of either 60 milligrams (mg) once c neuropathic pain compared to placebo in randomized, double-blind, phas between the once-daily and twice-daily dose, the once-daily dose was bet al, 2005; Raskin et al, 2005).

3) Generalized Anxiety Disorder

a) Duloxetine is effective for the treatment of generalized anxiety disorde Info CYMBALTA(R) delayed-release oral capsules, 2008). If duloxetine tre should periodically monitor their patients for long-term effectiveness (Proc multicenter, randomized, double-blind trial (n=487), monotherapy with dul comparable efficacy to extended-release venlafaxine 77 to 225 mg/day ar generalized anxiety disorder (Hartford et al, 2007).

4) Fibromyalgia

a) Duloxetine is indicated for the management of fibromyalgia (Prod Info was established in several randomized, placebo-controlled, double-blind t or women alone. In a 12-week, randomized, double-blind, placebo-contro was effective and safe in the treatment of fibromyalgia in female patients 2005). In another randomized, double- blind trial (n=207) trial, a 12-week fibromyalgia compared with placebo, and women were affected to signific reduction in pain severity seen at 3 months following treatment with oral d another multicenter, randomized, double-blind, placebo-controlled trial (n=

4.4 Mechanism of Action / Pharmacology

A) Duloxetine Hydrochloride

1) Mechanism of Action

a) Duloxetine is a dual-selective serotonin (5HT) and norepinephrine reup unrelated, the mechanism and pharmacodynamic characteristics of duloxe (Artigas, 1995; Pinder, 1997; Sharma et al, 2000). Duloxetine is the (+)-is structural similarity to fluoxetine and tomoxetine.

b) Duloxetine is a secondary amine, whereas venlafaxine and milnacipra to inhibit norepinephrine and 5HT uptake in preclinical studies; both dulox norepinephrine reuptake, whereas milnacipran was a more potent inhibito Duloxetine has exhibited higher potency at both reuptake sites than milna Goodnick, 1999). In vitro, duloxetine has not shown significant affinity for 5HT-1A, 5HT-1B, 5HT-1D, 5HT-2A, 5HT-2C, or opioid receptors (Artigas,

c) The in vitro activity of antidepressants has not always been predictive duloxetine compared to venlafaxine may not imply greater clinical efficacy duloxetine in inhibiting 5HT and norepinephrine reuptake (Wong et al, 19 serotonin/norepinephrine reuptake inhibitors (SNRIs) are essential to dete

d) Duloxetine has increased neural sphincter activity and bladder capacit has been investigated in urinary incontinence.

2) Review Articles

a) A review of the pharmacology, pharmacokinetic profile, and clinical eff al, 2005).

b) Advances in the treatment of depression, including duloxetine (Leonar

c) Mechanisms, pharmacology, pharmacokinetics, and clinical efficacy of

4.5 Therapeutic Uses

4.5.A Duloxetine Hydrochloride

Cancer pain

Diabetic peripheral neuropathy - Pain

Fibromyalgia

Generalized anxiety disorder

Major depressive disorder

Urinary incontinence

4.5.A.1 Cancer pain

See Drug Consult reference: MANAGEMENT OF CANCER-RELATED PA

4.5.A.2 Diabetic peripheral neuropathy - Pain

FDA Labeled Indication

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Duloxetine is indicated for the treatment of neuropathic pain asso
delayed-release oral capsules, 2008).
Duloxetine, when given at doses of either 60 milligrams daily or t
compared to placebo in randomized, double-blind, placebo-contr
al, 2005; Raskin et al, 2005).
No differences in pain relief between duloxetine 60 milligrams (m
trials, but the 60-mg once-daily dose was better tolerated than th
2005; Raskin et al, 2005).

c) Adult:

