DRUGDEX® Evaluations

GABAPENTIN

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Anticonvulsant
  Gamma Aminobutyric Acid (class)
  Neuropathic Pain Agent

2) Dosing Information
- **a)** Adult
  - **1)** Diabetic peripheral neuropathy
    - **a)** 900 to 3600 mg/day ORALLY in 3 divided doses (Backonja et al, 1998
  - **2)** Partial seizure; Adjunct
    - **a)** 12 yr and older, 300 mg ORALLY 3 times a day; may increase up to 1
      doses). Dosages up to 2400 mg/day have been well tolerated and doses
      administered to a small number of patients for a relatively short duration
  - **3)** Postherpetic neuralgia
    - **a)** 300 mg ORALLY on Day 1, 300 mg twice a day on Day 2, and 300 mg
      increase dosage up to 1800 mg/day (divided into 3 doses) (Prod Info NEU
      capsules, oral solution, 2007)
- **b)** Pediatric
  - **1)** Partial seizure; Adjunct
    - **a)** age 3 to 12 yr, initial, 10 to 15 mg/kg/day ORALLY in 3 divided doses
    - **b)** age 3 to 4 yr, maintenance, titrate upwards over 3 days to 40 mg/kg/da
    - **c)** age 5 to 12 yr, maintenance, titrate upwards over 3 days to 25 to 35 m

3) Contraindications
- **a)** hypersensitivity to gabapentin

4) Serious Adverse Effects
- **a)** Drug-induced coma
- **b)** Seizure
- **c)** Stevens-Johnson syndrome

5) Clinical Applications
- **a)** FDA Approved Indications
  - **1)** Partial seizure; Adjunct
  - **2)** Postherpetic neuralgia
- **b)** Non-FDA Approved Indications
  - **1)** Diabetic peripheral neuropathy

1.0 Dosing Information

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring Index)
B) Synonyms
Gabapentin
C) Orphan Drug Status
1) Gabapentin has been designated an orphan product for use in the treatmer
D) Physicochemical Properties
1) Molecular Weight
a) 171.24 (Prod Info Neurontin, 94) (Levy, 1989) (Prod Info Neurontin, 94
2) Partition Coefficient
a) The log of the partition coefficient (n-octanol/0.05M phosphate buffer) Neurontin®, 2003)
3) pKa
a) 3.68 and 10.7 (Levy, 1989) (Prod Info Neurontin, 94a)
4) Solubility
a) Systemic: Freely soluble in water and both basic and acidic aqueous s 2003)

1.2 Storage and Stability

A) Tablets and capsules should be stored at a controlled room temperature of 25 Fahrenheit). Excursions to 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) Neurontin(R), 2003a).
B) The oral solution should be kept refrigerated; 2 to 8 degrees Celsius (36 to 46 Neurontin(R), 2003a).
1) Extemporaneous Formulation - Oral route
a) Oral suspensions of gabapentin have been developed (Nahata, 1999). powder the contents of 67 capsules of gabapentin 300 milligrams (mg) us mixed in a 1:1 ratio of simple syrup NF with 1% methylcellulose. Similarly, gabapentin 300 mg may be mixed with 1:1 Ora Sweet: Ora Plus. Both pro gabapentin of 100 mg/milliliter in suspension. Both suspensions retained for 91 days at 4 degrees Celsius and for 56 days at 25 degrees Celsius. T drug was stable for 8 weeks at 25 degrees Celsius, this not recommende growth. Microbiological studies were not performed.

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage Adjustment During Dialysis

Dosage in Other Disease States

1.3.1 Normal Dosage

Oral route

Tinnitus

1.3.1.A Oral route

Diabetic peripheral neuropathy

Partial seizure; Adjunct

Postherpetic neuralgia

Social phobia

GABAPENTIN
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1.3.1.A.1 Diabetic peripheral neuropathy

a) Doses of 900 to 3600 milligrams/day administered orally in 3 divid treatment of pain and sleep difficulties associated with diabetic periph 1998).

1.3.1.A.2 Partial seizure; Adjunct

a) INITIAL THERAPY

1) 300 milligrams (mg) 3 times daily (Prod Info Neurontin(R), 20

a) gabapentin has been given in lower doses during initiatic milligrams 3 times daily was administered initially for 2 week times daily for the ensuing 3 months (Anon, 1990c). Others times a day on the first day of treatment; the dose was incre day on the second day (Sivenius et al, 1991b).

b) In a brief tolerability study, initiation of gabapentin at 900 associated with more dizziness on day 1 and throughout the was initiation at 300 milligrams per day, with titration to 900 However, incidences of the other common adverse events (were not different for the 2 initiation protocols (Fisher et al, 2

b) TITRATION

1) The dose may be increased using 300- or 400-mg capsules c Info Neurontin(R), 2003a).

c) MAINTENANCE THERAPY

1) 900 to 1800 milligrams given in 3 divided doses. In long-term mg have been well tolerated. The maximum time between doses (Prod Info Neurontin(R), 2003a).

d) As add-on therapy in patients with drug-refractory partial seizures reported with gabapentin 1200 milligrams daily in 3 divided doses (Ar 1991b). gabapentin 900 milligrams daily has not been consistently ef milligrams/day are usually ineffective (Crawford et al, 1987b; Sivenius

1) MAXIMUM DOSE

a) 2400 to 3600 milligrams/day has been administered (Pro

2) WITHDRAWAL

a) Discontinuation of gabapentin therapy should be done sl prevent rebound phenomena. Abrupt discontinuation may pr Info Neurontin(R), 2003a).

1.3.1.A.3 Postherpetic neuralgia

a) In adults with postherpetic neuralgia, the recommended initial dos milligram (mg) dose on Day 1, 600 mg/day on Day 2 (divided twice da (divided three times daily). The dose can then be titrated up as neede 1800 mg (divided three times daily). In clinical studies, efficacy was d doses from 1800 mg/day to 3600 mg/day, however no additional ben doses above 1800 mg/day (Prod Info NEURONTIN(R) oral tablets, or

1.3.1.A.4 Social phobia

a) Doses of 900 to 3600 milligrams/day divided in 3 doses have beer al, 1999).

1.3.1.B Tinnitus

See Drug Consult reference: DRUG THERAPY OF TINNITUS

C) Dose reductions, gabapentin discontinuation or substitutions with alternativ performed gradually over a minimum of 1 week (Prod Info Neurontin(R), 2003a

1.3.2 Dosage in Renal Failure

Dosage Based Upon Renal Function:

Creatinine Clearance (mL/min)	Total Daily Dose Range (mg/day)	Dose Frequency
60 or greater	900 - 3600	Equally divided (doses/day)
30 to 59	400 - 1400	Equally divided (doses/day)
15 to 29	200 - 700	Single dose
15 or less*	100 - 300	Single dose

* For patients with creatinine clearances (CrCl) of 15 mL/min or less, the dosa proportionally (patients with a CrCl of 7.5 mL/min should receive one-half the c

mL/min) (Prod Info Neurontin(R), 2003a).

1.3.5 Dosage Adjustment During Dialysis

A) Patients receiving hemodialysis should receive maintenance gabapentin d creatinine clearance (see dosage in renal failure) and a supplemental post-he after each 4 hours of hemodialysis (Prod Info Neurontin(R), 2003a).

Post-Hemodialysis Supplemental Dose	
Maintenance Dose Range (mg/day)	Supplemental Dose (mg)
100 - 900	125
125 - 1200	150
150 - 1800	200
200 - 2400	250
300 - 3600	350

1.3.6 Dosage in Other Disease States

A) In high-risk patients (eg, poor general status, low body weight, post- transp should take place in no more than 100-milligram increments (Fachinfo Neuron

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage Adjustment During Dialysis

1.4.1 Normal Dosage

Oral route

Rectal route

1.4.1.A Oral route

1.4.1.A.1 Partial seizure; Adjunct

a) INITIAL THERAPY

1) The starting dose for patients between 3 and 12 years of age milligrams/kilogram/day in 3 divided doses (Prod Info Neurotin(R

2) Initial doses should be 40 milligrams/kilogram/day in 3 divide up to under 5 years, based on a pharmacokinetic study in 48 chi (evenly distributed over the age range). For children 5 to 12 year be 30 milligrams/kilogram/day (Haig et al, 2001).

3) In a brief tolerability study, initiation of gabapentin at 900 milli with more dizziness on day 1 and throughout the 5 days of active 300 milligrams per day, with titration to 900 milligrams/day over 3 the other common adverse events (fatigue, ataxia, and somnole initiation protocols (Fisher et al, 2001).

b) TITRATION

1) The dose may be increased using 300- or 400-mg capsules, solution (Prod Info Neurontin(R), 2002.

c) MAINTENANCE THERAPY

For patients between 3 and 4 years of age:

40 milligrams/kilogram/day in 3 divided doses (Prod Info Ne

For patients 5 years of age and older:

25 to 35 milligrams/kilogram/day in 3 divided doses (Prod In

For patients over 12 years of age:

900 to 1800 milligrams given in 3 divided doses Prod Info N

2) Dosage interval between doses should not exceed 12 hours (Prod Info

1.4.1.B Rectal route

1) A study on two children found that gabapentin plasma concentrations a of gabapentin solution (capsule contents mixed with 5 milliliters mL of wat oral administration. Relative bioavailability was 0.29 and 0.17. The author administration of gabapentin is not satisfactory when oral dosing is interru

1.4.2 Dosage in Renal Failure

Dosage Based Upon Renal Function for patients 12 years old and older:

Creatinine Clearance(mL/min)	Total Daily Dose Range (mg/day)	Dose Frequenc
60 or greater	900 - 3600	Equally divided doses/day)
30 to 59	400 - 1400	Equally divided doses/day)
15 to 29	200 - 700	Single dose
15 or less	100 - 300*	Single dose

* For patients with creatinine clearances (CrCl) of 15 mL/min or less, the dosa proportionally (patients with a CrCl of 7.5 mL/min should receive one-half the d mL/min) (Prod Info Neurontin(R), 2003a). Gabapentin use in patients less thar compromised renal function has not been studied.

1.4.4 Dosage Adjustment During Dialysis

A) Patients 12 years or older receiving hemodialysis should receive maintena estimates of creatinine clearance (see dosage in renal failure) and a supplem administered after each 4 hours of hemodialysis. Gabapentin use in patients le compromised renal function has not been studied (Prod Info Neurontin(R), 200

Post-Hemodialysis Supplemental Dose	
Maintenance Dose Range (mg/day)	Supplemental Dose (mg)
100 - 900	125
125 - 1200	150
150 - 1800	200
200 - 2400	250
300 - 3600	350
(Prod Info Neurontin(R), 2002).	

2.0 Pharmacokinetics

Drug Concentration Levels

ADME

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Partial Seizures, greater than 2 mcg/mL (Sivenius et al, 1991).

a) Optimal plasma concentrations have not been established (Prod Info N Woster, 1995).

B) Time to Peak Concentration

1) Oral: 1.5 to 4 hours (Gidal et al, 1998; Andrews & Fischer, 1994; Hooper et

a) Time to peak concentration (t-max) was 2.31 hours after a single oral d month to 12 years (evenly distributed over the age range). Maximum conc 4.52 mcg/mL for those 1 to 59 months old (n=27) and 60 to 155 months (r those 2 years or younger was gabapentin syrup 10 mg/kg; subjects over 2 based on weight: 200 mg for 16 to 25 kg; 300 mg for 26 to 36 kg; 400 mg 2001a).

C) Area Under the Curve

1) 35 to 47 mcg/mL x hr (Gidal et al, 1998).

a) Determined with a single 600-mg dose (Gidal et al, 1998).

b) AUC values were 25.6 and 36.0 mcg x h/mL after a single oral dose in under 5 years (n=27) and 5 to 12 years (n=21), respectively. Dosing for th gabapentin syrup 10 mg/kg; subjects over 2 years received oral capsules to 25 kg; 300 mg for 26 to 36 kg; 400 mg for 37 to 50 kg (Haig et al, 2001a

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability

1) Tablets/capsules (900 mg dose): 60% (Prod Info Neurontin(R), 2003)

a) Bioavailability decreases with increasing doses:

DOSAGE (3 divided doses)	ORAL BIOAVAILABILITY
900 milligrams	60%
1200 milligrams	47%
2400 milligrams	34%
3600 milligrams	33%
4800 milligrams	27%
(Prod Info Neurontin(R), 2002)	

b) Approximately 50% to 60% is absorbed from the gastrointestinal t

c) Gabapentin plasma concentrations attained after rectal administra (capsule contents mixed with 5 milliliters mL of water) were much low administration. Relative bioavailability was 0.29 and 0.17 (Kriel et al,

B) Effects of Food

1) Slight (Prod Info Neurontin(R), 2003).

a) A 14% increase in area under the curve (AUC) and Cmax has bee taken with food (Prod Info Neurontin(R), 2003).

b) Gabapentin capsules that were opened and mixed with food did n (Gidal et al, 1998). Protein may actually favorably influence gabapent

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) less than 3% (Vollmer et al, 1986; Prod Info Neurontin(R), 2003).

2) OTHER DISTRIBUTION SITES

a) BRAIN, a lobectomy revealed GABAPENTIN concentrations in ep mcg/g and 6.75 mcg/mL, respectively (cortex/serum ratio of 0.8) (Oje

b) CEREBROSPINAL FLUID, steady-state cerebrospinal fluid levels approximately 20% of plasma concentrations (Prod Info Neurontin(R)

c) TISSUES, animal studies revealed highest concentrations in the p adipose tissue (Vollmer et al, 1986).

B) Distribution Kinetics

1) Distribution Half-Life

a) 0.1 hr (Graves & Leppik, 1991).

2) Volume of Distribution

a) 58 to 61 liters (Prod Info Neurontin(R), 2003; Vollmer et al, 1986).

1) Vd values were 2.76 L/kg and 1.80 L/kg after a single oral do under 5 years (n=27) and 5 to 12 years (n=21), respectively. Dos was gabapentin syrup 10 mg/kg; subjects over 2 years received 200 mg for 16 to 25 kg; 300 mg for 26 to 36 kg; 400 mg for 37 to

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Not metabolized (Prod Info Neurontin(R), 2003; Vollmer et al, 1986).
a) Excreted unchanged in the urine (Haig et al, 2001a).

2.3.4 Excretion
A) Kidney
1) Renal Clearance (rate)
a) 150 mL/minute (Vollmer et al, 1986).
1) In a study examining gabapentin pharmacokinetics in patients were administered a single 400 milligram dose of gabapentin. In clearance greater than 60 milliliter/minute (mL/min) had a gabap mL/min. Patients with a creatinine clearance less than 30 mL/mi clearance of 10 mL/min (Prod Info Neurontin(R), 2003).
2) Renal clearance rates were 7.40 mL/min/kg and 4.41 mL/min CHILDREN ages 1 month to under 5 years (n=27) and 5 to 12 ye for those 2 years or younger was gabapentin syrup 10 mg/kg; su capsules based on weight: 200 mg for 16 to 25 kg; 300 mg for 2((Haig et al, 2001a).
2) Renal Excretion (%)
a) 76% to 81% (Vollmer et al, 1986).
1) Percentage of dose excreted unchanged in the urine was 41. CHILDREN ages 5 to 12 years (n=21). Dosing of oral capsules v 16 to 25 kg; 300 mg for 26 to 36 kg; 400 mg for 37 to 50 kg (Haig
B) Other
1) OTHER EXCRETION
a) Feces, 10% to 23% (Vollmer et al, 1986).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 5 to 7 hours (Prod Info Neurontin(R), 2003; Hooper et al, 1991a; A 1986).
1) The elimination rate constant, plasma clearance, and renal cl proportional to creatine clearance (Prod Info Neurontin(R), 2003)
2) In patients with decreased renal function the elimination half l 400 mg oral dose, the mean gabapentin half life was 6.5 hours ir clearance greater than 60 milliliters/minute (mL/min) and was 52 clearance less than 30 mL/min (Prod Info Neurontin(R), 2003).
3) Elimination half-life was 4.44 hours after a single oral dose in 12 years (evenly distributed over the age range). Dosing for thos gabapentin syrup 10 mg/kg; subjects over 2 years received oral mg for 16 to 25 kg; 300 mg for 26 to 36 kg; 400 mg for 37 to 50 k

2.3.6 Extracorporeal Elimination
A) Hemodialysis
1) Dialyzable: Yes (Prod Info Neurontin(R), 2003; Prod Info Neurontin(R)
a) In anuric patients the apparent elimination half-life of gababentin v days and was reduced to 3.8 hours during dialysis (Prod Info Neuron

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.1 Contraindications
A) hypersensitivity to gabapentin

3.2 Precautions

A) abrupt discontinuation may precipitate status epilepticus
B) renal insufficiency
C) suicidality, increased risk of; based on data analysis of 199 placebo-controlled s
small elevated risk occurred as early as 1 week after starting therapy and continue
and Drug Administration, 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

Cardiovascular finding

Edema

Hypertension

Vasodilatation

3.3.1.A Cardiovascular finding
1) Hypertension, vasodilation and edema may develop with gabapentin tl

3.3.1.B Edema
1) Summary
a) Peripheral edema and facial edema were reported in gabapentin-t
Neurontin(R), 2003a).

3.3.1.C Hypertension
1) Summary
a) It may be advisable to monitor blood pressure in overdoses, as hy

a frequent adverse event following therapeutic doses of gabapentin (

3.3.1.D Vasodilatation

1) Summary

a) Vasodilation (1.1%) was reported in gabapentin-treated patients (

3.3.2 Dermatologic Effects

Alopecia

Dermatological finding

Drug-induced rash

Rash

Stevens-Johnson syndrome

3.3.2.A Alopecia

1) Summary

a) Acute alopecia has been described as an adverse event following 1997).

3.3.2.B Dermatological finding

1) Acne, alopecia, eczema, pruritus, skin rashes and Stevens- Johnson s

3.3.2.C Drug-induced rash

1) Summary

a) Acne, eczema and pruritus have occasionally occurred with gabap Neurontin(R), 2003a; Sivenius et al, 1991a; Anon, 1990b; Crawford e

3.3.2.D Rash

1) Summary

a) Skin rashes have been occasionally associated with gabapentin th due to a maculopapular skin rash has also occurred (Prod Info Neurc 1991a; Anon, 1990b; Crawford et al, 1987a).

2) LITERATURE REPORTS

a) 58-year-old man, after beginning therapy with gabapentin 300 mill developed a mild pruritic, erythematous, macular rash. Therapy conti excellent pain control with increased gabapentin (2400 mg/daily). At 5 the rash spread to thighs and forearms. Gabapentin was reduced to Gabapentin was discontinued but restarted after the neuropathic pair other drugs. A similar rash reoccurred despite a slower titration. Topi pruritus and intensity of the rash (Gould, 1998).

3.3.2.E Stevens-Johnson syndrome

1) Summary

a) Several cases of Stevens-Johnson syndrome have been reported et al, 1999; Gonzalez-Sicilia et al, 1998)

2) Incidence: rare

3) LITERATURE REPORTS

a) A 26-year-old woman with a history of Stevens-Johnson Syndrom carbamazepine therapy developed a skin eruption with gabapentin th Gabapentin had been titrated up in 300-mg increments. On the eighth developed a pruriginous, erythematous eruption on the proximal thigh distal lower extremities. There was no systemic involvement. The ras discontinued.

b) A 32-year-old, HIV-positive woman developed Stevens-Johnson s gabapentin therapy. It spread to her face and upper trunk with a skin necrolysis with slight perivascular infiltrates of lymphocytes in the der gabapentin was discontinued (Gonzalez-Sicilia et al, 1998).

3.3.3 Endocrine/Metabolic Effects

Blood glucose abnormal

Endocrine finding

Gynecomastia

Thyroiditis

Weight change finding

3.3.3.A Blood glucose abnormal

1) Summary

a) Fluctuations in blood sugar levels below 3.3 millimole/Liter and ab
to 5.5) have been reported in clinical studies. Caution should be exer
Info Neurontin(R), 1998).

3.3.3.B Endocrine finding

1) The most commonly reported adverse effects are glucose level chang
weight fluctuations.

3.3.3.C Gynecomastia

1) Summary

a) CASE REPORT - Gynecomastia, along with weight gain, occurrec
GABAPENTIN for thoracic pain. The patient had undergone thoracot
metastasized, poorly differentiated cancerous tumor was found in his
Afterwards he experienced severe post-thoracotomy pain. He was ur
morphine, fentanyl, diclofenac, amitriptyline, venlafaxine, bupivacaine
10%. A year or more later, gabapentin 2100 mg/day was introduced i
patient reported a significant decrease in pain (from 8 to 3 on a 10-pc
several weeks, the patient complained of painful gynecomastia. He w
testosterone, FSH, and LH levels, though he had a normal response
that gabapentin may have produced selective hypothalamic insufficie
hormone axis in this terminal cancer patient and that effect may have
et al, 2000).

3.3.3.D Thyroiditis

1) Summary

a) A 28-year-old woman being treated for bipolar II disorder develope
gabapentin 4800 milligrams daily (Frye et al, 1999). Physical sympton
nonsustained sinus tachycardia, mild hand tremor, and heat intoleran
microunits/milliliter. An I-123 uptake scan revealed a normal-sized ho
uptake of 1% at 24 hours. Gabapentin was discontinued and her sym
function tests returned to baseline.

3.3.3.E Weight change finding

1) Summary

a) Weigh loss associated with anorexia and weight gain related to in
reported in up to 5% of gabapentin- treated patients (Prod Info Neuro

2) LITERATURE REPORTS

a) Twenty-eight of 44 patients treated for seizure disorder with gabap
(Toledo et al, 1997). Ten patients gained more than 10% of their base
5% to 10%, 16 patients had no change, and 3 patients lost 5% to 10%
increase started between the second and third months of therapy and

3.3.4 Gastrointestinal Effects

Abdominal discomfort

Gastrointestinal tract finding

Pancreatitis

3.3.4.A Abdominal discomfort

1) Summary

a) Abdominal pain and flatulence have been reported (Prod Info Neu has been noted infrequently during gabapentin therapy (Sivenius et a et al, 1987a).

3.3.4.B Gastrointestinal tract finding

1) Summary

a) Nausea and vomiting have been reported infrequently during gaba 1991a; Anon, 1990b; Crawford et al, 1987a). Constipation, diarrhea, and gingivitis have been reported with gabapentin therapy (Prod Info

2) Abdominal pain, constipation, diarrhea, dental abnormalities, dry mout been reported with gabapentin therapy. Gastric upset, nausea and vomiti case of pancreatitis was also noted.

3.3.4.C Pancreatitis

1) Summary

a) A case of pancreatitis has occurred with gabapentin treatment (Pr

3.3.5 Hematologic Effects

Hematology finding

Leukopenia

Purpuric disorder

3.3.5.A Hematology finding

1) Leukopenia and purpura have been reported with therapeutic doses of

3.3.5.B Leukopenia

1) Summary

a) Leukopenia has been reported in approximately 1.1% of gabapen with 0.3% of a placebo-controlled group (Prod Info Neurontin(R), 200

3.3.5.C Purpuric disorder

1) Summary

a) The manufacturer reports that purpura has frequently occurred wi most often described as bruises resulting from physical trauma (Prod

3.3.6 Hepatic Effects

3.3.6.A Hepatotoxicity

1) Summary

a) A 60-year-old man taking many concomitant medications develop attributed to gabapentin treatment (for pain). An earlier skin eruption, toxicoderma, cleared with 5 days of steroid treatment after discontinu metamizole. Jaundice and palpable hepatomegaly developed severa metamizole had been discontinued. Gabapentin (oral), which had bee 1800 milligrams per day, was then progressively reduced. Improveme leukocyte and eosinophil counts followed. None of the other concomi before improvement was evident (Lasso-de-la-Vega et al, 2001).