1) Duloxetine significantly improved diabetic peripheral neuropathic p
blind, phase 3 clinical trial. Patients (n=344; mean age, 60.7 +/- 10.6
peripheral neuropathic pain, which began in the feet with symmetric c
have baseline scores of at least 3 (mean, 5.6 +/- 1.5) on the Michigar
average pain severity mean score of 4 or more assessed with an 11-
randomization. Patients had to have stable glycemic control and glyc
depression, generalized anxiety disorder, or other specified psychiatr
duloxetine 60 mg once daily for 12 weeks followed by a dose reductio
mg twice daily (initiated at 60 mg daily for 3 days) for 12 weeks follow
(n=112), or placebo for 13 weeks (n=108). At baseline, mean duratio
diabetic neuropathy was 3.8 +/- 4.4 years for all patients, while a sign
groups in the mean Brief Pain Inventory (BPI) score: 60-mg once-dail
placebo group, 4.2 +/- 2.2. The change at 12 weeks from baseline in
in patient diaries, assessed with the same 11-point Likert scale used
improved ($p < 0.001$) in each of the duloxetine treatment groups (onc
group, -2.84 +/- 0.23 SE) compared to placebo (-1.39 +/- 0.23 SE). A
score, defined as a reduction of at least 2 points (30%), occurred in 6
placebo), 69% of the duloxetine twice-daily group ($p < 0.001$ versus p
in the weekly mean of the 24-hour worst pain score was significantly
groups (once-daily group, -3.21 +/- 0.25 SE; twice-daily group, -3.39
the change in the weekly mean of the night pain score (once-daily gro
< 0.001; placebo group, -1.83 +/- 0.24 SE). The median average daily
duloxetine twice-daily group (23.81 mg) compared to both the once-d
mg; $p < 0.001$). Significant improvements were also found in each du
Severity score, the Clinical Global Impression of Severity (CGI-Sever
Improvement score, the Sensory Portion of the Short Form McGill Pa
(EQ-5D) score, and various domains of the Short Form 36 (SF-36). T
(duloxetine once-daily, 28.1%; duloxetine twice-daily, 32.1%, and pla
more frequently in the duloxetine once-daily group compared to place
erectile dysfunction, and tremor occurred significantly more often in th
Significantly more patients discontinued treatment due to adverse ev
compared to the placebo group (7.4%) (Wernicke et al, 2006).

2) Duloxetine significantly improved diabetic peripheral neuropathy c
phase 3 clinical trial. Patients (n=348; mean age, 58.8 +/- 10.1 years)
bilateral peripheral neuropathy, which began in the feet with symmetr
to have baseline scores of at least 3 on the Michigan Neuropathy Scr
mean score of 4 or more assessed with an 11-point Likert scale (0, n
Patients with depression, generalized anxiety disorder, or other speci
randomized to duloxetine 60 mg once daily for 12 weeks followed by
(n=116), duloxetine 60 mg twice daily (initiated at 60 mg daily for 3 da
daily for the 13th week (n=116), or placebo for 13 weeks (n=116). At
and mean duration of diabetic neuropathy was 4.3 +/- 4.2 years for al
between treatment groups in the mean MNSI score: 60-mg once-daily

placebo group, 5.2 +/- 1.6. The change at 12 weeks from baseline in
in patient diaries, assessed with the same 11-point Likert scale used
improved ($p < 0.001$) in each of the duloxetine treatment groups (onc
group, -2.47 +/- 0.18 SE) compared to placebo (-1.6 +/- 0.18 SE). A c
score, defined as a reduction of at least 30%, occurred in 68.14% of t
64.04% of the duloxetine twice-daily group ($p=0.002$ versus placebo)
the weekly mean of the 24-hour worst pain score was significantly im
group, -2.97 +/- 0.2 SE, $p < 0.001$; twice-daily group, -2.84 +/- 0.2 SE
change in the weekly mean of the night pain score (once-daily group,
0.001; placebo group, -1.87 +/- 0.19 SE). The mean average daily do
group (202.52 mg) compared to the duloxetine twice-daily group (121
Significant improvements were also found in each duloxetine treatme
(BPI)-Severity score, the Clinical Global Impression of Severity (CGI-
Improvement score, the Sensory Portion of the Short Form McGill Pa
the BPI-Interference scale. No significant differences were found betv
Rating Scale, or between the 2 duloxetine groups for any endpoint. V
in the duloxetine twice-daily group compared to placebo, while nause
significantly more often in each duloxetine group compared to placeb
adverse events in the duloxetine twice-daily group (12.1%; $p=0.01$) c
the duloxetine once-daily group was 4.3%) (Raskin et al, 2005).

4.5.A.3 Fibromyalgia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Duloxetine is indicated for the management of fibromyalgia (Proc
Treatment with oral duloxetine 60 or 120 milligrams (mg) per day
fibromyalgia patients with or without current major depressive dis
blind, placebo-controlled trial (n=520) (Russell et al, 2008).
In a 12-week, randomized, double-blind, placebo-controlled trial
effective and safe in the treatment of fibromyalgia in female patie
2005).
A 12-week course of duloxetine was safe and improved some sy
were affected to significantly greater extent than men, based on

c) Adult:

In a multicenter, randomized, double-blind, placebo-controlled trial (n
per day for 3 months was safe and effective in reducing pain severity
depressive disorder; furthermore, efficacy was maintained at 6 month
female) meeting the American College of Rheumatology criteria for fi
higher on the average pain severity item (in the past 24 hours) of the
any current primary psychiatric diagnosis other than MDD were exclu
randomized to receive either duloxetine 20 mg/day (n=79), 60 mg/day
weeks (total, 3 months). In the 60 and 120 mg/day groups, duloxetine
weekly intervals to achieve target doses. The co-primary outcome me
pain to 10=worst pain) and the Patient Global Impression of Improver
much worse). Following assessment of the primary outcomes at 3 mo
fashion for up to 6 months; however, the duloxetine dose in the 20 m
mean BPI average pain severity score ranged from 6.4 to 6.8, and ap
current MDD diagnosis. An intention-to-treat analysis (included patier
revealed significant improvements in baseline BPI average pain seve
but not the 20 mg/day group, compared to placebo. For the co-primar
occurred with all 3 duloxetine doses compared to placebo. Improvem
therapy initiation in the 60 mg/day and 120 mg/day groups, and were
rates (defined as 50% or greater improvement from baseline in avera
in the duloxetine group, they were statistically significant only in the 1
(95% confidence interval, 3.7 to 18.1)) and not in the 20 mg/day (32.5
secondary outcomes at 3 months, both the duloxetine 60 mg/day and
placebo in the Clinical Global Impression-Severity scale scores, the F
Short Form Health Survey (mental component). However, the mean t
duloxetine groups versus placebo. At the 6-month endpoint, while sig
severity score were maintained in all 3 duloxetine groups compared t
the duloxetine 20/60 mg/day and 120 mg/day groups but not the 60 m

placebo (21.6%) in all 3 duloxetine groups (20/60 mg/day, 36.4%, p=
p=0.009). Notably, path analyses revealed that the direct analgesic e
greater proportion of the total treatment effect at 3 and 6 months thar
depressive symptoms. During 6 months of therapy, treatment-emerge
frequency than placebo included nausea (22.8% to 31.3% vs 13.2%)
20.4% vs 4.2%), somnolence (8% to 17% vs 4.2%), and fatigue (8.2%
outcomes at 3 and 6 months are presented in the table (Russell et al.

Outcome	Duloxetine 20 mg/day n=79 LS mean +/- SE	Duloxetine 60 n=150 LS mean +/- S
3-month results		
BPI average pain severity score	-1.92 +/- 0.27	-1.99 +/- 0.2*
PGI-I score	2.85 +/- 0.17**	3.04 +/- 0.13*
CGI-S score	-0.96 +/- 0.12	-1.06 +/- 0.1**
FIQ total score	-14.6 +/- 1.83*	-15.41 +/- 1.4*
6-month results		
BPI average pain severity score	-2.22 +/- 0.28*	-1.98 +/- 0.21*
PGI-I	2.79 +/- 0.17**	3.08 +/- 0.13

Key: mg=milligrams; LS=least squares; SE=standard error; BPI=Brie
Improvement; CGI-S=Clinical Global Impression-Severity; FIQ=Fibro
*p less than or equal to 0.05
**p less than or equal to 0.01
***p less than or equal to 0.001

1) In a 12-week, randomized, double-blind, placebo-controlled trial (r
was effective and safe in the treatment of fibromyalgia in female patie
age 49.6 years; 26% with current major depressive disorder) were ra
(n=118) or duloxetine 60 mg twice daily (n=116), or placebo (n=120).
was the primary outcome measure. Response to treatment was desc
endpoint. Overall, 39% (n=138) of subjects did not complete the stud
improved significantly more on the Brief Pain Inventory average pain
0.001). Significantly more patients treated with duloxetine had a decr
daily (55%; p less than 0.001); duloxetine 60 mg twice daily (54%; p=
symptoms were independent of the effect on mood and the presence
groups had significantly greater improvement compared with those in
interference scores, Fibromyalgia Impact Questionnaire, Clinical Glob
Improvement, and several quality-of-life measures. Overall, duloxetin
2) A 12-week course of duloxetine was safe and improved some syn
were affected to significantly greater extent than men, based on a rar
fibromyalgia symptoms were independent of whether or not subjects
met the criteria for fibromyalgia of the American College of Rheumato
disorder (DSM-IV). Randomization was to duloxetine 60 milligrams tw
subjects did not complete the study. After 12 months, total scores on
improved) by a significantly greater extent among duloxetine-treated
reductions of 13.46 and 7.93 points in the duloxetine and placebo gro
0.63 points lower in the duloxetine group, which was not significantly
27.7% and 16.7% for the duloxetine and placebo groups, respectively
(p=0.06). In secondary efficacy outcomes, those in the duloxetine gro
Inventory average pain severity score (p=0.008), in the Brief Pain Inv
of tender points (p=0.002), and FIQ stiffness score (p=0.048). These
status with respect to major depressive disorder. While female subjec
outcome measures, male subjects treated with duloxetine did not res
efficacy criteria. Significantly more subjects in the duloxetine group re
were generally mild or moderate in severity (most commonly insomni

4.5.A.4 Generalized anxiety disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category A
See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Duloxetine is indicated for the treatment of generalized anxiety d
capsules, 2008).
Monotherapy with duloxetine demonstrated comparable efficacy
placebo in the treatment of adult generalized anxiety disorder in
et al, 2007).
Patients with generalized anxiety disorder randomized to duloxet
symptoms and functioning compared to placebo in three random
2007; Prod Info CYMBALTA(R) delayed-release oral capsules, 2

c) Adult:

1) In a multicenter, randomized, double-blind trial (n=487), monother
more effective than placebo in the treatment of adult generalized anx
years; 62.6% female) had GAD illness of moderate severity at baseli
Depression Scale (HADS) anxiety subscale score of 10 or higher, an
Severity (CGI-S) scale. Additionally, all study patients were required f
or lower on all items in the Raskin Depression Scale, and the Covi An
score. Patients with any other primary DSM-IV Axis I diagnosis within
randomized to receive either duloxetine (n=162; mean age, 40.4 yea
years), or placebo (n=161; mean age, 41.9 years) orally once daily fo
initiated at 30 milligrams (mg)/day, increased to 60 mg/day after 1 we
maximum dose of 120 mg/day. Venlafaxine ER was initiated at 37.5 r
mg/day. Dosage adjustments were permitted based on the investigat
be increased if the CGI-Improvement (CGI-I) scale score was 3 or hig
duloxetine and venlafaxine study doses at 10 weeks were 107.73 mg
mg/day), respectively. At baseline, the mean Hamilton Anxiety Rating
duloxetine, venlafaxine ER, and placebo groups, respectively. An inte
postbaseline assessment) revealed significantly greater improvement
venlafaxine ER-treated patients compared to placebo. At 10 weeks, t
baseline in HAMA total score (primary endpoint) was -11.8 +/- 0.69 (p
equal to 0.001) for the duloxetine and venlafaxine ER groups, respec
Response rates when defined as a 50% or greater reduction from ba
placebo in the venlafaxine ER group (54% vs 37%; p less than or equ
between-group differences were evident as early as week 1 for the du
were maintained throughout the 10-week study. Among secondary ou
greater improvements over placebo in HAMA psychic anxiety factor s
and the HADS anxiety and depression subscales as well as on the C
Sheehan Disability Scale global improvement scores (p less than or e
significant between-group differences for mean change from baseline
treatment due to adverse events in both the duloxetine (14.2%) and v
or equal to 0.0001 for both). Nausea (31.5%), constipation (14.2%), s
commonly reported in the duloxetine group (Hartford et al, 2007).

2) Treatment with oral duloxetine effectively reduced generalized anx
in adults in a multicenter, randomized, double-blind, placebo-controlle
(mean, 43.8 years; 67.8% female) meeting the DSM-IV criteria for ge
were included. Following a 1-week, single-blind, placebo run-in, study
milligrams (mg) (n=168), duloxetine 120 mg (n=170), or placebo (n=1
tapering-off phase. Duloxetine was initiated at 60 mg/day; however, it
to titrate down to 30 mg/day before increasing gradually to 60 mg/day
HAMA total scores were 25, 25.2, and 25.8 in the duloxetine 60 mg/d
An intention-to-treat analysis (included patients with at least 1 postba
in anxiety symptom severity in the duloxetine-treated patients compa
change from baseline in HAMA total score (primary endpoint) was -1
equal to 0.001) for the duloxetine 60 mg/day and 120 mg/day groups
there was a 49% improvement from baseline in HAMA total scores fo
differences were evident as early as week 2 and were maintained thr
patients in the duloxetine groups had significantly greater improveme
somatic anxiety factor score, HAMA anxious mood (item 1), HAMA te
(HADS) (p less than or equal to 0.01 to 0.001 for all vs placebo). Add
greater improvement ratings over placebo at endpoint on the Clinical
Impressions Improvement scales (p less than or equal to 0.001 for all
demonstrated in the Sheehan Disability Scale global and specific dor
rates, defined as a 50% or greater reduction from baseline HAMA tot
(58%) and duloxetine 120 mg/day (56%) groups compared to placebo
significantly more patients in the duloxetine groups met remission crit
placebo (duloxetine 60 mg/day, 31% (p less than or equal to 0.01); du

placebo, 19%). Among study dropouts (24.2%), rates of discontinuati
duloxetine groups (60 mg/day, 11.3%; 120 mg/day, 15.3%; placebo,
commonly reported adverse event in the duloxetine groups (mild, 13.
7.1%). Dizziness was the most frequently reported discontinuation-er
were discontinued abruptly (60 mg/day, 9.9%; 120 mg/day, 8.6% vs
2007).