3.3.8 Musculoskeletal Effects

Backache

Fracture of bone

Myalgia

Myasthenia gravis

Rhabdomyolysis

3.3.8.A Backache

1) Incidence: 1.8% (Prod Info NEURONTIN(R) oral tablets, oral capsules
2) Backpain has been reported in 1.8% of the patients receiving gabaper ongoing antiepileptic treatment compared with 0.5% with placebo add-on NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

3.3.8.B Fracture of bone

1) Incidence: 1.1% (Prod Info NEURONTIN(R) oral tablets, oral capsules
2) Fracture has been reported in 1.1% of the patients receiving gabapent ongoing antiepileptic treatment compared with 0.8% with placebo add-on NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

3.3.8.C Myalgia

1) Incidence: 2% (Prod Info NEURONTIN(R) oral tablets, oral capsules, c
2) Myalgia has been reported in 2% of the patients receiving gabapentin ongoing antiepileptic treatment compared with 1.9% with placebo add-on NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

3.3.8.D Myasthenia gravis

See Drug Consult reference: DRUG-INDUCED MYASTHENIA GRAVIS

3.3.8.E Rhabdomyolysis

1) In a single case report, the administration of gabapentin appeared to ir year-old diabetic female. The patient had a history of type 2 diabetes mell dyslipidemia. She was taking multiple insulin injections daily, irbesartan 15 mg thrice daily, of which gabapentin was prescribed three weeks earlier fo initiation of gabapentin, her creatinine was 1.2 mg/dL, CPK was 142 units 21 units/L, and microalbuminuria was 170 mg/24 hours. On admission, th weakness of her lower extremities, muscle pain, fatigue along with decrea urine. Physical examination revealed proximal muscle tenderness and we reflexes, and decreased vibration sensation. Laboratory testing revealed e mg/dL, CPK of 75,680 units/L, AST of 1451 units/L, ALT of 453 units/L, LD level of 6.3 mmol/L, and positive for myoglobin in urine; indicative of acute thyroid hormones and troponin-I were in normal ranges. Muscle biopsy co rhabdomyolysis. Hemodialysis was initiated to remedy hyperkalemia and discontinued and parenteral fluids along with furosemide were initiated to showing gradual renal improvement. Six months following hospital discha asymptomatic, and her renal function and muscle enzymes were normaliz

3.3.9 Neurologic Effects

Abnormal reflex

Amnesia

Asthenia

Ataxia

Choreoathetosis

Dizziness

Drug-induced coma

Dysarthria

Dyskinesia

Headache

Hyperactive behavior

Insomnia

Nystagmus

Polyneuropathy

Seizure

Somnolence

Stuttering

Tremor

Vertigo

3.3.9.A Abnormal reflex

1) Incidence: 0.1% or greater (Prod Info NEURONTIN(R) oral tablets, ora

2) Abnormal reflex (increased, decreased, or absent reflex) was reported epilepsy patients greater than 12 years of age who received gabapentin (antiepileptic drug therapy in all adjunctive therapy clinical trials (except ne Info NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

3) In double-blind and open-label clinical trials, decreased reflex was rep patients who received gabapentin (n=1173) for treatment of neuropathic p was not established (Prod Info NEURONTIN(R) oral tablets, oral capsules

3.3.9.B Amnesia

1) Incidence: postherpetic neuralgia, 1.2%; epilepsy, 2.2% (Prod Info NE capsules, oral solution, 2007)

2) Amnesia has been reported in 1.2% of patients treated with gabapenti those treated with placebo (n=227) in controlled trials of patients with pos NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

3) Amnesia has been reported in 2.2% of patients treated with gabapenti treated with placebo (n=378) in controlled add-on trials of patients greater epilepsy (Prod Info NEURONTIN(R) oral tablets, oral capsules, oral soluti

3.3.9.C Asthenia

1) Incidence: 1% to 5.7% (Prod Info NEURONTIN(R) oral tablets, oral ca

2) Asthenia was reported in 5.7% of patients treated with gabapentin (n= with placebo (n=227) in controlled trials of patients with postherpetic neur oral tablets, oral capsules, oral solution, 2007).

3) Asthenia was reported in at least 1% (1 of 100) of epilepsy patients gr received gabapentin (n=4717) in addition to current antiepileptic drug ther clinical trials (except neuropathic pain trials) (Prod Info NEURONTIN(R) o solution, 2007).

3.3.9.D Ataxia

1) Incidence: postherpetic neuralgia, 3.3%; epilepsy, 12.5% (Prod Info NI capsules, oral solution, 2007)

2) Ataxia has been reported in 3.3% of patients treated with gabapentin (those treated with placebo (n=227) in controlled trials of patients with pos NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

3) Ataxia has been reported in 12.5% of patients treated with gabapentin treated with placebo (n=378) in controlled add-on trials of patients greater epilepsy. Ataxia was one of the adverse effects most frequently associate (0.8%) (Prod Info NEURONTIN(R) oral tablets, oral capsules, oral solutio

4) Truncal ataxia was reported in 48 children treated with gabapentin syr younger) or oral capsules in 200-mg doses for those 16 to 25 kg, 300-mg

400-mg doses for those 37 to 50 kg (over 2 years of age) in a single-dose
pediatric patients age 1 month to 12 years (evenly distributed over the ag

3.3.9.E Choreoathetosis

1) Incidence: less than 0.1% (Prod Info NEURONTIN(R) oral tablets, oral
2) Choreoathetosis was reported in less than 0.1% (1 of 1000) of epileps
age who received gabapentin (n=4717) in addition to current antiepileptic
therapy clinical trials (except neuropathic pain trials) (Prod Info NEURON
oral solution, 2007).
3) Two case reports described choreoathetosis related to adjunctive gab
mg/day in 2 institutionalized, mentally retarded patients. In one case, the
the severity of choreoathetoid movements lessening with decreasing dos
movements occurred intermittently for 10 weeks after discontinuation. In t
was attempted after discontinuation. Upon rechallenge, the patient develc
reaching a gabapentin dose of 1800 mg/day. The movements occurred 1
persisted for 1 to 2 hours. Increasing the dose to 3600 mg/day had no eff
the movements. Because the movements were not disabling and seizure
a decision was made to continue gabapentin therapy (Chudnow et al, 199

3.3.9.F Dizziness

1) Incidence: pediatrics, 2.5%; adults, 17.1% to 28% (Prod Info NEURON
capsules, oral solution, 2007)
2) Dizziness has been reported in 28% of patients treated with gabapenti
those treated with placebo (n=227) in controlled trials of patients with pos
NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).
3) In controlled add-on trials of epilepsy patients greater than 12 years of
17.1% of patients who received gabapentin (n=543) compared with 6.9%
(n=378) in addition to current antiepileptic drug therapy. Dizziness was on
frequently associated with gabapentin discontinuation (0.6%) (Prod Info N
capsules, oral solution, 2007).
4) Dizziness was reported in 2.5% of pediatric patients who received gab
1.6% of patients who received placebo (n=128) in addition to current antie
trials of patients 3 to 12 years of age with epilepsy (Prod Info NEURONTI
oral solution, 2007).

3.3.9.G Drug-induced coma

1) A case report described a drug-induced coma in a 65-year-old woman
patient, who had a history of untreated hypertension, was admitted to the
aneurysmal subarachnoid hemorrhage. The Glasgow coma scale was 15
initial generalized tonic clonic seizure. Subsequently, gabapentin 600 mg
initiated along with IV nimodipine, paracetamol, and oral omeprazole. A C
subarachnoid hemorrhage without clot. Six hours after ICU admission, an
communicating artery was treated by coil. Dilation of the ventricles was re
leading to the insertion of an external ventricular drainage which was linke
intracranial pressure. Because the patient was conscious with no motor sl
performed on day 1. Several hours later, the patient gradually progressed
Intracranial pressure, transcranial Doppler and PaCO(2) were all normal.
ventilatory assistance was provided, and a continuous infusion of sufenta
sedate her. Rebleeding or ischemic complication were ruled out by CT sc
4), sedation was maintained; sedatives were stopped temporarily each da
There was no improvement in consciousness. At day 8, vasospasm was
performed without sedation, revealed evidence of a reactive alternating c
down with less reactivity and rare spike foci on the anterior region indicati
of seizure resulted in a gabapentin dose increase to 900 mg 3 times daily
triphasic slow waves in addition to the previously described spike foci. He
and she became deeply comatose. Due to the consistent presence of slo
a diagnosis of metabolic encephalopathy was made. Gabapentin, omepra
paracetamol were discontinued on day 15. Oxcarbazepine was initiated ir
300 mg twice daily. Her neurological status improved and she gained con
21 and 28, controlled EEGs no longer showed the slow triphasic waves. M
after gabapentin discontinuation), 34, and 58 showed a progression towa
2007).

3.3.9.H Dysarthria

1) Incidence: 2.4% (Prod Info NEURONTIN(R) oral tablets, oral capsules
2) In controlled add-on trials of patients greater than 12 years of age with
in 2.4% of patients who received gabapentin (n=543) compared with 0.5%

placebo (n=378) in addition to current antiepileptic drug therapy (Prod Info oral capsules, oral solution, 2007).

3.3.9.I Dyskinesia

1) Two men developed generalized dyskinetic movements of the face an gabapentin 900 or 1200 mg/day. The men were being treated for anxiety. in resolution of abnormal movements within 1.5 to 3 days (Norton & Quarl

3.3.9.J Headache

1) Incidence: 3.3% (Prod Info NEURONTIN(R) oral tablets, oral capsules
2) Headache has been reported in 3.3% of patients treated with gabapen treated with placebo (n=227) in controlled trials of patients with postherpe NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

3.3.9.K Hyperactive behavior

1) Incidence: 1% to 4.7% (Prod Info NEURONTIN(R) oral tablets, oral ca
2) Hyperkinesia was reported in 2.5% of pediatric patients who received with 0.8% of patients who received placebo (n=128) in addition to current controlled trials of patients 3 to 12 years of age with epilepsy (Prod Info N capsules, oral solution, 2007).
3) In controlled trials of pediatric patients 3 to 12 years of age with epilep restlessness and hyperactivity) was reported in 4.7% of patients who rece compared with 2.9% of patients who received placebo (n=128) in addition therapy (Prod Info NEURONTIN(R) oral tablets, oral capsules, oral solutic
4) Hyperkinesia was reported in at least 1% (1 of 100) of epilepsy patient who received gabapentin (n=4717) in addition to current antiepileptic drug clinical trials (except neuropathic pain trials) (Prod Info NEURONTIN(R) o solution, 2007).

3.3.9.L Insomnia

1) Incidence: 0.1% or greater (Prod Info NEURONTIN(R) oral tablets, ora
2) Insomnia has been reported in more than 1% of patients treated with more frequent in those treated with placebo (n=378) in controlled add-on years of age with epilepsy (Prod Info NEURONTIN(R) oral tablets, oral ca
3) In double-blind and open-label clinical trials, insomnia was reported in received gabapentin (n=1173) for treatment of neuropathic pain condition established (Prod Info NEURONTIN(R) oral tablets, oral capsules, oral so
4) Insomnia is one of the most frequently reported adverse events followi gabapentin (Prod Info NEURONTIN(R) oral tablets, oral capsules, oral so

3.3.9.M Nystagmus

1) Incidence: 0.1% to 8.3% (Prod Info NEURONTIN(R) oral tablets, oral
2) In controlled add-on trials of epilepsy patients greater than 12 years of 8.3% of patients who received gabapentin (n=543) compared with 4% of t (n=378) in addition to current antiepileptic drug therapy (Prod Info NEURO capsules, oral solution, 2007).
3) In double-blind and open-label clinical trials, nystagmus was reported who received gabapentin (n=1173) for treatment of neuropathic pain conc established (Prod Info NEURONTIN(R) oral tablets, oral capsules, oral so

3.3.9.N Polyneuropathy

1) A case report described polyneuropathy in a 58-year-old man being tre neuropathic pain in his head, neck, and back. After beginning therapy with he developed a mild pruritic, erythematous, macular rash. Therapy contin control with increased gabapentin (2400 mg/daily). At 5 months, pruritus i thighs and forearms. Gabapentin was reduced to 1200 mg daily with no c discontinued but restarted after the neuropathic pain returned without resp rash reoccurred despite a slower titration. Topical triamcinolone relieved t rash; however, the patient was left with a constant burning sensation in hi Sedimentation rate was elevated at 35. Toxic polyneuropathy was suspec discontinued. After 1 month, the burning dysesthesia had decreased but p and light-touch below the mid-calf was decreased. Seven months later, th improved and were present only in the soles of his feet (Gould, 1998).

3.3.9.O Seizure

1) A case report described an exacerbation of seizures in a child with Ler adjunctive use of gabapentin. Both absence and myoclonic seizures recu

increase in dosage. After discontinuation of gabapentin, and addition of pl
myoclonic seizures occurred (Vossler, 1996).
2) Absence status was described in one patient during initiation of gabap
discontinued in this patient (Crawford et al, 1987a).

3.3.9.P Somnolence

1) Incidence: 8.4% to 21.4% (Prod Info NEURONTIN(R) oral tablets, oral
2) Somnolence was reported in 21.4% of patients treated with gabapentir
those treated with placebo (n=227) in controlled trials of patients with pos
NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).
3) In controlled add-on trials of epilepsy patients greater than 12 years of
19.3% of patients who received gabapentin (n=543) compared with 8.7%
(n=378) in addition to current antiepileptic drug therapy. Somnolence was
frequently associated with gabapentin discontinuation (1.2%) (Prod Info N
capsules, oral solution, 2007).
4) Somnolence was reported in 8.4% of pediatric patients who received g
with 4.7% of patients who received placebo (n=128) in addition to current
controlled trials of epilepsy patients 3 to 12 years of age (Prod Info NEUR
capsules, oral solution, 2007).

3.3.9.Q Stuttering

1) A case report described stuttering in a 58-year-old woman after being
intractable seizures. Gabapentin therapy was discontinued and within 4 d
(Nissani & Sanchez, 1997).

3.3.9.R Tremor

1) Incidence: postherpetic neuralgia, more than 1%; epilepsy, 6.8% (Proc
tablets, oral capsules, oral solution, 2007)
2) Tremor was reported in more than 1% of patients treated with gabaper
frequent in those treated with placebo (n=227) in controlled trials of patier
(Prod Info NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007
3) In controlled add-on trials of epilepsy patients greater than 12 years of
of patients who received gabapentin (n=543) compared with 3.2% of thos
in addition to current antiepileptic drug therapy (Prod Info NEURONTIN(R
solution, 2007).

3.3.9.S Vertigo

1) Incidence: 0.1% or greater (Prod Info NEURONTIN(R) oral tablets, ora
2) Vertigo was reported in at least 1% (1 of 100) of epilepsy patients grea
received gabapentin (n=4717) in addition to current antiepileptic drug ther
clinical trials (except neuropathic pain trials) (Prod Info NEURONTIN(R) o
solution, 2007).
3) In double-blind and open-label clinical trials, vertigo was reported in 0.
received gabapentin (n=1173) for treatment of neuropathic pain condition
established (Prod Info NEURONTIN(R) oral tablets, oral capsules, oral so

3.3.10 Ophthalmic Effects

Blurred vision

Diplopia

Visual field constriction

3.3.10.A Blurred vision

1) Blurred vision, amblyopia, and abnormal vision have been reported oc
therapy (Sivenius et al, 1991a; Prod Info Neurontin(R), 2003a).

3.3.10.B Diplopia

1) Diplopia has been reported following therapeutic doses of gabapentin
Neurontin(R), 2003a).

3.3.10.C Visual field constriction

1) A case of reversible concentric visual field constriction occurred in a 5

use. The woman had been diagnosed with polyneuropathy, which was ini
However, persistent dizziness with carbamazepine led to its discontinuati
gabapentin, which was initiated at 400 mg twice daily and titrated to 800 r
months of gabapentin therapy, the patient experienced episodes of disturl
and dizziness. Ophthalmological examination revealed concentric visual f
reduction of gabapentin dosage to 400 mg three times daily. Four months
worsened despite the reduced dosing and gabapentin was subsequently
visual evoked responses, and a brain MRI were normal, excluding conditi
in the hypophysial area. Improvements occurred over the following 9 mon
examinations. A follow-up examination 2 years after symptom-onset revea
complete resolution of the visual defects were noted at the 5 year follow-u
2006).

3.3.12 Psychiatric Effects

Disturbance in mood

Suicidal thoughts

Unable to concentrate

3.3.12.A Disturbance in mood

1) Summary

a) Gabapentin was associated with the occurrence of neuropsychiatr
involving pediatric epilepsy patients between 3 to 12 years of age. Th
the following categories: emotional lability (primarily behavioral proble
aggressive behaviors), thought disorder (including concentration prob
performance), and hyperkinesia (primarily restlessness and hyperacti
2003a).

b) There are reports of symptoms including anxiety, depression, emo
nervousness with gabapentin therapy. A case of mania has also beer
(R), 2003a; Leweke et al, 1999).

2) LITERATURE REPORTS

a) A 35-year-old woman receiving gabapentin 3200 mg/day monothe
(Leweke et al, 1999). Psychiatric symptoms disappeared within 5 day
discontinuation.

3.3.12.B Suicidal thoughts

1) Data reviewed by the US Food and Drug Administration suggest an in
or ideation may exist in patients receiving therapy with antiepileptic drugs
199 placebo-controlled clinical studies covering 11 different AEDs used fo
such as epilepsy, selected psychiatric illnesses, and other conditions, incl
pain syndromes. The analysis included 27,863 patients treated with AEDs
received placebo, and patients were aged 5 years and older. There were
patients in the AED treatment groups versus (vs) none in the placebo grou
occurred in 0.43% of patients in the AED treatment groups compared to 0
groups. This corresponded to an estimated 2.1 per 1000 (95% confidence
in the AED treatment groups having suicidal behavior or ideation than the
risk of suicidality was noted at 1 week after starting an AED and continued
compared to placebo, results were generally consistent among the drugs
subgroups. Patients treated for epilepsy, psychiatric disorders, or other co
risk for suicidality compared to placebo. Closely monitor patients treated w
worsening of depression, suicidality and other unusual changes in behavi
such as anxiety, agitation, hostility, mania, and hypomania (US Food and

3.3.12.C Unable to concentrate

1) Summary

a) Impaired concentration or memory has been reported within three
therapy (Prod Info Neurontin(R), 2003a; Ramsay, 1994a).

3.3.13 Renal Effects

Incontinence

Serum creatinine raised

3.3.13.A Incontinence

1) Summary

a) Three cases of bladder and rectal incontinence were reported whi (Gil-Nagel et al, 1997). All occurred within 1 to 4 weeks of starting ga upon discontinuation.

3.3.13.B Serum creatinine raised

1) A 59-year-old woman and a 49-year-old male with a history of renal ins experienced a 47.8% and 30% increase in serum creatinine, respectively discontinuation of lithium (Silvia & Spitznas, 2007).

a) Significant past medical history for the 59-year-old woman include (dose range of 450 mg/day to 2100 mg/day) and an episode of lithiun nephrogenic diabetes insipidus requiring hospitalization. Serum urea continued to rise and therefore, lithium was discontinued 6 years afte months prior to lithium discontinuation, the serum creatinine was 2.3 was started 1 week prior to discontinuation of lithium. The dose was t months later. Her serum creatinine continued to rise and reached a p 5.5 months after gabapentin initiation (a 47.8% increase). Clinical ber gabapentin was continued. The dose was reduced but the creatinine least 3 months (Silvia & Spitznas, 2007).

b) Significant past medical history for the 49-year-old male includes l 3 years. At some point in time, amiloride was added, presumably for discontinued due to worsening renal function (serum creatinine of 4 n interstitial fibrosis/nephritis secondary to lithium and possibly amilorid divalproex sodium was started but subsequently discontinued 6 mont patient refusal. Carbamazepine was started but gradually discontinue patient refusal. Gabapentin 100 mg/day was started 1 month prior to Gabapentin was titrated up to 300 mg/day within 1 month. His serum and plateaued at a peak of 5.2 mg/dL, after approximately 10 months increase). Clinical benefit was achieved; therefore, gabapentin was c 2007).

3.3.14 Reproductive Effects

Amenorrhea

Sexual dysfunction

3.3.14.A Amenorrhea

1) LITERATURE REPORT

a) Amenorrhea occurred in a 35-year-old women treated with gabap syndrome type 2. Gabapentin had been initiated at a dose of 300 mg gabapentin dose was increased to a total dose of 1800 mg/day. Thre reported complete cessation of menses with no other changes in sex cycles were normal and the patient had not experienced any prior ep measured follicle stimulating hormone level at the time was 4.8 Interr estradiol level was 55 IU/mL, both at the lower end of normal. At this down by 300 mg/day over 6 days. Two weeks later, the patient's mer 2004).

3.3.14.B Sexual dysfunction

1) Summary

a) Impotence has been reported in 1.5% of patients treated with ther (Prod Info Neurontin(R), 2003a). Anorgasmia has been reported in 2 2002; Montes & Ferrando, 2001; Labbate & Rubey, 1999).

2) LITERATURE REPORTS

a) Anorgasmia and decreased libido was reported in 2 women who r day (Grant & Oh, 2002).

b) A 41-year-old man being treated with gabapentin for hypomania f attain (Labbate & Rubey, 1999). He initially noted the problem with a the dose was increased to 600 mg 3 times daily, he found ejaculation

to achieve. One week after gabapentin discontinuation, he reported r
c) Anorgasmia occurred in a 36-year-old man after a short course of
bipolar I disorder. Due to this adverse drug-induced side effect, the p
Initially the patient was on lithium therapy (1200 mg/day). However, h
therapy after experiencing a first-degree atrioventricular block. He sta
with titration of 400 mg every 2 days to 400 mg 3 times a day. This th
episode which occurred after withdrawal of lithium. Two weeks later,
because it caused him difficulty in attaining orgasm. His sex drive and
discontinuation of gabapentin, he returned to normal orgasmic functio
the gabapentin dosing regimen, he relapsed into a new episode of hy
Ferrando, 2001).

3.3.15 Respiratory Effects

Disorder of upper respiratory system

Respiratory failure

Respiratory finding

3.3.15.A Disorder of upper respiratory system

1) Summary

a) Rhinitis and pharyngitis have occurred with gabapentin use (Prod

3.3.15.B Respiratory failure

1) Summary

a) Gabapentin therapy was associated with hypoventilation, hyperca
69-year-old man under treatment for chronic obstructive pulmonary d
anxiety disorder (Batoon et al, 2001) and hypoventilation requiring int
woman with end-stage renal disease on long-term hemodialysis (Jon

2) LITERATURE REPORTS

a) After taking multiple doses of gabapentin over two days, without ir
year-old woman with end-stage renal disease became hypoxic and s
was 80% on room air and she was subsequently intubated. She had
and a gabapentin level of 22.6 micrograms per milliliter. Following he
rapidly improved and she was extubated. This gabapentin level is les
of toxicity and suggests that gabapentin toxicity should be considered
gabapentin with end-stage renal disease show signs of impaired mer
2002).

b) Gabapentin therapy was associated with hypoventilation, hyperca
69-year-old man under treatment for chronic obstructive pulmonary d
anxiety disorder. The patient was admitted with shortness of breath a
he had started gabapentin 300 mg 3 times a day for painful peripher
initiation of gabapentin, he was hospitalized for severe hypercapnia,
(MV). His other medications were albuterol, ipratropium, clonazepam
hospitalization, he was again put on MV due to lethargy, respiratory d
attempts at extubation failed. On day 10, gabapentin was withdrawn
steroid, levofloxacin, clonazepam, and zolpidem were continued). Tw
and his carbon dioxide levels normalized. He continued to improve, a
remained stable. The authors suggest that caution be exercised if ga
COPD patients (Batoon et al, 2001).

3.3.15.C Respiratory finding

1) Summary

a) Viral infection, fever, coughing and pneumonia have been associa
(Prod Info Neurontin(R), 2003a).

2) Coughing, pharyngitis, respiratory failure, pneumonia, rhinitis and viral
gabapentin therapy.

3.3.16 Other

Summary

Drug withdrawal

Fatigue

3.3.16.A Summary

1) OTHER EFFECTS

a) Rebound and withdrawal symptoms may occur upon discontinuati

3.3.16.B Drug withdrawal

1) Five patients being treated with gabapentin augmentation for obsessiv experienced a rebound of symptoms after abruptly discontinuing gabapen Patients complained of markedly more pronounced and intense problems obsessional thinking, depression, and decreased sleep over their baseline

2) A 48-year-old woman with bipolar affective disorder developed catator discontinued (Rosebush et al, 1999). She had begun gabapentin during h hypomania. She has a history of intolerance to lithium, carbamazepine, va Gabapentin was slowly increased to 500 mg/day, but after 3 weeks, she b was tapered off over several days. Within 48 hours, she became immobile drink, rigidity, and absence of spontaneous movement. She remained cat with lorazepam eventually reversed the catatonia.