3) Duloxetine treatment effectively reduced generalized anxiety com
controlled, flexible-dose studies. The studies included patients betwe
generalized anxiety disorder. The study protocol called for titrating du
mg (n=168 and n=162) once daily for 10 weeks compared to placebo
was initially started at 30 mg once daily for 1 week before increasing
hydrochloride was initiated at 60 mg once daily; however, if patients
30 mg before increasing to 60 mg once daily. The mean dose at stud
104.75 mg/day. Duloxetine hydrochloride significantly improved gene
Hamilton Anxiety Scale (HAMA) total scores and the Sheehan Disabi
includes three main functioning life domains including work/school, s
Although duloxetine hydrochloride 120 mg once daily was shown to b
mg/day provided any additional benefit. Fifteen percent of patients re
increasing to 60 mg once daily. The most common adverse events w
insomnia, decreased appetite, and hyperhidrosis (Prod Info CYMBAL

4.5.A.5 Major depressive disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Duloxetine hydrochloride is indicated for the acute and maintena
CYMBALTA(R) delayed-release oral capsules, 2008).
Duloxetine was effective in treating major depression in several
Brannan et al, 2005; Nelson et al, 2005) and demonstrated non-i
physical symptoms of depression in one randomized, double-blir
Patients with major depressive disorder treated with duloxetine
overall relapse during the continuation phase following successfu
double-blind, placebo-controlled trial with an active treatment lea

c) Adult:

1) In a randomized, double-blind, placebo-controlled trial with an acti
of re-emergence of depressive symptoms and relapse following succ
beyond 12 weeks with continued treatment. In the active phase of the
at least moderate MDD (Hamilton Rating Scale for Depression (HRSI
Severity (CGI-S) score of 4 or greater) received open-label duloxetine
of the trial included patients with a HRSD17 score of 9 or less and a
either duloxetine 60 mg daily (n=136), or placebo (n=142) for 26 wee
placebo who relapsed (CGI-S score increase of 2 or more points and
reinitiate with duloxetine 60 mg daily, and duloxetine patients who rel
After the 26 week continuation phase, and a dose reduction of 50% f
drug for 1 week when the efficacy and safety data was collected. Ana
relapse during the continuation phase was longer in the duloxetine gr
duloxetine separating from placebo one month after randomization a
continuation phase comparing duloxetine (n=132), with placebo (n=1
the study's conclusion, the estimated probability of relapse was 19.7%
transient worsening of depressive illness indicated by an increase in
weeks after randomization in the continuation phase. Adverse effects
included nausea (2.1%), somnolence (0.8%), suicide attempt (0.6%),
significant mean changes in blood pressure or heart rate in the duloxe
phase included increases in serum aspartate aminotransferase or ala
during the course of the study (Perahia et al, 2006).

2) In two multicenter, double-blind studies of patients age 55 years a
significantly decreased scores for depression. Patients from 2 identic
(Hamilton Rating Score for Depression (HAMD17) of 15 or greater (m
Impression of Severity (CGI-S) score of 4 or greater (mean 4.37 plac
milligrams/day (mg/day) (n=47, 59.6% female), or placebo (n=43, 60.
Scales (VAS) overall pain score was 26 (on a 100 point scale). Presc
Analysis at week 9 revealed the mean total HAMD17 change from ba

placebo groups, respectively. Analyzing secondary endpoints reveale
placebo groups for CGI-S (-1.85 vs -1.21, p=0.016), overall painful ph
decreases in 4 of 5 subscales of the HAMD17 (significant in all, excep
(p=0.08), defined as a HAMD17 total score of 7 or less, after 9 weeks
patients, compared with 16.1% and 14.3% in placebo, respectively. F
greater, who received duloxetine 40 mg -120 mg/day (n=119, mean a
63.9 years, 58.9% female) revealed discontinuation due to adverse e
groups, respectively. The main reasons for discontinuation of duloxet
somnolence, and syncope. Treatment emergent adverse effects with
constipation, decreased appetite, insomnia, fatigue and decreased lib
experiencing syncope compared with 0% placebo (p=0.136) (Nelson
3) In a multicenter, double-blind, placebo controlled trial of patients w
physical symptoms, duloxetine therapy led to significant improvemen
placebo. Patients (mean age 40 years) with MDD (Hamilton Rating S
randomized to receive either duloxetine 60 milligrams daily (n=141) o
out phase. All patients were permitted to use nonnarcotic prescriptior
were not significantly different between the 2 groups, except for the H
p=0.022). In intent-to-treat analysis, the difference in mean BPI avera
(p=0.066), duloxetine -2.32 (n=132) and placebo -1.8 (n=136). In ana
2 of 7 mean changes in BPI pain interference measures (walking abil
placebo, was the nonsignificant mean change in depressive symptom
(-1.54 vs -1.58, p=0.829). There was one case of nephrolithiasis in th
discontinuation due to adverse effects was 14.2% vs 2.1% (p less tha
Main reasons for duloxetine discontinuation was nausea, fatigue, and
4) Duloxetine therapy was more effective than placebo and non-infer
physical symptoms of depression. In a randomized, double-blind, pla
depressive disorder, a Hamilton Depression Rating Scale (HAM-D) to
Impression (CGI) Severity rating (score of at least 4) received oral du
40 mg daily (in divided doses), paroxetine 20 mg daily, or placebo for
from baseline in the HAM-D total score and remission was defined as
dosing regimens of duloxetine produced significantly greater reductio
(mean difference, 3.62 points, 95% CI 1.38, 5.86; p=0.002 and 2.34 p
greater reduction in HAM-D total scores was also observed with dulo
(mean difference, 2.39 points, 95% CI 0.14, 4.65; p=0.037). Paroxeti
8, however at weeks 2, 4, and 6; paroxetine treatment was superior t
higher in patients treated with duloxetine 80 mg as compared with pla
remission rate in the duloxetine 80 mg group (50%) was significantly
patients in the duloxetine 40 mg group (35%; p=0.045) and the place
the paroxetine group (37%; p=ns). Significant reductions from baselir
treated with duloxetine 80 mg (reduction from baseline, 47%; -7.5 poi
placebo, however significant reductions were not seen with paroxetin
duloxetine and paroxetine were generally well tolerated and only insc
treated (80 mg) patients as compared with paroxetine-treated patient