3.3.16.C Fatigue

1) Summary

a) In available studies, the most common adverse effects of gabaper tiredness/fatigue usually within three days of initiating therapy (Crawf Hooper et al, 1991b; Sivenius et al, 1991a; Prod Info Neurontin(R), 2 Drowsiness has been reported in patients ranging from 15% to 45%. in 13% of patients in one large study (Sivenius et al, 1991a; Anon, 19

2) LITERATURE REPORTS

a) CHILDREN - Drowsiness was a side effects of oral gabapentin ex month to 12 years (evenly distributed over the age range) involved in study. Dosing for children 2 years or younger was gabapentin syrup children over 2 years old received oral capsules based on weight: 20 26 to 36 kg; 400 mg for 37 to 50 kg (Haig et al, 2001).

b) Increased tiredness was seen with gabapentin 2400 milligrams/da (p=0.03). Cognition, dysphoria, temper, fatigue, and worry were not s gabapentin therapy even at the highest dose (Leach, 1997).

c) In a small study drowsiness has been observed in up to 45% of pa 1991a). Tiredness and drowsiness have occasionally required withdr tiredness/fatigue were reported in 15% and 13% of patients, respecti (Anon, 1990b)

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Pr capsules, oral tablets, oral solution, 2005) (All Trimesters)

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

2) Australian Drug Evaluation Committee's (ADEC) Category: B1 (Batagol, 19

a) Drugs which have been taken by only a limited number of pregnant wo age, without an increase in the frequency of malformation or other direct human fetus having been observed. Studies in animals have not shown e occurrence of fetal damage.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) There is insufficient clinical experience with gabapentin in pregnancy t population. Since gabapentin is frequently prescribed with other anticonvu between maternal gabapentin use and fetal adverse effects can not be de adequate, well-controlled studies, the manufacturer recommends that gab pregnancy only if the the potential benefit outweighs the potential risk to t (R) oral capsules, oral tablets, oral solution, 2005).

5) Literature Reports

a) There are no well-designed studies in pregnant women that have eval the growing fetus. However, the Gabapentin Pregnancy Registry has colle fetuses exposed to the drug. In the women, one case of hypertension, on one case of eclampsia were reported during the pregnancies. There were

miscarriages and one elective abortion. Full term babies accounted for 77
deliveries occurred between weeks 32 to 36. Median birth weight (n of 29
(oz) (range 3 lb 7 oz to 9 lb 8 oz). The time and length of gabapentin expo
fully described. The following malformations were reported: hypospadia in
and valproate, congenital solitary kidney in a baby exposed to gabapentin
thereafter phenobarbital, and minor malformation of the left external ear c
gabapentin and lamotrigine throughout gestation. The above birth statistic
women with epilepsy and in the general population. The effects of gabape
elucidated from these results and caution should still used when consideri
individuals (Montouris, 2003).

b) Data from a limited study of 6 women who were administered gabaper
lactation demonstrated fetal accumulation of gabapentin. The women wer
from 900 to 3,200 milligrams (mg)/day. While 1 woman had a premature d
deliveries were uneventful and resulted in healthy children. At the time of
maternal gabapentin plasma concentration ratio was 1.74. The study inve
indicative of an active transplacental transport of gabapentin (Ohman et a

c) In rodent studies, gabapentin, dosed at 1 to 4 times the maximum dos
a mg per square meter (mg/mg(2)) to pregnant females has been shown t
ossification of several bones in the skull, vertebrae, forelimbs, and hindlim
approximately one-half the human dose of gabapentin (Prod Info NEURO
tablets, oral solution, 2005).

d) In reproductive studies, rats dosed prior to and during mating, and thro
approximately 1 to 5 times the maximum human dose of 3,600 milligrams
increased incidence of hydroureter and/or hydronephrosis and the offsprir
affected. In a teratology study, an increased incidence of postimplantation
pregnant rabbits exposed to 60, 300, and 1,500 milligrams/kilogram/day (
than 0.25 to 8 times the maximum human dose) (Prod Info NEURONTIN(
solution, 2005).

B) Breastfeeding

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

a) Available evidence and/or expert consensus is inconclusive or is inade
when used during breastfeeding. Weigh the potential benefits of drug trea
before prescribing this drug during breastfeeding.

2) Clinical Management

a) Gabapentin is secreted into human milk after oral administration. Limit
infants exposed to gabapentin through breast milk had minimal serum cor
effects. However, extensive studies are warranted and it is advisable that
through breast milk should be closely monitored to potential adverse effec
et al, 2006). Although a nursed infant may be exposed to a maximum dos
milligram/kilogram/day of gabapentin, until further data are available, the r
gabapentin should be used in nursing women only if the potential benefit t
to the infant (Prod Info NEURONTIN(R) oral capsules, oral tablets, oral so

3) Literature Reports

a) Data from a limited study of 6 women who were administered gabaper
lactation demonstrated extensive transfer of gabapentin to breast milk but
nursed infant. The women were given gabapentin doses ranging from 900
the time of delivery, the mean umbilical-to-maternal gabapentin plasma co
hours postpartum, the mean gabapentin plasma concentrations in the infa
levels (range 12 to 36%) with an estimated elimination half-life in the neor
Sampling of the breast milk was conducted before maternal intake of the r
approximately 10 to 15 hours following the last gabapentin dose. Based o
pairs, mean milk/maternal plasma gabapentin ratio was 1.0 (range 0.7 to
from delivery and the relative infant gabapentin dose was approximated to
(kg)/day, which was equivalent to 1.3 to 3.8% of the weight normalized do
No adverse effects were observed in the infants (Ohman et al, 2005).

b) A case report described gabapentin transfer into the breast milk of a la
administered gabapentin for chronic back pain. The 34-year-old woman h
milligrams (mg) three times daily (36.7 milligrams/kilogram/day (mg/kg/da
her 1.6-month-old male infant, weighing 3.1 kg, were studied over a 24-ho
determine the milk-plasma ratio and relative infant dose of gabapentin. Th
the relative infant dose was 2.34% of the weight-adjusted maternal dose.
0.86 mg/kg/day, which is approximately 3% of the children's dose of 25 to
plasma concentration in the infant was 0.4 milligrams/liter (mg/L), which w
mother's average drug plasma concentration of 6.7 mg/L. No adverse effe
(Kristensen et al, 2006).

4) Drug Levels in Breastmilk

a) Parent Drug

1) Peak Concentration in Infant
a) Following oral administration, gabapentin is secreted into hun
exposed to a maximum gabapentin dose of 1 milligram per kilogı
exposure on the nursing infant is unknown (Prod Info Neurontin(

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Lab Modifications

3.5.1 Drug-Drug Combinations

Aluminum Carbonate, Basic

Aluminum Hydroxide

Aluminum Phosphate

Dihydroxyaluminum Aminoacetate

Dihydroxyaluminum Sodium Carbonate

Evening Primrose

Ginkgo

Hydrocodone

Magaldrate

Magnesium Carbonate

Magnesium Hydroxide

Magnesium Oxide

Magnesium Trisilicate

Morphine

Morphine Sulfate Liposome

3.5.1.A Aluminum Carbonate, Basic

1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) giver
reduced gabapentin bioavailability by 20%. Bioavailability was reduced by
given two hours after the antacid. Therefore, gabapentin should be admin
antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct
hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.B Aluminum Hydroxide

1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) giver reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.C Aluminum Phosphate
1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) giver reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.D Dihydroxyaluminum Aminoacetate
1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) giver reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.E Dihydroxyaluminum Sodium Carbonate
1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) giver reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.F Evening Primrose
1) Interaction Effect: reduced anticonvulsant effectiveness
2) Summary: Theoretically, evening primrose oil may reduce the effective lowering the seizure threshold. Evening primrose oil is contraindicated in p 1998; Newall et al, 1996).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of evening primrose oil w
7) Probable Mechanism: evening primrose oil may reduce the seizure thr

3.5.1.G Ginkgo
1) Interaction Effect: decreased anticonvulsant effectiveness
2) Summary: In a case report, 2 patients with epilepsy previously well cor developed a recurrence of seizures after ingesting ginkgo extract. Seizure ginkgo was withdrawn (Granger, 2001a). An infant developed seizures aft

methylpyridoxine arising from ingestion of ginkgo seeds (Yagi et al, 1993a
methylpyridoxine, a neurotoxin, is found in ginkgo seeds (used as food in
ginkgo component from which commercially available extracts are derivec
majority of ginkgo leaf products should not contain sufficient amounts of 4
seizures. However, ginkgo products are not commonly assayed to assure
contained in the commercial product. Of concern are those instances whe
season and the potential introduction of contamination, 4'-O-methylpyrido
amounts to be problematic in vulnerable populations (eg, infants or those
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of ginkgo and anticonvul
seizures occur for the first time or recur in patients previously controlled b
inquire about the use of ginkgo seed or leaf extract. If possible, an assay
specific product to ascertain if 4'-O-methylpyridoxine is present.
7) Probable Mechanism: neurotoxin 4'-O-methylpyridoxine (found in leav
may cause seizures
8) Literature Reports
a) The serum of a 21-month-old patient with gin-nan food poisoning
methylpyridoxine levels. The serum concentration was 0.9 microgram
after ingesting ginkgo seeds, decreasing to 0.05 mcg/mL at 15.5 hou
the 4'-O-methylpyridoxine content was responsible for the tonic/clonic
consciousness observed. They further observed that infants are parti
1993).
b) Four to six milligrams of the neurotoxin 4'-O-methylpyridoxine hav
of Ginkgo biloba leaves which is the source of commercially-available
found in seeds (85 micrograms (mcg)/seed) and leaves (5 mcg/leaf)
July and beginning of August. The albumen of the seed can contain 1
this is reduced to 0.75-1.32 mcg/gram dry weight when boiled. The u
from 5.44-7.15 mcg/gram dry weight. The neurotoxin in ginkgo leaf w
was even detectable in homeopathic preparations. Specifically, 8.13
was found in Tebonin Forte(R), 9.77 mcg/mL in Rokan(R), 3.80 mcg/
mcg/mL in Gingium(R). Based on recommended daily intake, this tra
intake of 4'-O-methylpyridoxine of 48.78 mcg, 58.62 mcg, 11.40 mcg,
(R), Rokan(R), Kaveri Forte(R), and Gingium(R), respectively. Among
Ginkgo biloba Urtinktur Hanosan(R) and Ginkgo biloba Urtinktur DHU
0.589 mcg/mL of 4'-O-methylpyridoxine, respectively. However, the a
contained in medicinal extracts of ginkgo leaves may be too low to be
remains with the variance in 4'-O-methylpyridoxine content dependin
ginkgo was harvested (Arenz et al, 1996).
c) Seizures recurred in 2 patients, both with epilepsy that was well c
biloba (Gb). The patients (an 84-year-old woman and a 78-year-old n
at least 18 months prior to beginning therapy with Gb 120 milligrams
Both patients developed seizures within 2 weeks of beginning Gb the
free (without changing anticonvulsant therapy) after discontinuing Gb

3.5.1.H Hydrocodone
1) Interaction Effect: decreased bioavailability of hydrocodone
2) Summary: Coadministration of gabapentin and hydrocodone has been
concentration and area under the curve (AUC) values of hydrocodone in a
minimally increase gabapentin AUC (Prod Info NEURONTIN(R) oral table
2007). Therefore, caution is advised if these agents are coadministered a
monitored for lack of hydrocodone efficacy.
3) Severity: minor
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Concomitant use of gabapentin and hydrocodor
peak concentration of hydrocodone in a dose-dependent manner; gabape
(Prod Info NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007
coadministered and consider monitoring patients for lack of hydrocodone
7) Probable Mechanism: unknown
8) Literature Reports
a) Coadministration of gabapentin 125 to 500 mg (n=48) and hydroc
the Cmax and AUC values of hydrocodone in a dose-dependent fash
of hydrocodone alone. Following administration of gabapentin 125 m
hydrocodone decreased by 3% and 4%, respectively. After a gabape
hydrocodone Cmax and AUC were 21% and 22% lower, respectively

increased by 14% with concomitant use of hydrocodone and gabapen
interaction is not known (Prod Info NEURONTIN(R) oral tablets, oral

3.5.1.I Magaldrate

1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) given reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.J Magnesium Carbonate

1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) given reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.K Magnesium Hydroxide

1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) given reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.L Magnesium Oxide

1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) given reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.M Magnesium Trisilicate

1) Interaction Effect: decreased gabapentin effectiveness
2) Summary: The manufacturer reports that an antacid (Maalox(R)) given reduced gabapentin bioavailability by 20%. Bioavailability was reduced by given two hours after the antacid. Therefore, gabapentin should be admin antacid (Prod Info Neurontin(R), 2002).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving gabapentin should be instruct hours of taking gabapentin due to the potential to decrease the effectiven
7) Probable Mechanism: decreased gabapentin bioavailability

3.5.1.N Morphine

1) Interaction Effect: an increase in gabapentin plasma concentrations
2) Summary: Patients who require concomitant treatment with morphine gabapentin concentrations (Prod Info Neurontin(R), 2002a).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be carefully observed for signs somnolence or dizziness. The dose of gabapentin or morphine should be
7) Probable Mechanism: additive CNS depression

3.5.1.O Morphine Sulfate Liposome

1) Interaction Effect: an increase in gabapentin plasma concentrations
2) Summary: Patients who require concomitant treatment with morphine gabapentin concentrations (Prod Info Neurontin(R), 2002a).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients should be carefully observed for signs somnolence or dizziness. The dose of gabapentin or morphine should be
7) Probable Mechanism: additive CNS depression

3.5.3 Drug-Lab Modifications

3.5.3.A Urine total protein measurement

1) Interaction Effect: false-positive urine protein measurement using Ame
2) Summary: In patients receiving gabapentin with other antiepileptic dru measurements with the Ames N-Multistix SG(R) dipstick test have been n of urine protein in patients on gabapentin therapy, the more specific sulfos procedure is recommended (Prod Info NEURONTIN(R) oral capsules, sol
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: False-positive readings for urinary protein have Multistix SG(R) dipstick test when gabapentin was used in conjunction wit the more specific sulfosalicylic acid precipitation procedure is recommend patients receiving gabapentin (Prod Info NEURONTIN(R) oral capsules, s
7) Probable Mechanism: mechanism unknown

4.0 Clinical Applications

4.1 Monitoring Parameters

A) Therapeutic

1) Laboratory Parameters

a) There is no well-defined therapeutic range for GABAPENTIN and optir not been established.

b) In women who plan on becoming pregnant, obtaining concentrations c pregnant and during the pregnancy may be beneficial. Although, therapeu established, prepregnancy concentrations in an optimally-treated woman for comparison to concentrations during pregnancy, when concentrations

2007).
2) Physical Findings
a) Reduction in seizure frequency
B) Toxic
1) Laboratory Parameters
a) Routine monitoring of clinical laboratory parameters is not recommend
2) Physical Findings
a) Data reviewed by the US Food and Drug Administration suggest an in
or ideation may exist in patients receiving therapy with antiepileptic drugs
suicidality was noted at 1 week after starting an AED and continued to at
for epilepsy, psychiatric disorders, or other conditions were all at an increa
to placebo. Closely monitor patients treated with AEDs for emergence or
suicidality, and other unusual changes in behavior, which may include syr
hostility, mania, and hypomania (US Food and Drug Administration, 2008

4.2 Patient Instructions

A) Gabapentin (By mouth)

Gabapentin

Controls certain types of seizures in people who have epilepsy. Also treats pai
shingles (postherpetic neuralgia).

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

How to Use This Medicine:
Capsule, Tablet, Liquid
Your doctor will tell you how much of this medicine to take and how often.
take it more often than your doctor tells you to.
You may take this medicine with or without food.
Do not allow more than 12 hours between doses.
Measure the oral liquid medicine with a marked measuring spoon or medi
When used to treat seizures, gabapentin is usually taken with other anticc
other medicines your doctor has prescribed as part of your combination tr

If a Dose is Missed:
If you miss a dose or forget to take your medicine, take it as soon as you
next dose, wait until then to take the medicine and skip the missed dose.
Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine at room temperature, away from heat, moisture, and d
the refrigerator. Do not freeze.
Keep all medicine out of the reach of children and never share your medic

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over
and herbal products.
Make sure your doctor knows if you are also using morphine or hydrocodc
If you take an antacid (such as Maalox®), wait at least 2 hours before taki

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if yc
Do not stop using this medicine suddenly without asking your doctor. You
your dose before stopping it completely.
This medicine may make you dizzy or drowsy. Avoid driving, using machi
could be dangerous if you are not alert.
If you have a test done for protein in your urine, tell the healthcare provide

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 face or hands, swelling or tin
tightness in chest, trouble breathing
Clumsiness, problems with coordination
Extreme tiredness, slurred speech
Uncontrolled eye movement

If you notice these less serious side effects, talk with your doctor:
Behavior problems, hostility, restlessness, trouble concentrating, moodine
Blurred or double vision
Fever, cough, sneezing, sore throat, stuffy nose (especially in children)
Nausea, vomiting (especially in children)
Rapid weight gain
Shakiness
Swelling in your hands, ankles, or feet

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

4.3 Place In Therapy

A) Gabapentin has been demonstrated effective as an add-on anticonvulsant age partial seizures. The drug also appears effective in generalized seizures. Adverse gabapentin have been minimal. The ultimate place in therapy of gabapentin will de controlled add-on studies comparing the efficacy and safety of the drug with other

B) One potential advantage of gabapentin over other antiepileptic agents is its app most common adverse effects of the drug have been drowsiness, fatigue, and dizz hematologic, hepatic, or renal function tests have been observed, and the drug doe significantly with concomitant antiepileptic regimens. In 1 small study, gabapentin u no adverse effects on cognition (Mortimore et al, 1998).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Gabapentin is an amino acid structurally-related to the inhibitory neurotrans (GABA); however, its antiepileptic activity appears unrelated to any direct effec (Andrews & Fischer, 1994).

2) Animal studies have demonstrated the anticonvulsant activity of gabapentii by interference with GABAergic transmission or provoked by excitatory amino al, 1987). Although gabapentin appears to possess GABA-mimetic properties mechanism of action remains unclear. The drug has no significant effect on G not bind to GABA or benzodiazepine receptors or influence the neural uptake pharmacologically active doses (Crawford et al, 1987; Sivenius et al, 1991). In 1996) in which in vivo measurements of GABA in human brain were made usi spectroscopy, occipital lobe concentrations were higher in patients taking gab that gabapentin increases GABA synthesis. An effect of gabapentin on central been postulated by some investigators (Rao et al, 1988).

3) GABA is the major inhibitory neurotransmitter in the central nervous systen transmission is involved in the pathogenesis of epilepsy (AMA Department of addition to valproic acid, several other agents have been developed in an effo inhibition, including progabide (GABA prodrug and GABA agonist) (Crawford & (GABA transaminase inhibitor) (Rimmer & Richens, 1984; Gram, 1988). The r of epilepsy will ultimately depend upon how well it compares with all of these a

4) The analgesic action of gabapentin has been demonstrated in animal mode prevented allodynia and hyperaglesia. Pain related responses in neuropathic p inflammation models were prevented or decreased by gabapentin. Immediate altered. The mechanism by which gabapentin exerts its analgesic effects is un 2003).

B) REVIEW ARTICLES

1) Dosages and formulations of antiepileptic drugs used to treat pediatric epil (Bourgeois, 2002).

2) Basic reviews of the treatment of seizures have been written; these include status epilepticus (Willmore, 1998), treatment of the elderly (Rowan, 1998), an adults (Feely, 1999; Mattson, 1998). Pediatric seizure management has also b Pellock, 1998).

3) With the addition of the newer antiepileptic drugs, polypharmacy in epilepsy (Schneiderman, 1998; Guberman, 1998).

4) Reviews on the use of gabapentin for bipolar disorder have been published Botts & Raskind, 1999).

5) The role of gabapentin for pain management has been discussed (Wetzel &

6) Reviews of the pharmacology and clinical use and safety of gabapentin are Ramsay, 1994).

7) Reviews of newer antiepileptic medications, including a summary of clinica recommendations for use, are available (Bauer, 1997 (German)). (Dichter & B

4.5 Therapeutic Uses

Acute intermittent porphyria - Seizure

Alcohol withdrawal syndrome

Amyotrophic lateral sclerosis

Antineoplastic adverse reaction, Taxane - Myalgia

Bipolar disorder

Cancer pain - Neuropathic pain

Charles Bonnet syndrome

Ciguatoxin causing toxic effect

Clozapine adverse reaction - Drug-induced epilepsy

Cluster headache

Cocaine dependence

Complex regional pain syndrome, type I - Pain

Dementia

Dementia - Problem behavior

Diabetic peripheral neuropathy

Essential tremor

Fibromyalgia

Generalized seizure

Hemifacial spasm

Hiccoughs, Intractable

Hot sweats

Intracranial tumor - Seizure

Mania

Migraine; Prophylaxis

Multiple sclerosis, Complications

Neuropathic pain

Neuropathy due to human immunodeficiency virus

Nystagmus

Orthostatic tremor

Panic disorder

Partial seizure

Partial seizure, Refractory

Partial seizure; Adjunct

Phantom limb syndrome

Postherpetic neuralgia

Postoperative pain

Priapism

Pruritus

Restless legs syndrome

Sensory disorder

Shortlasting, unilateral, neuralgiform pain with conjunctival injection and tearing sy

Social phobia

Spasticity

Spinal muscular atrophy

Tardive dyskinesia

Tinnitus

4.5.A Acute intermittent porphyria - Seizure

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:

Appears to be safe when used in patients with porphyria (Zadra et al, 199

3) Adult:

a) A 23-year-old woman was safely treated with gabapentin 1200 milligra associated with acute intermittent porphyria (Zadra et al, 1998). She beca abdominal pains. She had previously experienced attacks while on pheny valproate.

4.5.B Alcohol withdrawal syndrome

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RA

2) Summary:

In a randomized, double-blind trial (n=100), high-dose gabapentin led Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) score outpatients with alcohol withdrawal (Myrick et al, 2009).
In a randomized, double-blinded, placebo-controlled trial, gabapentin reducing the amount of rescue medications received in the first 24 ho Mainz Alcohol Withdrawal Scores (MAWS), or in reducing the numbe discontinuations within the first 48 hours of therapy in patients with al to severe alcohol withdrawal syndrome (Bonnet et al, 2003).

3) Adult:

a) In a randomized, double-blind trial (n=100), high-dose gabapentin led Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) scores co outpatients with alcohol withdrawal. Patients with alcohol dependence and and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteri score of 26 or higher, and a CIWA-Ar score of 10 or greater who voluntee withdrawal received 4 days of gabapentin or lorazepam. One of the follow gabapentin were administered: 1) 200 milligrams (mg) 3 times daily for 3 day 4 (600 mg arm; n=16); 2) 300 mg 3 times daily for 3 days, then 300 m arm; n=28; mean age, 38.4 +/- 1.82 years (yr); mean drinks/day in previou or 3) 400 mg 3 times daily for 3 days, then 400 mg twice daily on day 4 (h 40.5 +/- 2.25 yr; mean drinks/day in previously 14 days, 16.8 +/- 2.18 drin was discontinued after one near syncopal event and 2 patient-reported se patients in this arm were not included in the final analysis. The lorazepam administered as 2 mg 3 times daily for 3 days, then 2 mg twice daily on da 1.83 yr; mean drinks/day in previously 14 days, 11.4 +/- 1.11 drinks). CIW daily during the medication phase and on 1, 2, and 7 days posttreatment received oral thiamine 100 mg daily for 12 days. Patients could take blind gabapentin or lorazepam as needed on days 1 to 4 to treat subjective syn there were no significant differences (p=0.75) in supplemental medication lorazepam-treated patients. The mean CIWA-Ar score was significantly lo arm but not the low-dose gabapentin arm compared with the lorazepam a (gabapentin: low-dose, 4.52 +/- 39 (standard error (SE)); high-dose, 3.14 0.38 (SE); high-dose gabapentin versus (vs) lorazepam p less than 0.05) (gabapentin: low-dose, 1.79 +/- 0.32 (SE); high-dose, 1.03 +/- 0.31 (SE); high-dose gabapentin vs lorazepam p less than 0.01). Mean alcohol cravi analog scale of zero millimeters (mm) (no discomfort) to 100 mm (greates less than 0.05) lower in patients who received gabapentin (gabapentin: lo dose, 28.73 +/- 4.6 (SE)) compared with lorazepam (42.7 +/- 4.7 (SE)) du however, alcohol craving scores were not significantly different between th phase (gabapentin: low-dose, 13.9 +/- 5.3 (SE); high-dose, 20.4 +/- 4.8 (S Mean anxiety scores (evaluated using the Zung Anxiety Scale) were signi patients who received gabapentin (gabapentin: low-dose, 32.11 +/- 1.74 ((SE)) compared with lorazepam (36.98 +/- 1.5 (SE)) during the medicatio score was significantly (p less than 0.01) improved in the high-dose gabap gabapentin arm compared with lorazepam arm during the follow-up phase 1.3 (SE); high-dose, 28.8 +/- 1.2 (SE); lorazepam: 33.9 +/- 1.1 (SE)). Duri in the low-dose gabapentin arm had significantly (p less than 0.01) improv (BDI) scores and patients in the high-dose gabapentin arm had significant sleep scores evaluated using the Epworth Sleepiness Scale compared wi The incidence of patient-reported adverse effects did not differ between th arms (p=0.74) (Myrick et al, 2009).

b) Gabapentin was not better than placebo in reducing the amount of res first 24 hours of treatment, in decreasing patient's Mainz Alcohol Withdrav reducing the number of premature trial discontinuation within the first 48 h treat alcohol withdrawal. A double-blinded, randomized, placebo-controlle milligrams 4 times daily (n=32) with placebo (n=29) in patients with alcoho severe alcohol withdrawal syndrome (as defined by a MAWS greater than administered full doses for 3 days and then treatments were tapered dow of rescue medication (clomethiazole) doses required in the first 24 hours gabapentin and placebo arms, respectively (p=0.96). The differences betv not statistically different in the first 48 hours of the study (p=0.4). Frequen statistically different between treatment arms (p=0.74). However, nausea frequently with the use of gabapentin. Mean gabapentin levels were 4.63, micrograms/milliliter at day 1, 2, and day 5, respectively (Bonnet et al, 20

c) Six patients were successfully treated with gabapentin for alcohol with patients had an average score of 17 on the Clinical Institute Withdrawal fo R, 10 or higher indicates moderate withdrawal). Gabapentin 400 milligram the first 3 days, followed by 400 mg twice daily for 1 day, and 400 mg dail

decreased on the CIWA-R to 11 on day 1, 2 on day 2, and 0 on day 3.
d) A 38-year-old man with obsessive-compulsive disorder (OCD) and alc
craving after being treated with gabapentin (Chatterjee & Ringold, 1999).
his paroxetine to augment his OCD therapy. Gabapentin was started at 3(
increased to 1200 mg 3 times daily over 2 months. He stopped drinking w
approximately 3 weeks after beginning gabapentin. His avoidant OCD bel

4.5.C Amyotrophic lateral sclerosis

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Possible efficacy was found in a phase II study (Miller et al, 1996); howev
gabapentin therapy in a follow-up phase III study (Miller et al, 2001)

3) Adult:
a) A 9-month course of oral gabapentin failed to provide beneficial effects
lateral sclerosis (ALS), according to a controlled, multicenter phase III tria
Enrollees were randomized to placebo (n=96) or gabapentin 1200 milligra
months (gabapentin titrated over 4 to 6 weeks to total 3600 mg/day). The
decline was not significantly different between groups (maximum voluntar
arm muscles measured bilaterally for shoulder and elbow flexion and exte
0.021 units/week; gabapentin group minus 0.020 units/week. There were
differences on the ALS Functional Rating Scale (p=0.2), rapid foot tap exe
protocol (p=0.17). ALS symptoms (such as cramps, fasciculations, stiffnes
gabapentin, nor was the mortality rate (deaths: 7 placebo, 6 gabapentin).
more frequently in the gabapentin group were lightheadedness, drowsines
difference in dropout rates occurred across the 2 groups. The results of th
phase II trial in which gabapentin 2400 mg/day appeared to slow the rate
et al, 1996).
b) In a randomized, double-blinded study of 117 patients, gabapentin wa
of arm strength (as measured by mean arm score) in patients with amyotr
compared to placebo, although the difference was not statistically significa
gabapentin was 800 milligrams 3 times daily over the course of 6 months
well tolerated. Gabapentin was not found to have any effect on forced vita

4.5.D Antineoplastic adverse reaction, Taxane - Myalgia

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Effective in 2 case reports (van Deventer & Bernard, 1999)

3) Adult:
a) Gabapentin successfully allowed the continuation of 2 taxane-based c
been limited by the development of severe myalgias (van Deventer & Ber
48-year-old woman with breast cancer with pulmonary nodules developec
arms, back and neck after 2 cycles of paclitaxel. She had no improvemen
acetaminophen. Gabapentin 400 milligrams (mg) 3 times daily on the day
then for 4 to 5 days afterward significantly improved her symptoms. The s
woman with uterine leiomyosarcoma who developed pulmonary and hepa
with docetaxel but by the fourth cycle she developed grade III myalgias. T
acetaminophen and dexamethasone. Gabapentin 300 mg twice daily beg
and continuing to the eighth day dramatically improved her symptoms.

4.5.E Bipolar disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Demonstrates efficacy in bipolar disorder in case reports, retrospectiv
(Cabras et al, 1999; Ghaemi et al, 1998; Sheldon et al, 1998; Schaffe
Further case-controlled studies are warranted

3) Adult:

a) In this open-label, safety and varying dosage study, gabapentin was fc
mania and hypomania in patients with bipolar and schizoaffective disorde
(n=22) were initially started on gabapentin 300 milligrams/day (mg/day). D
every 4 days as tolerated to a maximum daily dose of 2400 mg/day. The r
mg/day. Any benzodiazepines and neuroleptics were continued at a cons
Mood stabilizers such as lithium, carbamazepine, and valproate were tape
compared to baseline, significant reductions were seen in Clinical Global
versus 2.1; p less than 0.0001) and Brief Psychiatric Rating Scale (BPRS
than 0.0001) after 16 weeks of treatment. Sedation was the most commor
improved with continued treatment.

b) In a naturalistic and retrospective study, gabapentin add-on therapy w
of patients with mood disorders (Ghaemi et al, 1998). Patients suffered fr
disorder (n=10), bipolar disorder type I (n=13), bipolar disorder type II (n=
otherwise specified (NOS) (n=8). Moderate or marked response on the Cl
Improvement scale was seen in 30% of patients. Patients with bipolar disc
response with 11 out of 27 patients (41%) improving. Response rates for
out of 13 (15%) and for unipolar major depressive disorder were only 2 ou
responses between the groups were not clinically significant.

c) A 73-year-old woman with severe bipolar disorder benefited from gaba
1998). She had been unable to tolerate lithium and valproate. Gabapentin
twice daily. She did well on a combination of gabapentin, venlafaxine, anc

d) In an open study, a positive response to gabapentin therapy was dem
patients. All patients had been refractory to standard mood stabilizing dru
combination with other medicines including antianxiety agents, antidepres
anticonvulsants. The response was judged by both the treating psychiatris
Schaffer, 1997).

4.5.F Cancer pain - Neuropathic pain

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Effective in case reports (Caraceni et al, 1999)

3) Adult:

a) Gabapentin provided pain relief in most patients with neuropathic canc
analgesics (Caraceni et al, 1999). Consecutive cancer patients with neuro
treated with gabapentin doses of 600 to 1200 milligrams added to their op
scales for the assessment, global pain scores, burning pain intensity, and
decreased. In 9 patients with allodynia, 7 patients reported disappearance
Twenty out of 22 patients judged gabapentin as efficacious in reducing the

4.5.G Charles Bonnet syndrome

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

A case of Charles Bonnet syndrome resolved with low-dose gabapentin th

3) Adult:

a) Complex visual hallucinations completely remitted after use of gabape
a diagnosis of Charles Bonnet's syndrome. The patient had a 10-year hist
degeneration, and for 2 years, she had experienced persistent and daily v
hallucinations included visions of medieval women, knights in bright colors
or torsos; they occurred most frequently in the morning and evening, only
moved when her eyes moved. The patient had no psychiatric history and
her visions. Her medications included an angiotensin II antagonist and diu
hypertension, and pain killers (tilidine) for polyarthrosis. She had tried per
treat her hallucinations, but without effect. Electroencephalography and cr

abnormalities. Gabapentin 300 milligrams/day was initiated. The patient e
episode on each of the next 2 days. After that, the hallucinations stopped.
further episodes of hallucinations were reported, no visual deterioration ha
caused no side effects (Paulig & Mentrup, 2001).

4.5.H Ciguatoxin causing toxic effect

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Symptomatic improvement in 2 cases (Perez et al, 2001)

3) Adult:

a) Two patients, stricken with ciguatera poisoning, had significant improv
with GABAPENTIN. The patients were a 30 year-old woman and a 37-yea
dusky grouper in the Dominican Republic and both were disabled for wee
neurotoxin. The first patient had an episode of diarrhea, followed in severa
intense pruritus of the hands, legs, and breasts, especially with exposure
generalized pruritus and sharp, shooting pains in her legs. Gabapentin 40
was begun a month after the onset of symptoms. Improvement was rapid.
stopped. Within a few hours, both women had a return of symptoms; on re
relief occurred. Gabapentin was given for an additional 21 days. After the
the first patient had only minor dysesthesia and the second patient had sc
continue the medication (Perez et al, 2001).

4.5.I Clozapine adverse reaction - Drug-induced epilepsy

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Gabapentin prevented clozapine-induced seizures in a 65-year-old, chron
2001)

3) Adult:

a) Gabapentin was effective as a prophylactic agent in the prevention of
year-old chronic schizophrenic women, with no prior history of seizures, h
medication regimen of haloperidol 10 milligrams (mg) per day and procycl
four week period clozapine was gradually increased to 37.5 mg daily. The
clonic seizure 2 days after the last increase in dose and the clozapine was
mg/day, was added prophylactically to prevent seizures and the clozapine
mg per day. Due to a lack of therapeutic response the clozapine was to be
clozapine taper, gabapentin was also decreased to 600 mg/day due to co
day the patient had a second tonic-clonic seizure and the clozapine was w

4.5.J Cluster headache

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Mitigated cluster headache in one case refractory to other agents (Ta
Further study is needed

3) Adult:

a) Oral gabapentin provided complete relief of cluster headache in a 38-y
had been only slightly diminished with other therapeutic agents; gabapent
for prophylaxis of his headaches. The patient had a 24-year history of hea
by neurologists who diagnosed cluster headache, according to criteria of t
Society. His right-sided headaches occurred in a temporal pattern, only in
warm to cold weather. The 2-hour headache episodes typically appeared
going to bed, and continued for a period of 14 to 21 days. Amitriptyline, m
blockers, phenytoin, and indomethacin brought some partial relief (on a sc

from 100 to between 70 and 85). Gabapentin 300 milligrams twice daily w
after the time his headaches had begun. After 2 doses, his pain had decre
possible 100), and after 3 doses, he experienced complete resolution of p
gabapentin successfully aborted his headaches. The fourth year, the patie
gabapentin (300 mg twice daily) before November, and had no headache
headache period. The only side effect was transient drowsiness. The auth
in additional patients before gabapentin can be recommended for cluster

4.5.K Cocaine dependence

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Possibly reduces cocaine craving and use in cocaine-dependent patients
2001) (Raby, 2000)

3) Adult:

a) Investigators from a 24-week, open-label trial reported that the averag
urine screens decreased in patients with cocaine dependence treated with
initiated as 200 milligrams (mg) twice daily for 2 days, then increased to 4
600 mg twice daily for 2 days, and then increased to 1200 mg twice daily.
800 to 2400 mg/day. Of the original 11 patients, 2 dropped out after week
Seven of the 9 remaining patients also participated in a structured substa
were obtained up to 3 times a week as part of the substance use program
considered to be cocaine positive and the average proportion of missed s
and 21% during treatment (p greater than 0.5). Baseline urine screens we
to starting gabapentin and were cocaine positive an average of 53.11 time
were collected in the 24 weeks after gabapentin initiation and were cocain
less than 0.01 when compared to baseline). Sedation was reported in 2 p

b) Oral GABAPENTIN therapy was apparently well-tolerated and may re
cocaine use in some cocaine- dependent subjects (DSM-IV), based on a
al, 2001). Gabapentin was initiated as 300 milligrams (mg) twice daily for
twice daily, for a course of therapy expected to last for 8 weeks. Of 30 sub
return after week 1; of 18 remaining, 14 completed week 4, and 6 comple
completed week 4 were included in the intent-to- treat analysis. Eighty-six
14) were positive for cocaine at baseline compared to 29% (4 of 14) at we
frequency of cocaine craving decreased from baseline to week 8 (78% to
frequency; p=0.004). Mean number of days till relapse was 21 days. The
were transient nausea and sedation, which occurred in 1 subject each. Th
subject-retention rate.

c) Two cocaine users experienced markedly reduced cravings for cocain
gabapentin therapy (Raby, 2000). A 42-year-old man had been addicted t
to heroin since the age of 28. His treatment for drug withdrawal had includ
imipramine for depression (75 to 300 milligrams (mg)/day). He continued
especially in times of difficulties. While continuing imipramine (200 mg/da
titration over a week to 400 mg twice daily (serum concentration 12.4 mg/
cocaine had disappeared. A 31- year-old woman was diagnosed with schi
abuse. Bimonthly injections of fluphenazine 50 mg controlled her psychoti
(up to 20 mg/day) was also given as supplementation to control auditory h
use of crack cocaine. She began gabapentin and reached a dose of 1200
mg/L). Over a 9-month course of gabapentin, her only relapse was a one-
cigarettes. Neither patient reported significant side effects, such as ataxia
postulated to restore the GABA- mediated inhibitory feedback action of nu
ascending mesolimbic dopaminergic neurons, resulting in decreased activ
projecting to the nucleus accumbens (a site identified with addictive beha

4.5.L Complex regional pain syndrome, type I - Pain

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Patients experience dramatic results in pain associated with reflex sy

Mellick, 1997; McGraw & Kosek, 1997)
Controlled studies are needed to define the role for REFLEX SYMPA

3) Adult:

a) In a case series, 6 patients who had experienced years of severe, intra multiple treatments including nerve blocks and drug therapy for their reflex experienced dramatic results with gabapentin therapy (Mellick & Mellick, 1 900 milligrams (mg) per day, however, some patients required higher dos Specific improvements were reduced hyperpathia, allodynia, hyperalgesia soft tissue manifestations.

4) Pediatric:

a) Two cases of improved pain relief in patients with REFLEX SYMPATH described including one of a 9-year-old girl (McGraw & Kosek, 1997). She her feet which was initially treated with gabapentin 100 mg three times pe mg three times daily for 4 months. At that time the medication was tapere for 6 months.

4.5.M Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPT

4.5.N Dementia - Problem behavior

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Gabapentin use improved behavioral symptom scores in 20 patients dementia
Effective in case reports of disruptive behavior and agitation

3) Adult:

a) Gabapentin use in 20 patients with probable Alzheimer's and dementia as measured with the Neuro-Psychiatric Inventory and the Cohen-Mansfie 15 months of therapy. Patients were between 68 and 76 years old (mean with dementia (DSM IV) and probable Alzheimer's. Patients had been trea therapy (donepezil or rivastigmine) for a mean duration of 8.8 months. Ag with delusions had become evident an average of 6 months after the initia therapy. Gabapentin was initiated at 100 milligrams (mg) twice daily. After was titrated to 300 mg twice daily and then after 2 weeks, 300 mg three ti gabapentin was 980 mg daily. The NeuroPsychiatric Inventory (NPI) and Inventory (CMAI) were used to assess behavioral symptoms. At 7 months scores had improved significantly (p less than 0.001 for both measures). S demonstrated significant improvements in agitation, anxiety, apathy, aggr disturbance scores (p less than 0.05). However, hallucination, depression eating disturbances scores were not significantly changed. Sedation and adverse events reported (Moretti et al, 2003)(Pers Comm, 2004).

b) In a case series, gabapentin was associated with at least minimal impr for the treatment of behavioral disorders in dementia (Herrmann et al, 200 years, with behavioral problems and Alzheimer's disease (n=7), vascular dementia (n=1), or alcoholic dementia (n=1) received gabapentin at an ini twice daily. Over 8 weeks, gabapentin was given in doses ranging from 2 (average dose was 900 mg/day). Two patients completed only 2 weeks of emergent adverse events. Utilizing the Neuropsychiatric Inventory and the Inventory, 2 patients were rated as much improved, 3 as minimally improv minimally worse after 8 weeks. Adverse events included gait instability, se sweating. The authors concluded that there may be a subgroup of patient that might respond to gabapentin.

c) Improvement with gabapentin therapy was reported in 4 patients with (Roane et al, 2000). Three of the patients had Alzheimer's disease and 1 was used in doses of 300 to 2400 milligrams daily. Clinical improvement cursing, threatening, moaning, crying, task perseverating, and hitting. One due to sedation and disorientation. Other adverse effects included headac ambulation.

d) A 62-year-old man with dementia, not otherwise specified, became les gabapentin (Low & Brandes, 1999). He also had a history of cerebrovascu a possible head injury. His other psychiatric medications included haloper trial of paroxetine. He continued to be agitated until gabapentin was starte

(mg) daily and increased to 300 mg 3 times daily. Within 10 days, he beca
e) A 92-year-old woman with disruptive behavior secondary to Alzheimer
gabapentin 200 milligrams every 8 hours (Goldenberg et al, 1998). Her di
as ceaseless vocalization and insomnia with restlessness. Trazodone hac
haloperidol caused increased confusion. During a 2-month follow-up her b
with no adverse effects.
f) Two cases of gabapentin being useful for behavior problems have bee
An 87-year-old male with Alzheimer's disease had his agitation and assau
weeks of receiving gabapentin titrated to 100 milligrams (mg) 3 times daily
Alzheimer's disease exhibited improved functioning with gabapentin titrate
a progressive agitation and displayed behaviors such as striking out.

4.5.O Diabetic peripheral neuropathy

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

As effective as amitriptyline for the treatment of pain associated with
1 study (Morello et al, 1999a)
Low doses of 900 milligrams/day are only minimally effective (Gorsor

3) Adult:

a) Gabapentin was effective for the treatment of pain and sleep difficulties
peripheral neuropathy (DPN) (Backonja et al, 1998). In a double-blind, 8-v
(mean age 53 years) with painful DPN for 1 to 5 years were randomized t
(n=82) or placebo (n=80). During the first 4 weeks, gabapentin was increa
milligrams (mg) to 3600 mg. Doses were only decreased if intolerable adv
3600 mg/day dose was achieved by 67% of the gabapentin-treated patier
was a daily pain score measured on an 11-point Likert scale. There was a
the gabapentin scores and placebo from week 2 through week 8 (p less th
significant differences seen in mean sleep interference scores at week 1 t
Also using the short-form McGill Pain Questionnaire, gabapentin patients
pain scores (p less than 0.01). The gabapentin group did experience more
dizziness, somnolence, and confusion. This study shows that gabapentin
those patients able to tolerate it.
b) There was no difference as measured by pain scales and global pain s
gabapentin in the treatment of diabetics with peripheral neuropathy pain (
patients with stable glycemic control (n=21) received either gabapentin or
were then crossed-over to the other arm of therapy for 6 weeks with a 1-w
Dosage was adjusted based on the patient's response with gabapentin do
milligrams (mean dose 1565 mg) and amitriptyline doses ranging from 25
Both drugs significantly decreased pain scores from baseline (both p less
provided moderate or greater pain relief in 67% of patients while gabapen
patients (p=0.26). There was no statistically significant difference in occur
the drugs except for increased weight gain with amitriptyline.
c) Gabapentin was only minimally effective for the treatment of painful dia
900 milligrams/day . In a double-blind, crossover trial, patients received ei
and then were crossed-over to the other therapy with a 3-week washout p
by 300 mg every 3 days to a stable dosage of 900 mg daily. Patients were
questionnaire, global assessment of pain relief, a visual analogue scale, a
A significant difference in pain relief with gabapentin over placebo was se
questionnaire (p=0.03). Moderate or excellent pain relief was reported by
6 in placebo only, and 3 with both agents (p=0.11). The authors suggest t
are needed (Gorson et al, 1999).

4.5.P Essential tremor

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Mixed results have occurred (Gironell et al, 1999a; Pahwa et al, 1998)

3) Adult:

a) In a comparative, double-blind, crossover, placebo-controlled study, ga three times daily was as effective as propranolol 40 mg three times daily v treatment of patients with essential tremor (Gironell et al, 1999a). Patients initially receive either gabapentin, propranolol, or placebo for a two-week crossed-over to the other 2 arms with a 1-week washout period between t with gabapentin and propranolol treatment were seen in the Tremor Clinic clinical examination and motor task performance as compared to placebo respectively). No differences in self-reported subjective disability scale or from accelerometry were noted between the 3 groups.
b) In a double-blind, placebo-controlled crossover study of 20 patients wi 1800 milligrams (mg) per day was no different than placebo at improving t assessed at baseline and after 2 weeks of therapy using the Fahn-Tolosa Patients were crossed over to the opposite treatment after at least a five d differences in tremor symptoms, patient-rated global disability or global im treatment when compared to baseline. Two patients withdrew from the stu therapy with gabapentin (Pahwa et al, 1998).

4.5.Q Fibromyalgia

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

In a 12-week, randomized, double-blind, placebo-controlled, multicen 1200 to 2400 milligrams/day was safe and efficacious in the treatmer associated with fibromyalgia in adults (Arnold et al, 2007)

3) Adult:

a) Gabapentin was safe and efficacious in the treatment of pain and othe fibromyalgia in adults in a randomized, double-blind, placebo-controlled, r 90% women; 97% Caucasian) meeting the American College of Rheumat who had a score of 4 or greater on the average pain severity item of the B included. Patients with pain from structural or regional rheumatic disease, arthritis, or autoimmune disease were among those excluded. Patients we oral gabapentin (n=75) or placebo (n=75) for 12 weeks. Gabapentin was i bedtime and titrated weekly for 6 weeks up to a maximum dose of 2400 m 1200 mg at bedtime). Dosage reductions to a minimum 1200 mg/day dos not tolerate 2400 mg/day; however, the study dose was stable for at least Following the 12-week study period, gabapentin was decreased by 300 m median gabapentin dose was 1800 mg/day (interquartile range, 1200 to 2 of acetaminophen or over-the-counter NSAIDs, and occasional use of sed concomitant medications or herbal agents with CNS effects and other ana the study. The primary efficacy outcome measure was pain severity meas (short form) average pain severity score (0-10 scale; 0=no pain, 10=pain response to treatment was defined as a 30% or greater reduction in the B Based on longitudinal analysis, the mean +/- SD BPI average pain severit decreased from 5.7 +/- 1.4 at baseline to 3.2 +/- 2 at 12 weeks in the gaba a decrease from 6 +/- 1.5 at baseline to 4.6 +/- 2.6 at 12 weeks in the plac mean difference between groups for the primary endpoint was -0.86 (95% -0.04; p=0.039). In the intent-to-treat population, the estimated mean diffe primary endpoint was -0.92 (95% CI, -1.75 to -0.71; p=0.015). Intent-to-tre (38/75) of gabapentin-treated patients responded compared to 31% (23/7 (p=0.014). Among secondary endpoints, patients in the gabapentin group reductions compared to placebo in Fibromyalgia Impact Questionnaire tot groups, -8.4; 95% CI, -13 to -3.3; p=0.001), Clinical Global Impression of between groups, -0.66; 95% CI, -1.08 to -0.24; p=0.002), and Medical Ou Index score (difference between groups, -11.5; 95% CI, -18.6 to -4.4; p=0 treatment differences observed in the gabapentin group for depressive sy pressure pain thresholds were not statistically significant compared to pla with gabapentin were mostly mild to moderate and included dizziness (25 lightheadedness (14.7%), which occurred more frequently than with place

4.5.R Generalized seizure

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Demonstrates efficacy as add-on therapy in patients with generalized seiz
et al, 1991b; Crawford et al, 1987b; Crawford et al, 1987b)

3) Adult:
a) GABAPENTIN has shown efficacy in the treatment of secondarily gene
1991b; Crawford et al, 1987b). A reduction in tonic-clonic seizures by 50%
patients in 1 small study (n=11) employing a lower dose of GABAPENTIN
et al, 1987b). A median reduction in tonic-clonic seizures of 36% with GAI
1800 milligrams is reported. A significant reduction in absence seizures w
investigators. Additional placebo-controlled and comparative studies are r
the drug in primary generalized seizures (Bauer, 1987).

4.5.S Hemifacial spasm

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Effective in case reports of hemifacial spasm (Bandini & Mazzella, 1999)

3) Adult:
a) In a series of case reports, gabapentin was effective in 5 patients (34 t
spasm (Bandini & Mazzella, 1999). Patients received gabapentin 900 to 1
improvement of spasms. One patient complained of mild somnolence and
giddiness. Neither discontinued medication due to these effects.