4.5.A.6 Urinary incontinence

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE

b) Summary:

Duloxetine 40 milligrams orally twice daily decreased the frequer
(n=271) and Hispanic (n=368) women in the DESIRE (Duloxetin
populations) study (Weinstein et al, 2006).
Two 12-week, phase 3, randomized, double-blind, placebo-contr
conducted in study centers in four continents (n=458) showed sig
in women receiving duloxetine for stress urinary incontinence (M
Duloxetine 80 milligrams/day was more effective than placebo at
mixed urinary incontinence in an 8-week, randomized, double-bli
Patient discontinuation rates due to adverse events, nausea beir
2006; Dmochowski et al, 2003; Millard et al, 2004).

c) Adult:

1) Mixed Urinary Incontinence

a) In an 8-week, multicenter, randomized, double-blind trial (n=5
than placebo at reducing incontinence episode frequency (IEF) i
aged between 19 to 85 years (mean, 53 years) with a history of e

MUI (UPMUI), or balanced MUI for 3 or more of the previous cor
week were randomized to receive either duloxetine 40 mg twice
15.5 IEF/week). The validated Stress/Urge Incontinence Questio
SPMUI, UPMUI, or balanced MUI. While antimuscarinic agents v
19.4% of duloxetine and placebo subjects, respectively, used an
norepinephrine) concurrently during the study. Patients recorded
throughout the study by documenting voids, stress urinary incont
episodes. In the intent-to-treat analysis (n=588), duloxetine subje
(primary endpoint) compared to placebo subjects (mean change
between groups, -3.5 to -0.17; p=0.049). This difference persiste
(SUI mean change, -3.76 vs -2.87; 95% CI for difference betwee
2.33; 95% CI for difference between groups, -1.59 to -0.22; p=0.
duloxetine vs placebo regardless of whether the subtype was as
results (p=0.0013 and p less than 0.001, respectively), results fo
process (p=0.0183 and p=0.176, respectively). Balanced MUI su
regardless of assignment method (p=1 and p=0.777, respectively
in time between voids (secondary endpoint) compared with place
minutes; p=0.002). Quality of life, as measured on a scale of 0 (l
Quality of Life Questionnaire, increased more in duloxetine patie
95% CI of difference between groups, 1.36 to 6.31; p=0.002), an
much better" or "much better" according to the Patient Global Im
subjects (p=0.001). A significantly greater number of placebo pat
patients (78%), with adverse effects being the most common rea
(TEAEs) occurred in 61.3% of duloxetine subjects vs 44.8% of pl
common complaint in both groups (18% vs 4.5%, respectively; p
duloxetine patients and at a rate greater than 5% included dry m
(6.7%) (Bent et al, 2008).

2) Stress Urinary Incontinence

a) The Duloxetine Efficacy and Safety for Incontinence in Racial
label, multicenter study, demonstrated non-inferiority efficacy in A
receiving duloxetine for stress urinary incontinence compared to
and Hispanic women with characteristics similar to Caucasian w
older, at least 7 incontinence episodes per week at baseline, and
included in the study. Baseline characteristics of patients in the A
and Hispanic (mean age, 47.4 years; range, 20-86 years) subgro
years; range, 18-97 years) were significantly different ($p < 0.05$)
Incontinence Quality of Life (I-QOL) and Patient Global Impressi
number of pads used per week. All patients received duloxetine
week lead-in period. Non-inferiority efficacy was determined by c
episode frequency in the African-American and Hispanic subgrou
treatment. All three subgroups had significant improvement ($p <$
baseline (African-American group, 7 versus (vs) 21 episodes/we
Caucasian group, 5 vs 19.25 episodes/week (-75%)). Additionall
less than 0.001) in quality of life questionnaire scores after treatr
scale (African-American group, 71.5 vs 51.7 points; Hispanic gro
and the Patient Global Impression of Improvement (African-Ame
Caucasian group, 66.6% improved); however, significantly less (
reduction in incontinence episode frequency compared with Cau
of patients completed the study, and the most common reason fo
common adverse event occurring in 21.8 to 28% of patients and
(African-American group, 6.6%; Hispanic group, 5.7%; Caucasia
(p less than 0.05) in Hispanic patients compared to Caucasian p
7.4%), and somnolence (12.2% vs 7%) (Weinstein et al, 2006).