4.5.T Hiccoughs, Intractable

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
May be effective as add-on or sole treatment for intractable hiccups (Porz
2000)

3) Adult:
a) Gabapentin partially improved symptoms in 3 cases involving hiccup ir
Two of the 3 patients had previously tried combinations of metoclopramid
chlorpromazine, or haloperidol with mixed success. Gabapentin 300 millig
starting dose in all cases. In 1 case, it was added to metoclopramide and
cases it was started as the sole agent. In all cases, the response was pro
occurred in 2 patients and in 1 patient the hiccup returned 10 days later w
efficacy was not assessed as patients could only be followed between 6 t
b) Clinicians reported 4 cases of IDIOPATHIC CHRONIC HICCUPS in w
occurred after the addition of GABAPENTIN to cisapride and omeprazole
baclofen (Petroianu et al, 2000). The recommended protocol includes initi
milligrams (mg) 3 times daily and omeprazole 20 mg once daily. If this du
times daily would be added, and if the triple therapy fails, gabapentin 400
The therapy, if successful, would be continued for 6 months, then gradual
the 4 reported cases (males; 55, 58, 74, and 75 years of age), medication
unsuccessfully included carbamazepine, promethazine, levomepromazine
meperidine, tiapride, flunitrazepam, nordazepam, clorazepate, amitriptylin
pantoprazole, as well as mistletoe extract, other herbal remedies, and acu

4.5.U Hot sweats

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Reduced the frequency and severity of hot flashes in postmenopausa
May be effective in treating tamoxifen-induced hot flashes (Pandya e

3) Adult:

a) Low-dose gabapentin effectively controlled hot flashes in postmenopa double-blind, placebo- controlled trial, women (n=59) experiencing an ave day accompanied by sweating received gabapentin 300 milligrams (mg) t weeks. Following 12 weeks of treatment, gabapentin-treated patients had mean hot flash frequency and a 54% decrease in the mean hot flash com frequency and severity) from baseline as compared with 29% and 31% re (p=0.02 and p=0.01, respectively). After the blinded trial, patients were gi 5-week open-label treatment period in which the gabapentin dose could b Similar results were found in the open- label study. The most common ad somnolence (20%), dizziness (13%), and rash with or without peripheral e 2003).

b) In a randomized, double-blind, placebo controlled trial (n=420), gabap hot flashes in women with breast cancer at a dose of 300 mg three times assigned placebo (n=137), gabapentin 100 milligrams (mg) (n=139), or ga to be taken three times a day for 8 weeks. The mean age of the patients v an average of two or more hot flashes per day and most of them were tak patients kept a journal and reported symptoms severity and duration of th the study and during weeks 4 and 8 of treatment. Evaluable data was ava (119 placebo, 123 gabapentin 300 mg, and 129 gabapentin 900 mg) and placebo, 114 gabapentin 300 mg, and 120 gabapentin 900 mg). A higher from the gabapentin 900 mg group due to side-effects, but only a very sm ineffective treatment. The opposite was found in the placebo group with m treatment not being helpful. It was found that gabapentin 300 mg per day any comparison. There was no significant difference among all the groups episodes. The differences in severity and frequency of hot-flash episodes 900 mg per day group compared to either of the other study groups . The flash severity score from baseline in the placebo, gabapentin 300 mg and -21% (-5.45), -33% (-7.50), and -49% (-9.97), respectively, at week 4 (p=0 7.75) and -46% (-9.94), respectively, at week 8 (p=0.007). The percentag frequency from baseline in the same 3 groups were -18% (1.98), -28% (-2 respectively, at week 4 (p=0.0002), and -15% (-2.25), -30% (-2.86), and - 8 (p=0006). Somnolence or fatigue was the main reason for patients to wi gabapentin 900 mg group (Pandya et al, 2005).

c) In a pilot, non-comparative study, gabapentin decreased the severity, TAMOXIFEN-INDUCED HOT FLASHES. Patients (n=22) were postmeno tamoxifen for breast cancer for at least 1 month who experienced more th Following a 1-week baseline period, gabapentin was administered as 300 1 month. Daily diaries were used to evaluate the hot flashes. Four patient nausea, rash and excessive sleepiness and 2 patients were not evaluable remaining patients, the mean frequency and duration of hot flashes decre 0.001 for both measures). Daily severity scores based upon the number a experienced in a day also decreased 52.6% (p less than 0.001). Of the 16 study, 50% had a complete elimination of hot flashes (Pandya et al, 2004)

4.5.V Intracranial tumor - Seizure

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Effective as adjunct therapy in an open trial of patients with refractory intracranial tumors (Perry & Sawka, 1996)
Controlled studies are needed to validate these results

3) Adult:

a) Add-on therapy with GABAPENTIN was effective in an open-label trial refractory seizures associated with intracranial tumors. The majority of pa (glioblastomas, metastases, and malignant astrocytoma). Gabapentin wa 2400 milligrams per day; all of the patients responded with at least a 50% and half of the patients became seizure-free. Most of the patients were al cranial irradiation which may have contributed to improvement in their clin 1996).

4.5.W Mania

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Possibly effective in moderate cases (Erfurth et al, 1998)

3) Adult:

a) In a case series report, gabapentin therapy was useful in 3 out of 6 pa add-on therapy and in 4 out of 8 patients as monotherapy (Erfurth et al, 1 4800 milligrams daily. In the add-on group scores on the Bech-Rafaelsen declined from 37.7 to 7.8; additional valproic acid was used in 3 out of 6 p scores declined from 27.8 to 9 in 4 out of 8 patients completing the study.

4) Pediatric:

a) A 13-year-old boy with manic episode, bipolar I disorder, and attention the addition of gabapentin 1500 milligrams to his carbamazepine therapy previously failed divalproex and could not tolerate lithium. His initial Young 27 and decreased to 6 after 7 months of gabapentin.

4.5.X Migraine; Prophylaxis

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Efficacy and safety demonstrated in a controlled trial (Mathew et al, 2001)

3) Adult:

a) Oral GABAPENTIN 2400 milligrams (mg)/day taken in 3 divided doses frequency of migraine headaches and was generally well tolerated, basec trial (n=87). Enrollees had 3 to 8 migraine headache episodes per month months (with or without aura); subjects were randomized to gabapentin or dosing occurred during a 4-week baseline period. The first 4 weeks of the considered the titration phase. Gabapentin dosing on day 1 was 300 mg; 7, 1500 mg on day 14, 2100 mg on day 21, and 2400 mg on day 28 (all di gabapentin-treated patients stabilized on 2400 mg/day. During the last 4 v period, the median rate of migraine was 2.7 for the gabapentin 2400-mg/c group (p=0.006). A 50% reduction rate for migraines in the last 4 weeks c was achieved by 46.4% and 16.1% of the gabapentin 2400- mg/day and c (p=0.008). Average number of days with migraine during the last 4 weeks groups, respectively (p=0.006). Drug-related adverse events (somnolence commonly) occurred in 67.3% of the treatment group and 48.9% of the co adverse events amounted to 13.3% and 6.7% of the gabapentin and plac authors believe that gabapentin therapy represents an advance in the pro (Mathew et al, 2001).

4.5.Y Multiple sclerosis, Complications

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Effective for multiple sclerosis complications including trigeminal neuralgia dysesthetic or paresthetic symptoms, and spasticity (Khan, 1998; Solaro e Dunevsky & Perel, 1998)

3) Adult:

a) Refractory trigeminal neuralgia completely resolved in 6 out of 7 multip gabapentin (Khan, 1998). Patients were started on gabapentin 300 milligr until effective. Effective doses ranged from 900 to 2400 mg/day. In 6 patie resolved while 1 patient had a marked improvement.

b) Gabapentin was useful for paroxysmal symptoms in multiple sclerosis 1998). In an open study, MS patients with trigeminal neuralgia, painful ton

paresthetic symptoms refractory to other treatments received gabapentin
patients dropped out due to nausea or poor compliance. In the trigeminal
patients experienced complete resolution of symptoms. Improvement beg
Painful tonic spasm was relieved in 9 out of 11 patients completing the stu
being seen within 3 days. Only partial improvement was seen in the 2 pati
disturbances completing the study.

c) Gabapentin 900 to 2700 milligrams (mg) daily in 3 divided doses was s
on subjective and objective spasticity measures in 22 multiple sclerosis (M
randomized, placebo-controlled, double-masked, crossover trial. All subje
form of MS and were divided into two groups which received either gabap
fashion. Gabapentin was dosed initially at 300 mg three times daily and in
to a maximum dose of 900 mg three times a day. Interference with functio
(p=0.003), Modified Ashworth (p=0.04), painful spasm (p=0.03), plantar st
spasm severity (p=0.01) scores were significantly improved when patients
compared to when they were assigned placebo. Significant improvements
scales, including fatigue impact (p=0.006), global assessment (p=0.0001)
(p=0.002), painful spasm (p=0.002), spasm frequency (p=0.0001), and sp
compared to baseline. Gabapentin treatment also yielded improved score
physician-administered scales including clonus score (p=0.002), deep ten
Ashworth Scale (p=0.0005), and plantar stimulation scale (p=0.008). Plac
gabapentin in measures of fatigue reduction (p=0.03) and decreases in de
Subjects reported improvements in activities of daily living and in appetite
adverse events were reported (Cutter et al, 2000).

d) Two patients with multiple sclerosis obtained marked improvement in s
spasm with gabapentin therapy (Dunevsky & Perel, 1998). A 41-year-old
(modified Ashworth Scale) in the left lower limb and grade 2 for the right lo
take a few steps with a walker. After 3 months of gabapentin 400 milligrar
+1 for the left and 1 for the right limb. She could walk 75 to 100 meters wi
a 52-year-old male, had grade 2 spasticity for both lower limbs and upper
meters with a cane. After 3 months of gabapentin 300 mg 3 times daily, sp
lower limbs and normal in the left upper limb. The patient could ambulate

e) A 36-year-old woman with multiple sclerosis had her continuous "tight"
gabapentin (Samkoff et al, 1997). The pain had been refractory to amitript
carbamazepine. Gabapentin 300 milligrams/day (mg/day) was titrated to 3
improvement in pain.

4.5.Z Neuropathic pain

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Pain associated with multiple neuropathic syndromes including: DYSESTH
NEURALGIA, and direct nerve injury has been relieved (Serpell, 2002) (T
(Otley, 1999)

3) Adult:

a) Mean weekly pain diary scores were reduced in patients given gabape
neuropathic pain. In a randomized, double-blinded, placebo-controlled stu
receive gabapentin (n=153), at an initial dose of 900 milligrams/day (mg/d
placebo (n=152). Gabapentin was increased to 1800 mg/day and then 24
in patients who did not show at least a 50% reduction in overall pain. Pati
By the end of the titration period, 101 patients were taking 2400 mg/day o
1800 mg/day and 27 were taking 900 mg/day. Certain concomitant medic
patients were reported as taking prohibited medications during the study.
stable doses, which may have affected efficacy estimates. Investigators d
patients belonged. Efficacy was assessed using mean weekly pain dairy s
from daily patient assessments of pain on an 11-point Likert scale. In the
diary score decreased from 7.1 at baseline to 5.6 at week 8 (21% decreas
7.3 to 6.3 (14%) in the placebo arm (p=0.048). At weeks 1, 3, 4, 5, and 6,
diary scores between the arms were significantly different (p less than 0.0
there was no longer a statistical difference between the 2 arms. By week
pain symptoms were not different between the two arms (p greater than 0
were associated with the use of gabapentin (Serpell, 2002).

b) A retrospective analysis of 2 years of patient data (n=38) in one practi
some relief to 76% of patients with neuropathic pain that resulted from spi

of gabapentin was 900 milligrams (mg) per day and the median maintena
(range 900 mg to 4800 mg). Nine of 38 patients discontinued treatment w
adverse effects and 5 for lack of efficacy. Among those patients for whom
months of therapy (n=11), mean pain scores on a zero-to-10-point scale c
5.23 at 1 month, 4.59 at 3 months, and 4.13 at 6 months (p less than 0.00
c) A 19-year-old woman was successfully treated for chronic neuropathic
woman had a history of chronic right eye pain, which was refractory to tria
nonsteroidal antiinflammatory drugs, opioids, multiple corrective surgeries
block with local anesthetic. Post-enucleation of the eye, the women report
character of the pain. Gabapentin was initiated at 300 milligrams (mg) dai
300 mg three times a day. By 2 weeks, the patient reported complete pair
the 3 months of follow-up (Sloan et al, 2003).
d) Gabapentin relieved the pain caused by PILOLEIOMYOMAS in 54- ye
undergone a hysterectomy at age 41 for dysfunctional uterine bleeding as
leiomyomatosis, which had first been noticed when she was pregnant at a
numerous painful, red-brown, oval nodules on her right side, including her
woman rated her pain 8 on a scale of 1 to 10 (10 being the most severe).
gabapentin 300 milligrams daily for 3 days, twice daily for 3 days, and the
end of 2 weeks, there was nearly complete resolution of leiomyoma-relate
where the pain was remarkably reduced (pain rating, 3 on a scale of 10).
were mild dizziness and fatigue. The woman continued the same dose as
2002).
e) A 69-year-old woman had her dysesthetic pain after reconstructive sur
(Otley, 1999). The woman had a basal cell carcinoma of the right upper lip
cheek transposition flap. She developed disturbing dysesthetic pain 2 mo
antidepressant therapy and acetaminophen had no effect. She was starte
daily and titrated up to 300 mg 3 times daily. Within 2 weeks the pain had
taper off the gabapentin without reoccurrence of the pain. After 10 weeks
of the gabapentin with only minimal pain reoccurring.
f) A 60-year-old woman suffered exquisite facial pain secondary to being
which was relieved by gabapentin (Lucier & Franm, 1997). Gabapentin 15
increased to 300 mg provided relief after 2 days. The dose was eventually
discontinued after 5 months without recurrence.
g) Two cases of trigeminal neuralgia responsive to gabapentin have beer
one case, the patient reported gabapentin 300 milligrams (mg) 3 times da
baclofen without the dizziness she had experienced. In another case, the
gabapentin 2400 mg/day. She had been refractory to carbamazepine and
and baclofen.

4) Pediatric:

a) Neuropathic pain secondary to pacemaker revision surgery in a 12-yea
block responded to gabapentin therapy (McGraw & Stacey, 1998). Two m
suffered from constant knifelike pain. The pain worsened despite diazepa
antiinflammatory agents. It was somewhat alleviated by amitriptyline and
milligrams infused intravenously over 20 minutes relieved the pain for 6 h
gabapentin increased over 3 weeks to 300 milligrams 3 times daily with a
months the gabapentin was weaned without recurrence of pain.

4.5.AA Neuropathy due to human immunodeficiency virus

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Gabapentin was superior to placebo for the treatment of HIV-associa
multicenter, prospective, randomized, double-blind, placebo-controlle
(n=26) (Hahn et al, 2004).
Efficacy documented by case series (La Spina et al, 2001)

3) Adult:

a) Gabapentin was superior to placebo for the treatment of HIV-associate
multicenter, prospective, randomized, double-blind, placebo-controlled tria
(n=26). Adult patients must be diagnosed with symptomatic HIV-associate
by a neurologist and had completed a baseline pain diary over 1 week pri
definition for HIV-SN diagnosis included distal sensory symptoms (paresth
abnormal sensory signs (elevated vibratory threshold or pin hyperalgesia)
reflexes. Prestudy and during-study use of central analgesics was not per

analgesics (paracetamol, diclofenac) must be decreased to a minimum or
randomized to receive gabapentin (GBP) 400 milligrams (mg) daily titrate
1200 or 2400 mg/day in 3 divided doses (n=15; median age 46 years (yr);
4-week, double-blind treatment phase or to placebo (n=11; median age 4
After the double-blind treatment phase, the study was unblinded and the
increase GBP up to 3600 mg/day and the placebo group could initiate GB
primary outcome was improvement in pain, measured by the difference in
to week 4 based on the Visual Analogue Scale of the Short-Form McGill P
patients had a significant change in median pain score from baseline to w
to 2.85 (p less than 0.05) vs 4.7 to 3.3 (p=0.646), respectively. The chang
baseline to week 4 correlated with a 44.1% improvement vs a 29.8% impr
compared with placebo arm, respectively. Further, GBP was associated w
interference score at week 4 from baseline (-48.9% vs -11.6%) relative to
with common adverse events of somnolence (80% vs 18.2%) dizziness (6
vs 27.3%), nausea (33.3% vs 18.2%) and headache (6.7% vs 9.1%) in the
respectively (Hahn et al, 2004).
b) GABAPENTIN as sole analgesic was effective in ameliorating neuropa
Pain symptomology was due to the disease itself (n=6), neurotoxic drugs
(n=4). Gabapentin was started at 300 milligrams (mg)/day and titrated by
3600 mg/day or highest tolerated dose. Mean dose during the study was
reporting analgesia at 300 mg/day. Pain was improved within mean 6 day
Mean pain score as assessed by a visual analog scale (VAS) decreased f
(p=0.0001). Pain which interfered with sleep decreased from baseline 60.
was at least 4 months in the majority of patients. Overall 1 of 19 patients e
gabapentin. The drug was well tolerated, and the only adverse event was
After the study ended, 15 patients were still on gabapentin; 4 patients stop
months due to complete or nearly complete pain relief. Another advantage
low potential for drug interactions with gabapentin as the drug is not meta
eliminated by renal secretion as unchanged drug (La Spina et al, 2001).
c) Oral GABAPENTIN 300 milligrams (mg) three times a day proved to b
POLYNEUROPATHY in a 41-year-old man positive for HIV infection but n
treatment. The patient was diagnosed with Mycobacterium tuberculosis, a
month history of paresthesias in his legs. His tuberculosis was successful
neurologic deficits in his lower extremities progressively worsened. He de
his legs, hard leg pain, and proprioceptor alterations. An electromyogram
symmetric sensorimotor polyneuropathy. Carbamazepine 400 mg 3 times
Low-dose gabapentin was introduced and gradually increased while carba
deficits slowly improved and in 1 month, the patient was able to walk with

4.5.AB Nystagmus

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Improves nystagmus (Averbuch-Heller et al, 1997) (Stahl et al, 1996)

3) Adult:

a) In a double-blind, crossover trial, gabapentin (up to 900 milligrams/day
baclofen (up to 30 milligrams/day) for acquired pendular nystagmus, howe
effective for downbeat nystagmus (Averbuch-Heller et al, 1997). In 15 pat
nystagmus, gabapentin significantly improved visual acuity and median ey
produced no significant change in visual acuity and only affected eye spe
patients with downbeat or torsional downbeat nystagmus, changes in me
less consistent with both drugs. In all 21 patients, gabapentin produced a
near visual acuity (p less than 0.05) and decrease in median eye speed (p
significant effect on visual acuity but did reduce median, vertical eye spee
b) In a pilot study, three patients with acquired forms of nystagmus exper
and improvement in vision with GABAPENTIN. In two of the patients, nyst
multiple sclerosis; the third patient experienced nystagmus following a bra
administered as a single 600-milligram dose which resulted in improveme
two of the patients who continued to take the drug, at doses of 900 to 150
improvement in vision was sustained after 5 weeks of treatment (Stahl et

4.5.AC Orthostatic tremor

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Improves orthostatic tremor symptoms in doses of 300 to 2400 milligrams Onofrj et al, 1998)

3) Adult:
a) In an open-label study of seven consecutive patients presenting with o doses of 300 to 1800 milligrams (mg) per day subjectively improved symp Patients were similarly diagnosed using strict clinical criteria and five patie with clonazepam, four without improvement. Subjectively, patients reporte to 80% (mean 73%). In one patient, gabapentin was added to clonazepan was 11 months and no patients had to discontinue therapy due to side eff included sedation, nausea, diplopia, unsteadiness, and constipation (Evid
b) Orthostatic tremor almost disappeared with gabapentin treatment in 3 1998). Patients were started on gabapentin 300 milligrams and increased increased to 2400 mg. Utilizing self-monitoring scales, tremor rating scale gabapentin was shown to improve tremor during the 1800 to 2400 mg trea (p less than 0.01).

4.5.AD Panic disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
GABAPENTIN was more effective in patients with greater illness severity, more efficacious than placebo (Pande et al, 2000)

3) Adult:
a) According to an 8-week, randomized, double-blind trial (n=103), impro disorder (DSM-IV) was not significantly greater comparing GABAPENTIN however, when study subjects were stratified for illness severity, the more receiving gabapentin showed significantly more improvement than those g Stratification divided patients according to scores on the Panic and Agora or more (n=53) versus scores of less than 20 (n=41). Of those with scores PAS-score reduction in gabapentin-treated subjects and a 4.88-point redu patients (p=0.04, least-squares mean change in scores). Women with scc likely to respond than men, regardless of treatment. Doses of gabapentin ranged from 600 to 3600 milligrams/day, and were increased as long as tl no limiting adverse effects were present. Side effects of gabapentin were dizziness; approximately 12% of gabapentin- and 4% of placebo-treated p adverse event. One serious event (an automobile accident) in a gabapent the investigator as unlikely to be medication-related (Pande et al, 2000).

4.5.AE Partial seizure

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Effective as monotherapy for partial seizures (Chadwick et al, 1998; Heilb 1997)

3) Adult:
a) In a randomized, double-blind clinical trial of 292 patients (12 years an partial seizures, gabapentin monotherapy at doses of 900 milligrams (mg) superior to gabapentin 300 mg per day and comparable in efficacy to ope per day. Patients were randomized to one of the three gabapentin regime for 24 weeks. The primary outcome of the study was the time to an exit ev tonic-clonic seizure, 3 simple or complex partial seizures, or status epilept significantly longer for patients receiving 900 mg or 1800 mg per day of ga mg per day gabapentin regimen (p=0.018; p=0.04, respectively). For the c

or withdrawal due to side effects, gabapentin 900 mg per day had the high
the 24 week evaluation. Dizziness, headache, and fatigue were the most
(Chadwick et al, 1998).
b) Gabapentin was effective as monotherapy for partial seizures in 23 of
a retrospective review (Heilbroner & Devinsky, 1997). Median duration of
months with a median dose of 1200 milligrams. During gabapentin therap
than 90% seizure reduction, 6 patients had a 50% to 89% reduction, 2 pa
reduction, 12 had no change and 1 had a 25% increase in seizures. Six o
in seizure frequency, had already experienced good seizure control and t
Specific seizure type did not predict response. Four patients discontinued
effects.

4) Pediatric:

a) In a case report concerning a 15-year-old female with focal epilepsy, g
three times daily was as effective and better tolerated than previous carba
caused allergic dermatologic reactions after successful treatment initially.
reduced from 600 mg/day to 200 mg/day for six months, at which point it
monotherapy was then continued, and the patient was seizure-free withou
months (Kindler, 1997).

4.5.AF Partial seizure, Refractory

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Ineffective as adjunctive therapy for refractory partial seizures (Korn-Merk

3) Pediatric:

a) Gabapentin showed little to no benefit in an open label trial in 52 childr
treated concomitantly with gabapentin 26 to 78 milligrams/kilogram (mg/k
other antiepileptic agent. Thirty four patients discontinued due to inadequa
increased seizure frequency while being treated with gabapentin, and 12
beginning of the trial but subsequently became tolerant to gabapentin anc
seizure control. Only 3 children continued to benefit from gabapentin thera
throughout the trial. Adverse events were minimal and most commonly inc
hyperactivity (Korn-Merker et al, 2000).

4.5.AG Partial seizure; Adjunct

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (3 to 12 years)
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Indicated as adjunctive therapy in the treatment of partial seizures wi
generalization in adults with epilepsy
Indicated for adjunctive therapy in the treatment of partial seizures wi
generalization for children over 12 years old and for adjunctive therap
seizures in children between 3 and 12 years old

3) Adult:

a) GENERAL INFORMATION: In open and controlled clinical studies, ad
oral doses of 900 to greater than 1600 milligrams daily has been effective
resistant partial epilepsy (simple partial seizures, complex partial seizures
seizures) (Baulac et al, 1998; Anon, 1998); (Hardin et al, 1998)(Sivenius e
Handforth et al, 1989; Bauer, 1987; Crawford et al, 1987b). With gabapen
reduction in the frequency of partial seizures by at least 50% has been re
(Sivenius et al, 1991b; Anon, 1990c). In studies investigating gabapentin
frequency has been halved in only 12% to 20% (Sivenius et al, 1991b; Cr
1200 to 2400 milligrams in patients with partial seizures refractory to othe
43% of patients reducing their seizure frequency by at least 50% (Leach,
studies are lacking, indirect analysis suggests that the efficacy of gabape
of valproic acid or vigabatrin as add-on therapy (Mumford, 1988; Gram, 1
al, 1987b).

b) Gabapentin was shown to be effective as add-on therapy in patients w

(Mayer et al, 1999). In this 26-week, open-label multicenter study, patients
partial seizures with or without secondary generalization (n=110) after pric
therapy were initiated on gabapentin, in addition to their existing AED regi
1200 milligrams/day (mg/day) within the first 5 days and was further titrate
2400 mg/day in increments of 400 mg after every second seizure for the f
frequency during the last 8 weeks of treatment was compared to that duri
59.7% of patients demonstrated a reduction in seizure frequency of 50% c
specific seizure types, simple partial seizures, complex partial seizures, a
clonic seizures, occurred in 63.3%, 60%, and 76.8% of patients, respectiv
reported in quality of life, and no correlation was found between trough pla
reduction in seizure frequency.

c) Gabapentin was shown to be effective as add-on therapy in patients w
(Mayer et al, 1999). In this 26-week, open-label multicenter study, patients
partial seizures with or without secondary generalization (n=110) after pric
therapy were initiated on gabapentin, in addition to their existing AED regi
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frequency during the last 8 weeks of treatment was compared to that duri
59.7% of patients demonstrated a reduction in seizure frequency of 50% c
specific seizure types, simple partial seizures, complex partial seizures, a
clonic seizures, occurred in 63.3%, 60%, and 76.8% of patients, respectiv
reported in quality of life, and no correlation was found between trough pla
reduction in seizure frequency.

d) In an open-label six-month observational study of 610 patients (mean
epilepsy, gabapentin add-on therapy (mean dose 1739 milligrams per day
50% or more in 34% of patients, with a median reduction of seizure freque
baseline seizure frequency of 7.2 per month and were taking 2.3 concomi
During the last 4- week evaluation period, 79 patients remained seizure fr
seizure-free patients at baseline. At six months, 57 patients (9.7%) had di
effects and 368 patients (62%) continued on gabapentin therapy. The mo
were somnolence, asthenia, and weight gain (Baulac et al, 1998).

e) A 20-week, open-label study of gabapentin add-on therapy (mean 160
patients with partial epilepsy reduced the combined frequency of complex
generalized seizures by half or more in 71% of patients (p=0.0001). Patie
eight or more complex partial seizures with or without secondarily general
months and taking stable doses of either carbamazepine, phenytoin, or b
improvements were also observed in the Quality of Life in Epilepsy (QOLI
Analysis by the type of seizure showed significant reductions only for com
Somnolence and dizziness were the most frequently reported side effects
discontinued therapy due to side effects prior to the end of the 20-week st

f) In a retrospective evaluation of 90 patients (7 months to 78 years) with
disorders, the addition of gabapentin therapy reduced seizure frequency i
gabapentin dose was found to be 1700 milligrams (mg) per day and 95%
drugs. The duration of treatment ranged from one to 14 months and gaba
patients due to side effects or lack of efficacy. The most frequently reporte
dizziness, headache, and weight gain (Hardin et al, 1998).

g) In one 14-week study, maximal reductions in partial seizure frequency
after 3 to 6 weeks of gabapentin therapy (600 to 1200 milligrams daily); af
in seizure frequency tended to be less (approximately 27%) (Anon, 1990c
tolerance development.

4) Pediatric:

a) The safety and efficacy of adjunctive gabapentin demonstrated in a 3-
controlled trial was sustained in an added 6-month open-label extension c
children 3 to 12 years of age with refractory partial seizures (n=237). Stud
as 24 to 70 milligrams/kilogram/day (initial dosing was 24 to 35 mg/kg/day
subjects were receiving sodium valproate or carbamazepine; other medic
lamotrigine, clobazam, phenytoin, or (rarely) phenobarbitone. Mean durat
154 days. For all partial seizures, 80 of 237 patients (34%) showed a posi
reduction in baseline partial seizure frequency (baseline as the period bef
177 patients with complex partial seizures, 103 (58%) were positive respo
generalized tonic-clonic seizures responded positively. Four patients were
label phase, while 42 patients had a 75% or greater reduction in seizure fr
phase, 12 patients (5%) experienced at least 1 episode of status epileptic
episodes (more than 4). Somnolence was the most commonly associated
Thirteen patients withdrew due to adverse effects; these effects included
lability, fatigue, ataxia, hyperkinesia, urinary incontinence, or confusion (A

4.5.AH Phantom limb syndrome

1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence favors e

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

In a randomized, double-blind, placebo-controlled, crossover clinical s gabapentin was more effective than placebo in alleviating postamputa weeks of therapy (Bone et al, 2002).

In a randomized, double-blind, placebo-controlled, crossover clinical s in patients with phantom limb pain and/or residual limb pain, gabaper measures of pain intensity compared to placebo (Smith et al, 2005).

There was no significant difference between gabapentin and placebo stump and phantom pain in a prospective, randomized, placebo-cont al, 2006).

Gabapentin reduced phantom limb pain in a case series of seven chil al, 2001).

3) Adult:

a) In a randomized, double-blind, placebo-controlled, crossover clinical st gabapentin was more effective than placebo in alleviating postamputation of therapy. Patients with established phantom limb pain for a minimum of amputation and a pain score of at least 40 millimeters (mm) on a 100-mm eligible for inclusion, and received 6 weeks of gabapentin therapy and 6 w 1-week washout interval followed the first period. Gabapentin was initiated with titration up to a maximum of 2400 mg daily in 3 divided doses. The pr pain intensity difference (PID) at the end of each treatment compared to b completed both arms of the study; analyses were performed using the inte least 1 dose of study drug). A large placebo effect was observed as there pain in weeks 2, 4, and 5 in the placebo group and in weeks 2, 3, and 5 in with baseline pain scores. Up to week 5 of the study, there was no signific scores between placebo and gabapentin. However, at week 6, there was receiving gabapentin at the end of the study period relative to placebo (VA p=0.025). There were no significant differences in the secondary outcome needed, sleep interference, HAD depression scale scores, and activities o (Bone et al, 2002).

b) In a randomized, double-blind, placebo-controlled, crossover clinical st in patients with phantom limb pain (PLP) and/or residual limb pain (RLP), affect measures of pain intensity compared to placebo. Patients with lowe months prior and an average pain score of at least 3 on a 0 to 10 numeric eligible for inclusion, and received 6 weeks of gabapentin therapy and 6 w random order; with a 5-week washout interval followed the first period. Ga milligrams (mg) on day 1 with titration up to a maximum of 3600 mg daily dose of 3600 mg was attained by 82% of patients during the first phase an second phase. The primary efficacy outcome was PLP (painful sensations amputated) and RLP (pain in the residual limb) measured using the NRS. differences observed in pre- to posttreatment pain intensity change scores versus placebo for any of the four types of pain intensity (average and wo RLP). There were also no significant differences noted for change scores depressive symptoms (CES-D), or pain interference (BPI) between the ga (Smith et al, 2005).

c) There was no significant difference between gabapentin and placebo i stump and phantom pain in a prospective, randomized, placebo-controlled required lower limb amputation due to peripheral vascular disease were e amputation of the foot or toes only were excluded. Eligible patients were r (n=21; age 70.8 +/- 11.9 years (yr); 52% male) or placebo (n=20; age 69.8 gabapentin arm received 300 milligrams (mg) orally on postoperative day mg on days 2 to 4, then by 300-mg increments every 2 days to a goal dos 13 to 30. Patients with a creatinine clearance (CrCl) between 30 and 60 m a maximum gabapentin dose of 1200 mg. Lower doses of gabapentin wer not tolerated; however, patients who received doses lower than 900 mg fo from the analysis. The study medication was provided in 3 divided doses days. The primary outcome was the incidence of phantom pain and the in pain on day 30. Intensity of pain was measured by a numeric scale of 0 to Questionnaire. The data analysis revealed no significant difference betwe incidence of phantom pain or in the intensity of stump and phantom pain.

phantom pain was 55% and 52.6% (risk difference, 2.4%; 95% CI, -28.9% gabapentin compared with placebo group, respectively. At day 30, the me was 1.5 (range, 0 to 9) and 1.2 (range, 0 to 6.6) in the gabapentin and pla (p=0.6). The corresponding median intensity of stump pain was 0.85 (rang 5.4), respectively (p=0.68). Common adverse effects, which were transier study medication were nausea, stomach ache, fatigue, confusion, nightma gabapentin (n=9) and placebo (n=8) groups. The author's note a study lim size (Nikolajsen et al, 2006).

4) Pediatric:

a) Gabapentin therapy provided successful control of phantom limb pain from 4 to 28 years of age. Within 2 months of beginning gabapentin, pain in 6 of 7 patients; in the seventh patient, pain was reduced to a tolerable l ranged from 14 to 40 milligrams/kilogram; commonly when the right dose occurred suddenly. Mean follow-up time with the cohort was 1.74 years. F taper the gabapentin, and had no recurrence of pain when the drug was t used gabapentin on an occasional basis when the phantom sensations w had reached almost complete resolution of phantom pain when his cance shortly thereafter. One patient who did not have resolution of pain reques Tapering was begun; when the dose had dropped from 800 to 600 mg thr a dramatic increase in phantom pain, and the dose was returned to 800 m receive maintenance doses of gabapentin, varying the dose between 800 There were minimal side effects with gabapentin therapy; 4 patients had r after several doses (Rusy et al, 2001).

4.5.AI Postherpetic neuralgia

FDA Labeled Indication

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Gabapentin is indicated for the management of postherpetic neuralgi NEURONTIN(R) oral tablets, oral capsules, oral solution, 2007).

In a randomized, double-blind, parallel-group, 9-week study (n=76) in neuralgia (PMH), gabapentin was as effective, but was tolerated bett compared to nortriptyline (Chandra et al, 2006).

Gabapentin treatment reduced the pain of postherpetic neuralgia, imp improved patients' quality of life in a randomized, double-blind, multic et al, 2001).

Two cases of acute herpetic neuralgia pain and 3 cases of postherpe responded to gabapentin therapy have been reported (Filadora et al,

Gabapentin was useful for postherpetic neuralgia and direct peripher chart review of pain patients receiving gabapentin for at least 30 days

3) Adult:

a) In a randomized, double-blind, parallel-group, 9-week study (n=76) in neuralgia (PMH), gabapentin was as effective, but was tolerated better wi nortriptyline. Adult PMH patients with a history of greater than 8 weeks of pain intensity of at least 40 millimeters (mm) on a 100 mm visual analog s randomization, and average pain score of at least 4 on the Likert scale du randomized after a 1-week run-in period to receive nortriptyline 25 milligra age 52.5 years; n=38) or gabapentin 300 mg orally three times daily (mea weeks. Doses were escalated based on tolerability and pain relief every 2 nortriptyline 50 mg three times daily and gabapentin 900 mg three times d pain score on the Likert scale was 5.8 +/- 1.4 and 5.6 +/- 1.1 in the nortrip respectively. VAS pain score was also comparable between treatment arr 5.3 +/- 1.3 and 4.8 +/- 1.2, respectively. Results of the study were based o population (n=70). For the primary efficacy outcome of change in pain sco baseline to study end, there was a 47.6% and 42.8% reduction in average and gabapentin groups, respectively, with 38.8% (n=14) and 38.2% (n=13 and gabapentin groups, respectively, showing improvement in their baseli than 50% improvement in baseline pain scores on the Likert scale was re patients, respectively, in the nortriptyline and gabapentin groups. For seco significant improvement in sleep scores (46% vs 52%, for nortriptyline and and Short Form McGill Pain Questionnaire (SF-MPQ) scores for pain were groups. Clinical effectiveness was improved (27.8% vs 23.8%, for nortript

respectively). Approximately two-thirds of patients in both groups moved t
in the categorical scale, and disability rating improved (41.5% vs 39.6%, f
respectively). The results of the primary and secondary outcomes, howev
significant differences between the 2 groups. In the nortriptyline group, 58
adverse events, with dry mouth (50%), constipation (22.2%), postural hyp
(16.7%) being the most common. Gabapentin was well tolerated with slee
(11.8%) adverse event reported (Chandra et al, 2006).

b) Gabapentin treatment reduced the pain of postherpetic neuralgia, impr
improved patients' quality of life. In a randomized, double-blind, multicente
underwent a week-long run-in period before beginning treatment with gab
(mg) per day or placebo. Gabapentin doses were started at 300 mg/day a
days. Dosing was stable at 1200 mg/day for days 4 to 7 and then titrated
doses were further titrated for patients randomized to 2400 mg/day. All do
continued for a total of 7 weeks of treatment. Pain relievers other than ace
acetaminophen/codeine were disallowed. Changes in pain scores from ba
significantly greater in the gabapentin groups (p less than 0.01). Reductio
the placebo group, 34.5% for gabapentin 1800 mg and 34.5% for gabape
scores were evident as early as one week after the start of treatment (whe
The proportion of patients experiencing more than a 50% reduction in pai
gabapentin 1800 mg and 2400 mg, respectively, and 14% with placebo. S
pattern similar to that of pain. Quality of life measures showed greater imp
with placebo. Gabapentin-treated patients experienced more adverse effe
The most common adverse events with gabapentin were dizziness and dr

c) Gabapentin reduced pain in patients with postherpetic neuralgia prese
healing of the rash. In a multicenter, double-blind study, patients received
over 4 weeks to the maximum tolerable dose (maximum dose 3600 milligr
After 8 weeks, the average pain score (11-point Likert scale) was significa
group (33.3%) versus placebo (7.7%; p less than 0.001). Mean scores for
Questionnaire also markedly improved for total pain (p less 0.001) and sp
sensory pain and affective pain (p less than 0.001). At the end of the stud
gabapentin categorized their pain as much or moderately improved versus
(Rowbotham et al, 1998).

d) Two cases of acute herpetic neuralgia pain and 3 cases of postherpeti
to gabapentin therapy were described. All occurred in the head and neck
unresponsive to narcotics, amitriptyline, acetaminophen, and ibuprofen. D
600 to 1800 milligrams (Filadora et al, 1999).

e) Gabapentin was useful for postherpetic neuralgia and direct peripheral
chart review of pain patients receiving gabapentin for at least 30 days. Th
was to rapidly increase gabapentin to 1600 milligrams/day and further incr
benefits were evident. Self-reported visual analog scales were reviewed.
score was observed in patients with neuropathic pain (p less than 0.0001)
0.04). No difference was seen for back pain. Further subgroup analysis sh
postherpetic neuralgia pain scores (53%, p less than 0.004) and diabetic
0.03). Patients with a greater than 75% decrease in pain score included 9
with postherpetic neuralgia (Rosenberg et al, 1997).

f) Gabapentin may be of benefit in the treatment of postherpetic neuralgia
woman whose pain was refractory to capsaicin, desipramine, and both pa
administered narcotic analgesics, therapy with gabapentin 300 milligrams
marked relief of symptoms (Segal & Rordorf, 1996).

4.5.AJ Postoperative pain

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Gabapentin reduced morphine consumption during the first 24 hours
however, it did not effect patient rated pain scores (Dierking et al, 200
Pre-incision or post-incision administration of gabapentin for open do
and rescue analgesic requirements (Pandey et al, 2005)

3) Adult:

a) Although pain scores did not differ, morphine consumption was reduce
abdominal hysterectomy in patients administered gabapentin. In a double
randomized to receive gabapentin or placebo. The study recruited 80 wor
subtotal abdominal hysterectomy with or without salpingo-oophorectomy.

patients were received 1200 milligrams (mg) of oral gabapentin or placebo or placebo 8, 16, and 24 hours after the initial dose. Morphine (0.15 mg/ki intravenously at wound closure. Postoperative pain was controlled using p morphine with a bolus dose of 2.5 mg and a 10 minute lock out period. If r administered additional morphine (2.5 mg) in the first postoperative hour. time 0 to 24 hours was a median 63 mg (interquartile range 53 to 88 mg) i 43 mg (interquartile range 28 to 60 mg) in the gabapentin arm (p less thar significant differences in reported adverse effects between the 2 arms (p g scores taken at time 2, 4, 22 and 24 hours were not significantly different inverse association between plasma levels of gabapentin at 2 hours and r was also reported (R(2)=0.24, p=0.008) (Dierking et al, 2004).

b) A double-blind, prospective, randomized, placebo-controlled study fou pre-incision or post-incision for open donor nephrectomy was superior to p using the visual analog scale (VAS) and rescue analgesic requirements. A open donor nephrectomy, were randomized into three groups: the pre-inc gabapentin 600 milligrams (mg) two hours before surgery and two placebo tube after surgical incision; the post-incision group (n=20) received two pla and gabapentin 600 mg through a nasogastric tube after surgical incision; received two placebo capsules before surgery and two placebo capsules surgical incision. Pain scores were recorded at rest using the VAS after ar care unit and at six hour intervals until 24 hours post-surgery. All patients controlled analgesia (PCA) pump (fentanyl 1 microgram/kilogram (mcg/kg interval of 5 minutes). The pre-incision and post-incision groups had signi time points compared to the placebo group (p less than 0.05). In addition, groups also used less fentanyl compared to the placebo group (563.3 +/- 924.7 +/- 417.5 mcg, respectively) (p less than 0.05). There were no differ group and the post-incision group in total fentanyl use and pain scores at 0.05 at all time points). Side effects were comparable in all study groups, the most commonly reported (Pandey et al, 2005).

4.5.AK Priapism

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Gabapentin was useful in the treatment of priapism in 3 cases (Perimenis

3) Adult:

a) Gabapentin was useful in the treatment of recurrent, refractory, idiopat patients. A case series reported the use of gabapentin in patients who hac episodes of priapism that was refractory to several oral treatments or alph etilephrine intracavernosal injections. Gabapentin was initiated at 400 mill Maintenance doses ranged from 900 to 2400 mg per day. Detumescence and 2 patients have not had a repeat episode for 16 to 24 months. The thi gabapentin after 6 months and had another priapism episode. He again re gabapentin and is currently maintained at 900 mg/day. He has not had an et al, 2004).

4.5.AL Pruritus

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:

Effective in case report of refractory brachioradial itching (Bueller et al, 19

3) Adult:

a) Gabapentin 300 milligrams (mg) six times daily was effective in elimina year-old woman with severe, refractory pruritus of the left forearm. Acupu antihistamines, and dietary modifications were all ineffective. Intramuscula for a short time, as were ice packs. An escalating gabapentin dose, startir increasing to 300 mg six times daily, eliminated the symptoms (Bueller et

4.5.AM Restless legs syndrome

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Results of a small study showed improvement of restless legs syndrome v
hemodialysis patients (Thorp et al, 2001)

3) Adult:
a) Oral GABAPENTIN therapy may improve symptoms of restless legs sy
based on a small double-blind, cross- over trial (n=16). Subjects were ran
gabapentin (300 milligrams administered 3 times weekly at the end of her
Following a 1-week washout period, subjects crossed over to the other th
criteria developed by the International Restless Legs Syndrome Study Gr
and after each treatment period. Mean baseline score on the questionnair
were 5.8 after placebo therapy compared with 3.0 after gabapentin therap
response to treatment as a score less than 6, there were 11 patients who
to placebo (p less than 0.01), 1 who responded to placebo and not to gab
both. Three subjects failed to complete the study; in 2 cases, somnolence
was the cause; a third participant died of myocardial infarction on placebo
2001).

4.5.AN Sensory disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Sensory deficits were ameliorated in 3 of 5 patients being treated with gab
(Chong et al, 2002)

3) Adult:
a) Of 5 patients with sensory deficits in addition to neuropathic pain, 3 ex
sensation while their neuropathies were being treated with gabapentin. Tv
diabetic neuropathy and one had neuropathic pain secondary to trigemina
gabapentin 400 to 600 milligrams 3 times per day, all 3 patients experienc
and/or area of neuropathic pain. In addition, sensation returned to areas p
unresponsive to temperature or touch (Chong et al, 2002).

4.5.AO Shortlasting, unilateral, neuralgiform pain with conjunctival injection

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
Improvement of symptoms in 1 case report (Graff-Radford, 2000)

3) Adult:
a) A 48-year-old man suffering from SUNCT SYNDROME (severe unilate
conjunctival injection and tearing, rhinorrhea, and subclinical sweating) fo
free when treated with oral GABAPENTIN. Symptoms included ocular, fac
left side; attacks consisted of burning, sharp, shooting pain with tearing ar
for 2 to 3 minutes and occurring up to 25 times a day. Under the direction
tried prednisone 60 milligrams (mg)/day for 4 weeks; the steroid relieved l
prednisone, his pain returned. He had also tried carbamazepine, verapam
dihydroergotamine, and indomethacin without benefit. Gabapentin was st
The patient experienced dramatic relief. Doses were increased to 600 mg
nearly complete pain relief. The patient had then moved to another area, a
syndrome when his gabapentin prescription ran out. On returning to the a
became pain-free at doses of 900 mg three times daily, and, with these m
be pain-free at 1 year. When he attempted to stop the gabapentin, his pai
2000).

4.5.AP Social phobia

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT
2) Summary:
Appears beneficial in the treatment of social phobia (Pande et al, 199
3) Adult:
a) Patients with social phobia appeared to benefit from gabapentin therap double-blind, 14-week study, patients randomly received either gabapenti (mg) twice daily (n=34) or placebo (n=35). During the first week the dose mg 3 times daily; thereafter, the dose could be increased in increments of maximum of 3600 mg/day. The gabapentin group improved significantly b the Liebowitz Social Anxiety Scale (LSAS) (p=0.008). Approximately 77% received doses of greater than 2100 mg/day. Also, patients over 35 years treatment effect than younger patients (p less than 0.05). LSAS scores pla 14. Dry mouth and dizziness were significantly more common in the gaba group (p=0.05).