b) Incontinence episode frequency (IEF) was reduced following
urinary incontinence in a randomized, double-blind, placebo-con
urinary incontinence of at least 3 months duration and experienc
duloxetine 40 milligrams twice daily or placebo for 12 weeks. The
than half of patients averaged two or more episodes daily. From
in the duloxetine group as compared with the placebo group (per
this effect was even stronger in patients with a baseline IEF of 14
respectively; p=0.022). In addition, the average voiding interval i
compared with those who received placebo (20.4 vs 8.5 minutes
patients in the duloxetine group also showed greater improveme
questionnaire as compared with patients in the placebo group (m
were significantly more frequent with duloxetine treatment than v
and resulted in significantly higher discontinuation rates in the du
respectively; p less than 0.001). In duloxetine-treated patients, th

headache (14.5%), insomnia (13.7%), constipation (12.8%), dry
(8.4%), anorexia (6.6%), vomiting (6.2%), and increased sweatin
c) Duloxetine was effective in the treatment of stress urinary inc
blind, placebo-controlled, multicenter trial. Women (n=683) 22 to
experiencing 7 or more episodes weekly received duloxetine 80
Incontinence episode frequency decreased by 50% to 100% in 5
placebo-treated patients (p less than 0.001). Mean improvement
score was also significantly better for patients in the duloxetine g
respectively; p less than 0.001). Adverse events occurred more f
24.1% vs 4.1%; p less than 0.001) and included nausea (22.7%)
constipation (9.6%), somnolence (8.7%), dizziness (7.6%), head

4.6 Comparative Efficacy / Evaluation With Other Therapies

Escitalopram

Paroxetine

Venlafaxine

4.6.A Escitalopram

4.6.A.1 Major depressive disorder

a) In an 8-week randomized, double-blind, placebo- and active-comparat
(n=684) with major depressive disorder (MDD), onset of efficacy for dulox
escitalopram 10 mg daily, and patients in both active treatment groups we
Patients aged 18 years or older (range, 18 to 79 years), meeting the DSM
Depression Rating Scale (MADRS) total score of 22 or greater and a Clini
greater were included. Patients were randomized to receive either duloxe
Hamilton Rating Scale for Depression (HAMD) Maier subscale score, 17.6
mean baseline HAMD score, 17.8), or placebo (n=137; mean age, 42.5 ye
acute treatment period. Onset of efficacy (primary endpoint) was defined a
week 2 that was sustained for the remainder of the acute treatment period
efficacy onset criteria was similar in the duloxetine and escitalopram grou
confidence interval (CI), -1.3% to 16.2%; p=0.097), and patients in both gr
placebo patients (21.5%; duloxetine vs placebo, p less than 0.001; escital
escitalopram was maintained following a per-protocol analysis. In an anal
were pooled, a significantly greater proportion of duloxetine patients achie
greater proportion of patients in both active treatment groups achieved eff
0.018 for both). The median time to onset was significantly shorter among
placebo-treated patients (23 days vs 41 days vs 55 days, respectively; du
less than 0.001), and median time to onset did not differ between escitalo
achieving a treatment response (secondary endpoint) by week 8, defined
similar among the duloxetine (48.7%), escitalopram (45.3%), and placebo
score of 7 or less) also did not differ between the groups (40.1% vs 33% v
complete the study were evenly distributed among the groups, and a simil
effects. Nausea more commonly caused discontinuation among duloxetin
respectively; p=0.02). Both nausea and dry mouth occurred more often in
patients and at a rate greater than 10% (nausea, 23.8% vs 12% vs 8.8%;
Although this study focused on the acute 8-week treatment period, subjec
for an additional 6 months (Nierenberg et al, 2007). During the 6-month ex
mg/day and the escitalopram dose ranged from 10 to 20 mg/day; placebo
assigned in a double-blind fashion to active treatment. Among the 431 pa
no significant differences in antidepressant efficacy between the duloxetin
probability of remission was 70% and 75% among the duloxetine and esc
significant difference between the groups was on the HAMD sleep subsca
improvement in insomnia than duloxetine-treated patients (mean change
discontinuation rates over the 8-month study were higher in the duloxetine
discontinuation due to adverse events were similar (12.8% vs 12%, respe
b) In a randomized, double-blind, fixed-dose, noninferiority trial (n=294), a
for the long term treatment of major depressive disorder (MDD), escitalop
outpatients aged 18 to 73 years old with MDD according to the DSM-IV (T
Rating Scale (MADRS) total score of 26 or greater, and with a Clinical Glo
were included. With the exception of obsessive-compulsive disorder, post