4.5.AQ Spasticity
1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT
2) Summary:
Reduced spasticity in five patients with spinal cord injury (Priebe et al, 199
3) Adult:
a) Gabapentin 1200 milligrams three times daily clinically reduced spastic injury (Priebe et al, 1997). This result occurred during the open-label stud double-blind study of gabapentin 400 mg three times daily versus placebo not significantly improve spasticity. However, when patients were allowed higher dose, the patients reported improvement. A further control trial is w

4.5.AR Spinal muscular atrophy
1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT
2) Summary:
An open-label study suggests possible benefit in patients with type II or ty ATROPHY (Merlini et al, 2003)
3) Adult:
a) After 12 months of gabapentin therapy, there were modest improveme three-point pinch scores (calculated as an arm mega-score) and statistica knee flexion, knee extension and foot flexion (calculated as a leg mega-sc type III spinal muscular atrophy. In an open-label, non- placebo-controllec to receive either gabapentin (n=61) or no treatment (n=59) for 12 months. was 1590 milligrams divided twice daily. Arm mega-scores at 6 months w between the gabapentin and the non-treatment arms (5.77% versus 0% n baseline, p greater than 0.05). By 12 months, the median percent change baseline were 7.27% in the gabapentin group and 0% in the non-treatmer percent changes in leg mega-scores were 11.11% at 6 months and 12% a arm and 0% at 6 and 12 months for the non- treatment arm (p=0.02 and 0 use did not have any effect on forced vital capacity or most timed function

4.5.AS Tardive dyskinesia
1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT

2) Summary:
May have a role in the treatment of antipsychotic- induced tardive dyskine
3) Adult:
a) In an open-label, non-comparative study, gabapentin improved Abnorr (AIMS) scores in patients with antipsychotic-induced tardive dyskinesia. T at least 1 year (mean 5.2 years) and concomitant drug therapy was stable Gabapentin was initiated at 300 milligrams/day (mg/day), increased to 60(increased to 900 to 1200 mg/day by day 7. Patients were followed for 1 ye complete the study due to poor adherence (n=1), poor efficacy (n=1), and weight gain, dizziness, confusion, irritability and dysphoria were reported gabapentin. Mean AIMS scores showed statistically significant, time-relate decreased from 24.3 at baseline to 13.0 at 1 year (p less than 0.000). The improvement was 47.5% (range 14.3 to 72.4%). Larger clinical studies are effectiveness of gabapentin in this patient population (Hardoy et al, 2003)

4.5.AT Tinnitus
1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RAT
2) Summary:
In an 8-week, double-blind, randomized, placebo-controlled trial (n=1 between gabapentin and placebo in the relief of idiopathic tinnitus (Pi In a single-center, double-blind, randomized, placebo-controlled trial difference between gabapentin and placebo in the relief of moderate
See Drug Consult reference: DRUG THERAPY OF TINNITUS
3) Adult:
a) General Information
1) Gabapentin was ineffective in treating tinnitus based on reviewed al, 2007; Witsell et al, 2007; Bauer & Brozoski, 2006). According to 2 placebo-controlled trials involving nearly 200 patients with idiopathic t there was no statistically significant difference in the primary outcome Inventory score improvement between gabapentin therapy (at doses placebo. Furthermore, no difference in subjective perceived improver between treatment arms (Piccirillo et al, 2007; Witsell et al, 2007). Th symptomatic relief of tinnitus is questionable.
b) Clinical Trials
1) In an 8-week, double-blind, randomized, placebo-controlled trial (r between gabapentin and placebo in the relief of idiopathic tinnitus. Pa years (mean, 57 +/- 8.2 years), with a history of tinnitus for at least 6 Additionally, enrolled patients were required to have a Tinnitus Handi 0 to 100; higher score indicative of a more severe condition) of 38 or randomized to receive gabapentin at a maintenance dose of 900 to 3 or matching placebo (n=56) for 8 weeks. Gabapentin was initiated at doses daily for 1 week, followed by gradual dose titration in 900-mg v weeks until reaching a maximum daily dose of 3600 mg that was mai While 86% of the patients in the active treatment arm reached a dosa of the patients achieved a maintenance dosage of 2700 mg/day and Approximately 65% of the patients had history of tinnitus for 6 years c experienced bilateral tinnitus. The vast majority of the subjects also re disturbances. At baseline, approximately 50% of patients had THI sc scores were 49.53 +/- 17.85 and 51.77 +/- 18.03 in the gabapentin ar Based on the modified intent-to-treat analysis of 115 patients who ha study medication during the maintenance-dose period and provided a assessment, there was no statistical difference in the primary outcom improvement from baseline to study end point at week 8 between the (difference from baseline, 11.3 vs 11; between-group difference, 0.3; Furthermore, the between-group difference in the number of patients meaningful change in THI score (difference of 20 or greater from bas significant (gabapentin, 37% vs placebo, 32%; p=0.56). Statistically n gabapentin and placebo were not affected by age, sex, race, or histo efficacy outcomes, there were no significant between-group differenc bother and global improvement (Piccirillo et al, 2007).
2) In a single-center, double-blind, randomized, placebo-controlled tr significant difference between gabapentin and placebo in the relief of

range, 29 to 84 years; mean, 55 +/- 11 years), with a history of nonpu
tinnitus for at least 3 months of duration were randomized to receive
matching placebo (n=24) for 6 weeks. Gabapentin was initiated at 30
then 900 mg/day given in 3 divided doses daily for 1 week, followed b
mg/day that was maintained for an additional 2 weeks. During week 5
tapered to 900 mg and 300 mg per day, respectively. Efficacy was ev
month after the end of the study medication taper. The vast majority
of tinnitus for 6 months or longer, with 59% experiencing bilateral tinn
tinnitus symptoms of moderate or worse bother. The mean baseline
score (primary outcome measure) was 37.8 +/- 23 in the gabapentin
placebo arm (p not significant). While both groups reported a significa
end of week 4, there was no statistically significant difference in the c
gabapentin and placebo arm at corresponding intervals (p above 0.96
Total Mood Score change was noted between treatment arms (p abo
absence of hearing loss did not affect efficacy outcomes (Witsell et a

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amitriptyline

Baclofen

Lamotrigine

Lorazepam

Nortriptyline Hydrochloride

Propranolol

Ropinirole

Topiramate

4.6.A Amitriptyline

4.6.A.1 Diabetic peripheral neuropathy

a) There was no difference as measured by pain scales and global pain s
gabapentin in the treatment of diabetics with peripheral neuropathy pain (
patients with stable glycemic control (n=21) received either gabapentin or
were then crossed-over to the other arm of therapy for 6 weeks with a 1-w
Dosage was adjusted based on the patient's response with gabapentin do
milligrams (mean dose 1565 mg) and amitriptyline doses ranging from 25
Both drugs significantly decreased pain scores from baseline (both p less
provided moderate or greater pain relief in 67% of patients while gabapen
patients (p=0.26). There was no statistically significant difference in occur
the drugs except for increased weight gain with amitriptyline.

4.6.B Baclofen

4.6.B.1 Nystagmus

a) In a double-blind, cross-over trial, gabapentin (up to 900 milligrams/da
baclofen (up to 30 milligrams/day) for acquired pendular nystagmus, howe
effective for downbeat nystagmus (Averbuch-Heller et al, 1997). In 15 pat
nystagmus, gabapentin significantly improved visual acuity and median ey
produced no significant change in visual acuity and only affected eye spe
patients with downbeat or torsional downbeat nystagmus, changes in mec
less consistent with both drugs. In all 21 patients, gabapentin produced a
near visual acuity (p less than 0.05) and decrease in median eye speed (p
no significant effect on visual acuity but did reduce median, vertical eye sp

4.6.C Lamotrigine

4.6.C.1 Mood disorder

a) Preliminary results from a cross-over study (randomized, double- blind may be superior to GABAPENTIN, as well as placebo, for the improveme (n=31) (Frye et al, 2000). Study subjects included bipolar I (11), bipolar II the bipolar, 23 were rapid-cycling); all had tried other mood stabilizing age those who had responded by 6 weeks were 52% for lamotrigine, 26% for based on the Clinical Global Impression (CGI) scale modified for bipolar il gabapentin); responders were defined as those who were much or very m Both agents were well-tolerated. The one exception was a patient who de lamotrigine; the rash progressed to toxic epidermal necrolysis, requiring tr made a full recovery. A trend showed that subjects tended to lose weight weight gained on gabapentin. Lamotrigine was initiated at a dose of 25 mi titrated to 50 mg/day in week 2, 50 to 100 mg/day in week 3, 150 to 300 m 500 mg for weeks 5 to 6. Gabapentin was given at an initial daily dose of the end of week 1, 2700 mg by the end of the second week, 3600 mg by v 4800 mg by week 5 to 6. Mean daily doses as of week 6 were 274 mg for gabapentin.

4.6.C.2 Adverse Effects

a) In healthy volunteers, cognitive difficulties were associated with topirar lamotrigine had only minimal effects (Martin et al, 1999a). Healthy young receive topiramate 5.7 milligrams/kilogram (mg/kg), lamotrigine 7.1 mg/kg were titrated up over 4 weeks. Neurobehavioral performances were then and 4 weeks. For the visual serial addition test, the topiramate group mad week 2 (p less than 0.02) and during week 4 (p less than 0.004) than the On the symbol digits modalities test, the topiramate group performed poor gabapentin at week 2 (p less than 0.005) and worse than the lamotrigine 0.04). On memory tests at week 2 the topiramate group was worse than th 0.05). The lamotrigine group was below that of the gabapentin group but a week 4 the groups were similar. The topiramate group also reported more week 4 compared to the lamotrigine and gabapentin groups (p less than 0 hostility symptoms than the lamotrigine group at week 4 (p less than 0.02) should be evaluated.

4.6.D Lorazepam

4.6.D.1 Alcohol withdrawal syndrome

a) In a randomized, double-blind trial (n=100), high-dose gabapentin led Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) scores co outpatients with alcohol withdrawal. Patients with alcohol dependence and and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteri score of 26 or higher, and a CIWA-Ar score of 10 or greater who voluntee withdrawal received 4 days of gabapentin or lorazepam. One of the follow gabapentin were administered: 1) 200 milligrams (mg) 3 times daily for 3 day 4 (600 mg arm; n=16); 2) 300 mg 3 times daily for 3 days, then 300 m arm; n=28; mean age, 38.4 +/- 1.82 years (yr); mean drinks/day in previou or 3) 400 mg 3 times daily for 3 days, then 400 mg twice daily on day 4 (h 40.5 +/- 2.25 yr; mean drinks/day in previously 14 days, 16.8 +/- 2.18 drin was discontinued after one near syncopal event and 2 patient-reported se patients in this arm were not included in the final analysis. The lorazepam administered as 2 mg 3 times daily for 3 days, then 2 mg twice daily on da 1.83 yr; mean drinks/day in previously 14 days, 11.4 +/- 1.11 drinks). CIW daily during the medication phase and on 1, 2, and 7 days posttreatment received oral thiamine 100 mg daily for 12 days. Patients could take blind gabapentin or lorazepam as needed on days 1 to 4 to treat subjective syn there were no significant differences (p=0.75) in supplemental medication lorazepam-treated patients. The mean CIWA-Ar score was significantly lo arm but not the low-dose gabapentin arm compared with the lorazepam a (gabapentin: low-dose, 4.52 +/- 39 (standard error (SE)); high-dose, 3.14 0.38 (SE); high-dose gabapentin versus (vs) lorazepam p less than 0.05) (gabapentin: low-dose, 1.79 +/- 0.32 (SE); high-dose, 1.03 +/- 0.31 (SE); high-dose gabapentin vs lorazepam p less than 0.01). Mean alcohol cravi analog scale of zero millimeters (mm) (no discomfort) to 100 mm (greates less than 0.05) lower in patients who received gabapentin (gabapentin: lo dose, 28.73 +/- 4.6 (SE)) compared with lorazepam (42.7 +/- 4.7 (SE)) du however, alcohol craving scores were not significantly different between th phase (gabapentin: low-dose, 13.9 +/- 5.3 (SE); high-dose, 20.4 +/- 4.8 (S

Mean anxiety scores (evaluated using the Zung Anxiety Scale) were signi
patients who received gabapentin (gabapentin: low-dose, 32.11 +/- 1.74 (
(SE)) compared with lorazepam (36.98 +/- 1.5 (SE)) during the medicatio
score was significantly (p less than 0.01) improved in the high-dose gaba
gabapentin arm compared with lorazepam arm during the follow-up phase
1.3 (SE); high-dose, 28.8 +/- 1.2 (SE); lorazepam: 33.9 +/- 1.1 (SE)). Duri
in the low-dose gabapentin arm had significantly (p less than 0.01) improv
(BDI) scores and patients in the high-dose gabapentin arm had significant
sleep scores evaluated using the Epworth Sleepiness Scale compared wi
The incidence of patient-reported adverse effects did not differ between th
arms (p=0.74) (Myrick et al, 2009).

4.6.E Nortriptyline Hydrochloride

4.6.E.1 Postherpetic neuralgia

a) In a randomized, double-blind, parallel-group, 9-week study (n=76) in p
neuralgia (PMH), gabapentin was as effective, but was tolerated better wi
nortriptyline. Adult PMH patients with a history of greater than 8 weeks of
pain intensity of at least 40 millimeters (mm) on a 100 mm visual analog s
randomization, and average pain score of at least 4 on the Likert scale du
randomized after a 1-week run-in period to receive nortriptyline 25 milligra
age 52.5 years; n=38) or gabapentin 300 mg orally three times daily (mea
weeks. Doses were escalated based on tolerability and pain relief every 2
nortriptyline 50 mg three times daily and gabapentin 900 mg three times d
pain score on the Likert scale was 5.8 +/- 1.4 and 5.6 +/- 1.1 in the nortrip
respectively. VAS pain score was also comparable between treatment arr
5.3 +/- 1.3 and 4.8 +/- 1.2, respectively. Results of the study were based o
population (n=70). For the primary efficacy outcome of change in pain sco
baseline to study end, there was a 47.6% and 42.8% reduction in average
and gabapentin groups, respectively, with 38.8% (n=14) and 38.2% (n=13
and gabapentin groups, respectively, showing improvement in their baseli
than 50% improvement in baseline pain scores on the Likert scale was re
patients, respectively, in the nortriptyline and gabapentin groups. For seco
significant improvement in sleep scores (46% vs 52%, for nortriptyline and
and Short Form McGill Pain Questionnaire (SF-MPQ) scores for pain were
groups. Clinical effectiveness was improved (27.8% vs 23.8%, for nortripty
respectively). Approximately two-thirds of patients in both groups moved t
in the categorical scale, and disability rating improved (41.5% vs 39.6%, f
respectively). The results of the primary and secondary outcomes, howev
significant differences between the 2 groups. In the nortriptyline group, 58
adverse events, with dry mouth (50%), constipation (22.2%), postural hyp
(16.7%) being the most common. Gabapentin was well tolerated with slee
(11.8%) adverse event reported (Chandra et al, 2006).

4.6.F Propranolol

4.6.F.1 Essential tremor

a) In a comparative, double-blind, crossover, placebo-controlled study, ga
three times daily was as effective as propranolol 40 mg three times daily v
treatment of patients with essential tremor (Gironell et al, 1999). Patients
initially receive either gabapentin, propranolol, or placebo for a two-week
crossed-over to the other 2 arms with a 1-week washout period between t
with gabapentin and propranolol treatment were seen in the Tremor Clinic
clinical examination and motor task performance as compared to placebo
respectively). No differences in self-reported subjective disability scale or
from accelerometry were noted between the 3 groups.

4.6.G Ropinirole

4.6.G.1 Restless legs syndrome

a) Investigators of an open-label, pilot study did not find significant differe
efficacy of ropinirole and gabapentin for treatment of idiopathic restless le
randomized to receive either gabapentin 300 milligrams (mg) 2 hours befo
0.25 mg in the late afternoon and 2 hours before bedtime (n=8). Doses we
gabapentin and 0.25 mg for ropinirole until symptoms of restless leg synd
disappeared. After 4 weeks of therapy, mean gabapentin doses were 750
and mean ropinirole doses were 0.78 mg (range 0.25 to 1.5 mg). Polysom

number of periodic leg movements per hour of sleep time (PLMS index) h
arm from 39.2 times to 22.6 (p=0.012) and the number of arousals, due to
sleep, per hour of sleep time (PLMS arousal index) decreased from 6.7 to
efficiency, total sleep time, sleep latency and duration of slow wave sleep
the ropinirole arm, the PLMS index decreased from 48.4 to 13.2 times (p=
arousal index did not significantly change (8.6 versus 9.3, p=0.123). Unlik
the ropinirole arm had significant changes in their sleep architecture comp
sleep (p=0.007), less deep (p=0.001) and REM sleep (p=0.003), less tota
efficiency (p=0.01). Six to 10 months later, gabapentin patients were still o
900 mg per day). Of the 8 patients on ropinirole, only 3 were still on therap
experience sufficient relief and was switched to gabapentin and the other
take any medications. Mild and transient numbness, dizziness, sleepiness
with gabapentin use. Ropinirole was associated with nausea and sleepine
transient (Happe et al, 2003).

4.6.H Topiramate

1) Adverse Effects

a) In healthy volunteers, cognitive difficulties were associated with topirar
lamotrigine had only minimal effects (Martin et al, 1999). Healthy young a
receive topiramate 5.7 milligrams/kilogram (mg/kg), lamotrigine 7.1 mg/kg
were titrated up over 4 weeks. Neurobehavioral performances were then
and 4 weeks. For the visual serial addition test, the topiramate group mad
week 2 (p less than 0.02) and during week 4 (p less than 0.004) than the
On the symbol digits modalities test, the topiramate group performed poor
gabapentin at week 2 (p less than 0.005) and worse than the lamotrigine
0.04). On memory tests at week 2 the topiramate group was worse than th
0.05). The lamotrigine group was below that of the gabapentin group but a
week 4 the groups were similar. The topiramate group also reported more
week 4 compared to the lamotrigine and gabapentin groups (p less than 0
hostility symptoms than the lamotrigine group at week 4 (p less than 0.02)
should be evaluated.

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DRUGDEX® Evaluations

PIMOZIDE

0.0 Overview

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

2) Dosing Information
- **a)** Adult
  - **1)** Gilles de la Tourette's syndrome
    - **a)** initial, 1-2 mg a day ORALLY in divided doses; may increase dosage gradually every other day to a MAX dose of 10 mg/day or 0.2 mg/kg/day whichever is smaller
- **b)** Pediatric
  - **1)** Safety and effectiveness not established in children under age 12
    - **a)** Gilles de la Tourette's syndrome
      - **1)** initial, 0.05 mg/kg/day ORALLY preferably taken once at bedtime; the dosage may be increased every third day to a maximum of 0.2 mg/kg/day not to exceed 10 mg/day

3) Contraindications
- **a)** aggressive schizophrenics when sedation is required
- **b)** concurrent administration of pemoline, methylphenidate or amphetamines that may cause motor and phonic tics
- **c)** concurrent administration with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, and droperidol
- **d)** concurrent administration with sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, tacrolimus, ziprasidone, sertraline, and macrolide antibiotics
- **e)** concurrent administration with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects, and less potent inhibitors of CYP3A4 (zileuton, fluvoxamine)
- **f)** congenital or drug-induced long QT syndrome
- **g)** high doses (greater than 10 mg/day)
- **h)** history of cardiac arrhythmias
- **i)** hypersensitivity to pimozide
- **j)** Parkinson's disease
- **k)** patients with known hypokalemia or hypomagnesemia
- **l)** severe central nervous system depression
- **m)** simple tics or tics not associated with Tourette's syndrome

4) Serious Adverse Effects
- **a)** Agranulocytosis
- **b)** Cholestatic jaundice syndrome
- **c)** Death
- **d)** Disorder of hematopoietic structure
- **e)** Drug-induced lupus erythematosus, Systemic
- **f)** Ineffective thermoregulation, Heatstroke or hypothermia
- **g)** Leukopenia
- **h)** Neuroleptic malignant syndrome
- **i)** Obstipation
- **j)** Paralytic ileus
- **k)** Priapism
- **l)** Prolonged QT interval
- **m)** Seizure
- **n)** Thrombocytopenia
- **o)** Torsades de pointes

5) Clinical Applications
- **a)** FDA Approved Indications
  - **1)** Gilles de la Tourette's syndrome

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

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

B) Synonyms
Pimozide

C) Physicochemical Properties

1) Molecular Weight

a) 461.56 (Canada, 1997)

2) Solubility

a) Systemic: Less than 0.01 mg per mL in water (Prod Info Orap, 96).

1.2 Storage and Stability

A) Oral route

1) Store Orap(R) tablets at controlled room temperature, 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) (Prod Info Orap(R), 2003). Dispense in a light resistant container.

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

1.3.1 Normal Dosage

Chronic schizophrenia

Gilles de la Tourette's syndrome

1.3.1.A Chronic schizophrenia

1) SUMMARY

a) Usual daily oral doses range from 2 to 12 milligrams and doses up to 20 mg have been used. Moderate doses of neuroleptic drugs, defined as between 165 and 375 milligram equivalent of chlorpromazine, were preferred in the maintenance therapy of chronic psychosis in a meta-analysis of 22 randomized control trials (Bollini et al, 1994). The association between dose and clinical effectiveness and side effects was assessed. At doses greater than 375 milligram equivalent of chlorpromazine, there was no incremental clinical improvement seen, and adverse reactions occurred at a significantly higher rate.

2) Effective doses in chronic schizophrenia have been 2 to 12 milligrams daily (Kolivakis et al, 1974b; Cesarec et al, 1974); (Lapierre & Lavallee, 1975; Simms & Burnside, 1975)(Claghorn, 1974a; Gross, 1974b; DeSilva & Masheter, 1971; Janssen et al, 1972a). The optimal maintenance dose for patients previously maintained on other psychotic agents appears to be 6 mg daily (Pinder et al, 1976b). In all studies, lower doses are initiated (2 mg daily) and increased based upon clinical response.

3) Evidence from clinical studies suggest that pimozide may be more effective in the treatment of autistic patients with chronic schizophrenia and associated emotional withdrawal, delusions and hallucinations, as opposed to the agitated and aggressive patients (Janssen et al, 1972a; Pinder et al, 1976b).

4) There is no relationship between types of previous antipsychotic medications and response to pimozide (Pinder et al, 1976b).

5) Pimozide was equally effective in doses of 3 or 8 milligrams daily in the treatment of schizophrenia; however, extrapyramidal symptoms were significantly higher in patients taking 8 milligram doses. The author recommends initial doses of 3 milligrams daily (Fleischhauer, 1978).

1.3.1.B Gilles de la Tourette's syndrome

1) A slow and gradual introduction of pimozide is required to suppress tics; the dose should be carefully titrated to balance tic suppression with the untoward side effects of the drug. The manufacturer recommends initial doses of 1 to 2 milligrams/day in divided doses, increasing thereafter every other day; most patients are maintained effectively on doses of less than 0.2 milligram/kilogram/day, or 10 milligram/day, whichever is less. Doses of 0.2 milligram/kilogram/day or 10 milligrams/day should not be exceeded (Prod Info Orap (R), 2003).
2) Doses of 2 to 12 milligrams daily have been effective in GILLES DE LA TOURETTE SYNDROME (Ross & Moldofsky, 1978b).

1.3.1.C IMPORTANT NOTE
1) Sudden, unexpected deaths have occurred in patients receiving HIGH DOSES of Orap(R), ie, doses greater than 10 milligrams (Mulcahy, 1999).

1.3.1.D SINGLE DAILY DOSE
1) Due to the long half-life of pimozide, the drug may be administered once daily (Pinder et al, 1976b). Other reports have indicated that 4 times the initial single daily dose was effective when administered weekly in chronic schizophrenia (once weekly to a maximum of 60 milligrams). In one study, the average dose of pimozide weekly was 40 milligrams (range, 10 to 60 milligrams) (McCreadie et al, 1982b).

1.3.2 Dosage in Renal Failure
A) Reductions in dose do not appear necessary in renal failure due to the small amount of pimozide excreted unchanged in the urine (less than 1% unchanged drug) (Baro et al, 1972a).

1.3.3 Dosage in Hepatic Insufficiency
A) Reductions in dose should be considered in severe hepatic insufficiency since a large portion of the drug is metabolized in the liver (Baro et al, 1972a).

1.3.4 Dosage in Geriatric Patients
A) An initial dosage of 1 milligram/day is recommended in geriatric patients (Semla et al, 1997).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

1.4.1 Normal Dosage

Oral route

Gilles de la Tourette's syndrome

1.4.1.A Oral route
1) Doses of 1 to 2 milligrams daily have been effective in the treatment of schizophrenic and behavioral symptoms in children age 9 to 14 years (Pangalila-Ratulangi, 1973). Other data indicate the efficacy of 1 to 3 milligrams pimozide daily in adolescents 13 to 20 years of age with childhood or juvenile schizophrenia (LeVann, 1971).

1.4.1.B Gilles de la Tourette's syndrome
1) The manufacturer recommends an initial dose of 0.05 milligram/kilogram taken at bedtime. Every third day the dose may be increased to a maximum of 0.2 mg/kg but should not exceed 10 mg/day. Dose-response data concerning the effects of pimozide on tic manifestations in children younger than 12 years are unavailable (Prod Info Orap(R), 2003).
2) PIMOZIDE had a similar safety profile in 36 children ages 2 to 12 years as it did in older patients, according to a 24-week open label study. Thus, there are no safety findings that would preclude its use in pediatric patients 2 to 12 years of age. However, the manufacturer does not recommend its use in pediatric patients for any condition other than Tourette's syndrome as the drug has not been evaluated in other childhood disorders (Prod Info Orap(R), 2003).
3) Others recommend starting doses in both adults and children of 1 milligram pimozide at bedtime, with dose increases of 1 milligram every 5 to 7 days until symptoms are observed to decrease by at least 70%, or adverse effects occur without symptomatic benefit (or if symptoms decrease and adverse effects occur at the same time). If toxicity interferes slightly with functioning, dose reductions of 1 milligram weekly are suggested. If toxicity is severe, the dose should be reduced by one half immediately; titration should be

reinstituted at intervals ranging from 7 to 30 days after disappearance of severe adverse effects (Shapiro et al, 1987).

1.4.1.C IMPORTANT NOTE

1) Sudden, unexpected deaths have occurred in patients receiving HIGH DOSES of Orap(R), ie, doses greater than 10 milligrams (Mulcahy, 1999).

1.4.2 Dosage in Renal Failure

A) Reductions in dose do not appear necessary in renal failure due to the small amount of pimozide excreted unchanged in the urine (less than 1% unchanged drug) (Baro et al, 1972a).

1.4.3 Dosage in Hepatic Insufficiency

A) Reductions in dose should be considered in severe hepatic insufficiency since a large portion of the drug is metabolized in the liver (Baro et al, 1972a).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Peak Response

a) Schizophrenia: 1 to 3 weeks (Fleischhauer, 1978a); (Chouinard, 1970).

B) Duration

1) Single Dose

a) Schizophrenia, oral: 24 to 48 hours (Pinder et al, 1976a).

2.2 Drug Concentration Levels

A) Time to Peak Concentration

1) Oral: 6 to 8 hours (Prod Info Orap(R), 2003a; McCreadie et al, 1979; Baro et al, 1972).

a) Peak plasma levels following single 6 mg and 24 mg doses were 4 ng/mL and 16 ng/mL at 6 hours, respectively (McCreadie et al, 1979).

b) Following multiple doses of 6 mg once daily for 4 days, peak plasma concentrations were 4, 5, 8, and 10 ng/mL on each successive day (McCreadie et al, 1979).

c) Following a single 2 mg oral dose of pimozide in children with Tourette's syndrome, peak plasma concentrations of 7.2 ng/mL were achieved in approximately 7 hours (Sallee et al, 1987).