secondary, current, comorbid anxiety disorder were included. Study patie
(n=151) or escitalopram 20 mg (initial dose, 10 mg/day; increased after 2
MADRS scores were 32.1 +/- 4.4 and 32.5 +/- 4.3 in the duloxetine and es
study, the mean change from baseline in MADRS score in the intent-to-tre
duloxetine were -23.4 and -21.7, respectively (p=0.055). Based on a per-p
(escitalopram minus duloxetine) in MADRS scores at 24 weeks was 0.67
which met the prespecified noninferiority criteria (ie, upper limit of the one
escitalopram was evident (ie, upper limit of the one-sided CI did not inclu
treatment differences of 2.54 (95% CI, p=0.011) and 2.21 (p=0.027), resp
81.6% (n=115) of escitalopram-treated patients were considered to be res
total score) compared with 73% (n=112) of duloxetine-treated patients. An
effective than duloxetine in CGI-I (p=0.039) score reduction from baseline
duloxetine in the Sheehan Disability Scale (SDS) work score reduction at
less than 0.05 for all). Significantly more patients on duloxetine reported in
compared to escitalopram, with almost twice the withdrawal rate due to ad
0.05) (Wade et al, 2007).

4.6.B Paroxetine

4.6.B.1 Major depressive disorder

a) Duloxetine therapy was more effective than placebo and non-inferior to
physical symptoms of depression. In a randomized, double-blind, placebo
depressive disorder, a Hamilton Depression Rating Scale (HAM-D) total s
(CGI) Severity rating (score of at least 4) received oral duloxetine 80 millig
divided doses), paroxetine 20 mg daily, or placebo for 8 weeks. Response
HAM-D total score and remission was defined as a HAM-D score of 7 or l
duloxetine produced significantly greater reductions in HAM-D scores fror
points, 95% CI 1.38, 5.86; p=0.002 and 2.34 points, 95% CI 0.19, 4.66; p=
D total scores was also observed with duloxetine 80 mg therapy as compa
95% CI 0.14, 4.65; p=0.037). Paroxetine therapy was not significantly diffe
paroxetine treatment was superior to placebo. The response rate at endpo
80 mg as compared with placebo (51% vs 31%, p=0.009, respectively). A
(50%) was significantly higher at endpoint as compared with remission rat
and the placebo group (30%; p=0.008), but was not superior to patients in
baseline to endpoint in overall pain severity were observed in patients trea
points on VAS scale, 95%CI -25, 1; p=0.005), as compared with placebo,
or duloxetine 40 mg therapy as compared with placebo. Both duloxetine a
was reported significantly more often in duloxetine-treated (80 mg) patient
respectively; p=0.031) (Goldstein et al, 2004).

4.6.C Venlafaxine

4.6.C.1 Major depressive disorder

a) A meta-analysis of published, peer-reviewed, randomized, placebo-co
venlafaxine extended-release (XR) are significantly superior compared to
disorder and although there was a trend in favor of venlafaxine XR the dif
to duloxetine. A systematic literature search of Cochrane, EMBASE, and
independent reviewers. Data was obtained from 8 trials to evaluate efficac
a one week placebo lead-in period followed by either duloxetine 40 to 120
day for a minimum of 8 weeks. The primary outcomes were remission and
the Hamilton Rating Scale for Depression (HAM-D) score to less than or e
(MADRS) score of less than or equal to 10. Response was defined as an
MADRS scores. The secondary outcomes evaluated were dropout rates a
improved for duloxetine and venlafaxine XR and were statistically significa
difference was found for remission and response rates when duloxetine a
had a higher dropout rate due to lack of efficacy compared to those patien
0.001). More patients in the active drug treatment groups dropped out due
venlafaxine XR p less than 0.001). Again, when duloxetine and venlafaxin
were found for dropout rates due to lack of efficacy or adverse drug reacti
drugs. A sensitivity analysis was also performed and included 2 additional
with comorbid anxiety and one study for duloxetine dealing with patients v
results with both drugs having a statistically significant difference from pla

Outcome	Active Drug	Active Dr	
		Difference(a)	
Remission	duloxetine	0.142	0.0
	venlafaxine XR	0.178	0.0

Response	duloxetine	0.186	0.1
	venlafaxine XR	0.244	0.1
Dropout rate due to ADRs	duloxetine	0.057	0.
	venlafaxine XR	0.061	0.0
Dropout rate due to lack of efficacy	duloxetine	-0.111 (c)	-0.1
	venlafaxine XR	-0.107	-0.1
ADRs = adverse drug reactions; XR = extended release; CI = confide			
(a) The rate when meta-analytic rate of placebo is subtracted from th			
(b) Corresponding p value of the difference rate calculated with a Z-t			
(c) Negative difference rates indicate a larger effect for placebo.			

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