2.3 ADME

Absorption

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) More than 50% (Prod Info Orap(R), 2003a).

a) More than 50% of an oral dose of pimozide is absorbed and the drug undergoes significant hepatic first- pass metabolism (Prod Info Orap(R), 2003a).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver: Eextensive (Prod Info Orap(R), 2003a; Pinder et al, 1976a; Baro et al, 1972).

a) Metabolized via N-dealkylation (Prod Info Orap(R), 2003a; Pinder et al, 1976a; Baro et al, 1972).

b) PIMOZIDE is metabolized at least in part by cytochrome P450 IIIA (CYP3A) isoenzymes. Significant drug interactions may occur if pimozide is co-administered with drugs that inhibit CYP3A enzymes, ie,

macrolides (clarithromycin, erythromycin, dirithromycin, troleandomycin), azole antifungals (ketoconazole, itraconazole), protease inhibitors (ritonavir, saquinavir, indinavir, nelfinavir), nefazodone, and zileuton. Pimozide may also be metabolized by CYP1A2 isoenzymes and a theoretical potential exists for drug interactions between pimozide and drugs which inhibit CYP1A2 (Prod Info Orap(R), 2003a; Mulcahy, 1999).

B) Metabolites
1) 4, 4-bis-(4-fluorophenyl) butyric acid, (Prod Info Orap(R), 2003a; Baro et al, 1972).
2) 1-(4-piperidyl)-2-benzimidazolinone, (Prod Info Orap(R), 2003a; Baro et al, 1972).

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
a) 38% to 45% (Pinder et al, 1976a; Baro et al, 1972).
2) Excreted drug is 1% unchanged drug and two-thirds the 4-bis-(4-fluorophenyl) butyric acid metabolite (Baro et al, 1972).
3) Renal excretion is the major route of elimination of pimozide and its metabolites (Prod Info Orap(R), 2003a).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 53 to 55 hours (Prod Info Orap(R), 2003a; McCreadie et al, 1979).
1) An elimination half-life of 66 hours was reported in children with Tourette's syndrome following a single 2 mg oral dose (Sallee et al, 1987).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.1 Contraindications
A) aggressive schizophrenics when sedation is required
B) concurrent administration of pemoline, methylphenidate or amphetamines that may cause motor and phonic tics
C) concurrent administration with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, and droperidol
D) concurrent administration with sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, tacrolimus, ziprasidone, sertraline, and macrolide antibiotics
E) concurrent administration with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects, and less potent inhibitors of CYP3A4 (zileuton, fluvoxamine)
F) congenital or drug-induced long QT syndrome
G) high doses (greater than 10 mg/day)
H) history of cardiac arrhythmias
I) hypersensitivity to pimozide
J) Parkinson's disease
K) patients with known hypokalemia or hypomagnesemia
L) severe central nervous system depression
M) simple tics or tics not associated with Tourette's syndrome

3.2 Precautions
A) elderly patients with dementia-related psychosis (unapproved use); increased risk of death reported with both conventional and atypical antipsychotics when used to treat behavorial and psychological symptoms associated with dementia (US Food and Drug Administration, 2008)
B) concomitant administration with inhibitors of cytochrome P450 IA2 (CYP1A2) and CYP 3A4 enzymes
C) concomitant use of CNS depressants (exaggerated depression)
D) concomitant use of fluoxetine and pimozide may cause bradycardia
E) elderly patients (increased sensitivity)

F) epileptic patients (may exacerbate seizures)
G) grapefruit juice consumption
H) history of neuroleptic malignant syndrome, tardive dyskinesia
I) impaired liver or kidney function

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hepatic Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Other

3.3.1 Cardiovascular Effects

Cardiovascular finding

Dead - sudden death

Hypotension

3.3.1.A Cardiovascular finding

1) Sudden cardiac death, prolongation of the QT interval with possible ventricular arrhythmias, and hypotension are described with the administration of pimozide.

3.3.1.B Dead - sudden death

1) Summary

a) Sudden death is described with administration of pimozide. The mechanism may be due to PROLONGED QT INTERVAL and the development of VENTRICULAR ARRHYTHMIAS (Prod Info Orap(R), 2003; Fulop et al, 1987; Anon, 1985; Pinder et al, 1976; Huber et al, 1971).

2) LITERATURE REPORTS

a) During experimental studies of pimozide for conditions other than Tourette's syndrome, sudden, unexpected deaths occurred. Pimozide dosages were approximately 1 milligram/kilogram (mg/kg). It is speculated that prolongation of the QT interval predisposed patients to ventricular arrhythmia. The manufacturer recommends performing an electrocardiogram (ECG) before initiation of pimozide therapy and periodically thereafter, especially during periods of dose adjustment (Prod Info Orap(R), 2003).

b) Electrocardiogram (ECG) changes seen during clinical trials in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R), 2003).

c) The manufacturer of pimozide has reported sudden, unexpected deaths in some patients taking doses greater than 10 milligrams (mg). Deaths are due to ventricular dysrhythmia probably as a result of prolongation of the QT interval. Drug interactions with drugs inhibiting metabolism of pimozide and

resulting in increased plasma concentrations could result in QT prolongation (Anon, 1999).
d) An association with sudden death in schizophrenic patients has been postulated from doses in the 1 milligram/kilogram (mg/kg) range. The mechanism may be from prolongation of the QT interval (Anon, 1985; Fulop et al, 1987).
e) About 25% of patients taking therapeutic dosages of pimozide have prolonged QT intervals similar to those caused by the phenothiazines (Anon, 1985).
f) Most studies have reported no significant effect of pimozide therapy, in high or low doses, on the electrocardiogram (Pinder et al, 1976).
g) One report of T WAVE CHANGES on electrocardiogram has been reported with pimozide therapy; however, a definite cause/effect relationship was not established (Huber et al, 1971).

3.3.1.C Hypotension
1) Summary
a) Isolated reports of hypotension have been reported during treatment with pimozide (Pinder et al, 1976; Arfwidsson et al, 1971; Chouinard et al, 1970a).

3.3.2 Dermatologic Effects

Acne

Dermatological finding

Facial edema

Rash

3.3.2.A Acne
1) Summary
a) CASE REPORT - One case of ACNE VULGARIS has been reported possibly in association with pimozide administration (Chouinard et al, 1970a).

3.3.2.B Dermatological finding
1) Skin rashes, acne, and facial edema are described with the administration of pimozide.

3.3.2.C Facial edema
1) Summary
a) Facial edema has been reported with administration of pimozide (Morris et al, 1970a).

3.3.2.D Rash
1) Summary
a) ERYTHEMATOUS SKIN RASHES occurred infrequently during pimozide administration (Pinder et al, 1976).

3.3.3 Endocrine/Metabolic Effects

Hyperprolactinemia

Hyponatremia

Weight gain

Weight loss

3.3.3.A Hyperprolactinemia
1) Overview
a) Antipsychotic-induced hyperprolactinemia was reported in 65.6%, 45.1%, and 42.4% of women of childbearing potential, postmenopausal women, and men, respectively, in an open-label, clinical trial of patients treated with first-generation antipsychotics or risperidone at average doses of 4.2 to 5.2 mg/day. Compared to baseline, prolactin levels were significantly elevated (p less than 0.05) following use of first-generation antipsychotics (ie, chlorpromazine, droperidol, flupenthixol, fluphenazine, haloperidol, paliperidone, perazine, perphenazine, pimozide, trifluoperazine, and zuclopenthixol) or

risperidone in several clinical trials of patients with schizophrenia. Younger patients and women of childbearing potential have a greater risk for hyperprolactinemia following treatment with higher doses of these antipsychotics. Hyperprolactinemia may potentially result in menstrual disturbances, sexual dysfunction, bone mineral density (ie, osteopenia and osteoporosis), and breast and pituitary tumors (Bostwick et al, 2009).

2) Hyperprolactinemia has been reported with antipsychotic drugs; the elevation in prolactin persists during chronic administration (Prod Info Orapred(R), 2004). Pimozide is associated with increased serum prolactin (Delitala, 1977).

3) The effect of pimozide on hypothalamo-pituitary functions was studied in 13 children with behavior disorders. Pimozide was associated with an increase in serum prolactin levels. No significant influence on growth hormone or cortisol secretion was induced by hypoglycemia. Serum thyroxine and triiodothyronine were not influenced by pimozide (Suwa et al, 1984).

a) Management

1) Appropriate drug selection, monitoring and management are all important when prescribing antipsychotics that have the potential for inducing hyperprolactinemia. Prior to treatment with an antipsychotic, question patients regarding changes in libido or galactorrhea. Female patients should be assessed for menstrual abnormalities and male patients, for erectile or ejaculatory dysfunction. In the event that any of these symptoms are present, consider obtaining baseline prolactin levels. Patients should be informed of the potential for sexual dysfunction with antipsychotic use. Several weeks after an antipsychotic is initiated, obtain a prolactin level measurement. In cases where the patient experiences troublesome adverse effects related to elevated prolactin levels and discontinuing the antipsychotic is not an option, treatment with a dopamine agonist (eg, bromocriptine or cabergoline) should be considered (Bostwick et al, 2009).

3.3.3.B Hyponatremia

1) Hyponatremia has been reported during post-marketing use of pimozide; causality cannot be established (Prod Info Orapred(R), 2004).

3.3.3.C Weight gain

1) Weight gain has been reported in patients treated with pimozide for conditions other than Tourette's disorder (Prod Info Orapred(R), 2004).

3.3.3.D Weight loss

1) Weight loss has been reported in patients treated with pimozide for conditions other than Tourette's disorder (Prod Info Orapred(R), 2004).

3.3.4 Gastrointestinal Effects

Gastrointestinal tract finding

Loss of appetite

3.3.4.A Gastrointestinal tract finding

1) Summary

a) Pimozide has infrequently been associated with gastrointestinal side effects including anorexia, NAUSEA, ABDOMINAL PAIN, DIARRHEA, and CONSTIPATION (Kline et al, 1977a; Pinder et al, 1976; Singh, 1971).

2) Nausea, abdominal pain, diarrhea, constipation, and anorexia are associated with the administration of pimozide.

3.3.4.B Loss of appetite

1) Summary

a) Significant weight loss (average 5.4 kilograms) was reported in all patients receiving pimozide for maintenance treatment of chronic schizophrenia (McCreadie et al, 1982a).

3.3.6 Hepatic Effects

3.3.6.A Hepatotoxicity

1) Transient increases in alkaline phosphatase have occurred during pimozide treatment; however, a cause/effect relationship has not been established. No cases of hepatic damage have been reported (Huber et al, 1971).

3.3.9 Neurologic Effects

Extrapyramidal disease

Neuroleptic malignant syndrome

Neurological finding

Parkinsonism

Seizure

3.3.9.A Extrapyramidal disease

1) Summary

a) Extrapyramidal reactions to pimozide are the most frequent side effects of the drug, primarily TARDIVE DYSKINESIA, AKATHISIA, DYSTONIC REACTIONS, TREMORS and PARKINSONIAN SYMPTOMS, occurring in up to 15% of patients treated. Extrapyramidal reactions are generally dose-related in most patients and have been reversed by dose reduction in the majority (Prod Info Orap(R), 2003; Pinder et al, 1976).

2) LITERATURE REPORTS

a) Tardive dyskinesia (TD) due to pimozide seems to be rare, occurring in some patients on long-term therapy or after drug therapy has been discontinued. The risk may be greater for elderly patients on high-dose therapy (Prod Info Orap(R), 2003).

b) A 6-year-old autistic boy developed repeated episodes of ACUTE DYSTONIC REACTION while receiving pimozide and subsequently thioridazine. Acute dystonic reactions occur within the first few days of neuroleptic administration and they are well controlled with diphenhydramine in children (Ernst et al, 1993).

c) Tardive dyskinesia appeared in a 17-year-old boy following withdrawal from a combination of pimozide and thioridazine. The CHOREODYSKINETIC MOVEMENT of the limbs and the trunk cleared with anticholinergic drugs but were dramatically worsened by dopaminergic receptor blockers (Monteiro, 1985).

d) A case is reported of a 16-year-old female treated with pimozide 4 milligrams/day (mg/day) for 1 day, the dose increased to 6 mg/day for 1 day. She developed neck stiffness and OCULOGYRIC CRISIS, which resolved with benztropine 2 milligrams intramuscularly. The dose was reduced to 4 milligrams/day (mg/day) on day 3 but later in the day she suffered a tonic-clonic seizure. Pimozide was discontinued and no further seizures occurred (Larkin, 1983).

e) Some evidence indicates that pimozide exerts more prolific extrapyramidal effects than haloperidol (Haas & Beckmann, 1982a).

f) Extrapyramidal reactions respond readily to anticholinergic agents. Tardive dyskinesia was reported in 35% of patients receiving pimozide in one study (McCreadie et al, 1982a).

g) Pimozide has been mentioned as the causal agent in tardive dyskinesia (TD) in one review (Burke et al, 1982).

h) A single case of a 50-year-old alcoholic with late onset extrapyramidal side effects thought related to pimozide and alcohol withdrawal or alcohol intake was reported (Freed, 1982).

i) A severe dystonic reaction requiring discontinuance of pimozide and treatment with benztropine and diazepam was reported in a patient taking 4 milligrams/day for approximately 6 weeks (Logan et al, 1982).

j) Sixteen patients were given pimozide doses up to 60 milligrams/day for 28 days with few side effects. Most notable were mild extrapyramidal effects (tremors and PERIORAL DYSKINESIAS) which responded to antiparkinsonian medication. Side effects were never prominent enough to require discontinuance of therapy (Shopin & Selzer, 1977).

k) Extrapyramidal effects may occur with therapeutic use. Extrapyramidal effects appeared only in the pimozide group in a placebo-controlled trial (Huber et al, 1971).

3.3.9.B Neuroleptic malignant syndrome

1) Summary

a) Neuroleptic malignant syndrome has been reported after pimozide administration (Prod Info Orap (R), 2003).

2) Incidence: rare

3.3.9.C Neurological finding

1) Summary

a) AKATHISIA, SEDATION, and DROWSINESS, are described with the administration of pimozide (Prod Info Orap(R), 2003; Bloch et al, 1997; Kenway, 1973; Pinder et al, 1976; Singh, 1971; Kenway, 1973; Chouinard et al, 1970a).

2) Excitement, insomnia, sedation, tinnitus, headache, extrapyramidal effects, dystonic reactions and seizures are described with the administration of pimozide.

3) LITERATURE REPORTS

a) Drowsiness was reported in one 35-year-old patient receiving pimozide (Kenway, 1973).

b) Infrequently, pimozide has been associated with excitement, insomnia, anxiety, agitation, tinnitus, and headache (Pinder et al, 1976; Singh, 1971; Kenway, 1973; Chouinard et al, 1970a).

3.3.9.D Parkinsonism

1) Summary

a) Contrary to common belief, the results of a retrospective cohort study suggest that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

2) LITERATURE REPORTS

a) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar risk for the development of parkinsonism as does typical antipsychotic therapy. In a population-based, retrospective cohort study, adults (aged 66 years and older) with evidence of dementia were followed for up to 1 year for the development of parkinsonism symptoms associated with typical or atypical antipsychotic use. As compared with older adults receiving atypical antipsychotic therapy (ie, olanzapine, risperidone, quetiapine), incident parkinsonism was 30% more likely to occur in those taking typical antipsychotics (ie, chlorpromazine, haloperidol, perphenazine) (adjusted HR, 1.3; 95% CI, 1.04 to 1.58), and 60% less likely to occur in patient who did not receive either therapy (HR, 0.4; 95% CI, 0.29 to 0.43). Older adults using higher potency typical antipsychotics had almost a 50% greater risk of experiencing parkinsonism as compared with patients prescribed atypical antipsychotics (all were considered lower potency) (HR, 1.44; 95% CI, 1.13 to 1.84); however, in patients receiving lower potency typical antipsychotics, the risk of developing parkinsonism was no different from that in adults taking atypical antipsychotics (HR, 0.75; 95% CI. 0.48 to 1.15). In addition, a positive dose-related relationship was observed between the occurrence of incident parkinsonism and the use of atypical antipsychotics. The risk for developing parkinsonism was more than twice as great in patients using a high-dose atypical antipsychotic agent as compared with those prescribed a low-dose atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patients taking a typical antipsychotic were found to have a similar risk for the development of parkinsonism as patients receiving high-dose atypical antipsychotic therapy (p=ns). The authors conclude that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

3.3.9.E Seizure

1) Summary

a) Seizures are described with the administration of pimozide (Larkin, 1983; Burkitt & Faulkner, 1972; Pinder et al, 1976; Morris et al, 1970a).

2) Incidence: rare

3) LITERATURE REPORTS

a) A case report described a GRAND MAL SEIZURE in a 16-year-old girl during treatment of anorexia nervosa with pimozide. The seizure occurred after receiving 4 to 6 milligrams/day for 3 days. On the second day of treatment, the patient developed an oculogyric crisis which responded to benztropine (Larkin, 1983).

b) Pimozide may lower the seizure threshold in both epileptic and non-epileptic patients (Pinder et al, 1976).

c) Seizure activity has been reported during pimozide therapy. It is unclear if pimozide possesses epileptogenic potential, but the drug should be used cautiously in epileptic patients (Burkitt & Faulkner, 1972).

d) Seizures are described in three patients with no prior history of seizures and no exposure to epileptogenic drugs. All had been given pimozide and all had the dosage reduced or stopped prior to the seizures. The interval between the dosage change and the onset of seizures was 13 to 31 days. The dose given was not stated (Burkitt & Faulkner, 1972).

e) 13.3% (n=30) of patients given pimozide developed slight tremor and two of these had slight rigidity on doses increasing to 9 milligrams per day (Morris et al, 1970a).

3.3.10 Ophthalmic Effects

Blurred vision

Edema of eyelid

Eye / vision finding

Pupillary paralysis

Retinal pigment deposits

3.3.10.A Blurred vision

1) Summary

a) Blurred vision has occurred infrequently with pimozide therapy (Piyakulmala et al, 1977; Kline et al, 1977a).

3.3.10.B Edema of eyelid

1) Summary

a) Blurred vision has occurred infrequently with pimozide therapy (Piyakulmala et al, 1977; Kline et al, 1977a).

3.3.10.C Eye / vision finding

1) Blurred vision, edema of the eyelids (blepharedema), pupillary paralysis, OCULOGYRIC CRISIS, and retinal pigmentation are described with the administration of pimozide (Sharma et al, 1974).

3.3.10.D Pupillary paralysis

1) Summary

a) Pupillary paralysis was reported in a 24-year-old female following several weeks of therapy with pimozide 6 to 8 milligrams daily for schizophrenia (Crawford, 1971).

2) LITERATURE REPORTS

a) A patient developed parkinsonian tremor of the hands and legs and poor visual acuity followed by paralysis of the ciliary muscle of the eyes with fixed dilated pupils and paralysis of accommodation after pimozide administration. Benztropine 2 milligrams three times a day was administered resulting in alleviation of parkinsonian symptoms. The dose of pimozide was reduced to 2 milligrams daily and orphenadrine 50 milligrams (mg) three times a day was substituted for benztropine. Pupillary response gradually returned to normal over a period of 2 weeks (Crawford, 1971).

3.3.10.E Retinal pigment deposits

1) Summary

a) CASE REPORT - A single case of retinal pigmentation was reported in a patient on long-term fluphenazine who also received pimozide and haloperidol (McQueen, 1983). Other authors indicated no changes in ocular pigmentation with pimozide use as noted by slit-lamp examination (Pinder et al, 1976).

3.3.12 Psychiatric Effects

3.3.12.A Psychiatric sign or symptom

1) Summary

a) DEPRESSION, PHOBIAS and ANXIETY are described with the administration of pimozide (Prod Info Orap(R), 2003; Bloch et al, 1997; Kenway, 1973; Pinder et al, 1976; Singh, 1971; Kenway, 1973; Chouinard et al, 1970a).

2) Depression, anxiety, agitation and phobias are described with the administration of pimozide.

3) LITERATURE REPORTS

a) Four of 7 men being treated for stuttering with pimozide developed depression as measured on the Beck Depression Inventory (Bloch et al, 1997). Pimozide was started at 2 milligrams (mg)/day and increased, as tolerated, to 10 milligrams (mg). Three subjects became euthymic at 7 to 15 days after discontinuation. One subject was successfully treated with an antidepressant. Also, of these 4 subjects, 1 developed akathisia and 3 developed mild parkinsonian symptoms.

b) One of the main advantages of pimozide over other neuroleptics is its low propensity to produce sedation and drowsiness. Very few clinical studies have reported sedation as a significant side effect. Infrequently, pimozide has been associated with excitement, insomnia, anxiety, agitation, tinnitus, and headache (Pinder et al, 1976; Singh, 1971; Kenway, 1973; Chouinard et al, 1970a).

c) SCHOOL PHOBIA induced by pimozide was reported in an 11- year-old boy being treated for Tourette syndrome. This type of pimozide-induced SEPARATION ANXIETY may be unique to patients with Tourette syndrome (Linet, 1985).

d) Several patients developed dose-related dysphoria or depression with administration of pimozide (Bruun, 1988). In every case a "threshold dose" could be identified above which the patient complained of dysphoria.

e) Depression, and dysphoria are described as frequent adverse effects of pimozide (Shapiro et al, 1983).

3.3.13 Renal Effects

Nocturnal enuresis

Urinary incontinence

Urogenital finding

3.3.13.A Nocturnal enuresis

1) Summary

a) CASE REPORT - Nocturnal enuresis has been reported in one patient (9-year-old male) with Gilles de la Tourette syndrome during the 18 months of treatment with pimozide 1 to 4 milligrams at bedtime (specific onset not described). Enuresis was controlled by administering pimozide as a single dose in the morning instead of the evening (Shapiro, 1981).

3.3.13.B Urinary incontinence

1) Summary

a) CASE REPORT ? Shapiro reported on a 9 year old with Tourette's syndrome treated with pimozide (3 milligrams at night) and methylphenidate (5 milligrams twice daily) for 1 1/2 years. Although the child had a history of night time enuresis prior to using the drug, when given the drug at bedtime control was lost. Methylphenidate was discontinued without effect on enuresis. When pimozide was stopped or when given in the morning, night time enuresis did not occur (Shapiro, 1981).

3.3.13.C Urogenital finding

1) Nocturnal enuresis, urinary incontinence, and sexual dysfunction are described with the administration of pimozide.

3.3.14 Reproductive Effects

3.3.14.A Sexual dysfunction

1) Summary

a) IMPOTENCE was reported in a 37-year-old male following 2 months of treatment with pimozide 60 milligrams daily for psychosis. The patient could not maintain an erection and this persisted for one month. Pimozide was discontinued and erection was possible 2 weeks later. However, psychosis recurred resulting in readministration of pimozide. The patient exhibited EJACULATION DISTURBANCES when the dose was increased gradually from 4 to 12 milligrams daily. With doses of 16 milligrams daily the patient again became impotent (Ananth, 1982).

3.3.16 Other

Death

Fever

3.3.16.A Death

1) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with dementia. Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the dementia cohort was stratified based on place of residence (community versus long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined (Gill et al, 2007).

2) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with cancer and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882

and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

3) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all timepoints studied after beginning therapy (within 180 days: RR, 1.37; 95% CI, 1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI, 1.14 to 1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI, 1.15 to 1.45), without dementia (RR, 1.45; 95% CI, 1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI, 1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided (Wang et al, 2005).

3.3.16.B Fever

1) Summary

a) Severe HYPERPYREXIA requiring discontinuance of therapy was reported in one of twenty patients receiving pimozide (Huber et al, 1971).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Orap(R), 1999bl) (All Trimesters)

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

2) Australian Drug Evaluation Committee's (ADEC) Category: B1(Batagol, 1996)

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) There has not been sufficient clinical experience to establish the safety of pimozide in general during pregnancy. If possible, use of pimozide during pregnancy should be avoided.

5) Literature Reports

a) There are no studies or published case reports on the use of pimozide in pregnant women. Although studies conducted in rats and rabbits have shown that pimozide is not teratogenic, oral doses up to 8 times the maximum human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation and is similarly observed in rodents administered other antipsychotic drugs (Prod Info Orap(R), 1999bl).

B) Breastfeeding

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

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

2) Clinical Management

a) No reports describing the use of pimozide during human lactation are available and the effects on the nursing infant from exposure to the drug in milk are unknown. It is not known if pimozide affects the quantity and composition of breastmilk. Until more data is available, use caution when considering the use of pimozide in lactating women.

3) Literature Reports

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

drug excreted into milk have been located.

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Acecainide

Ajmaline

Ajmaline

Amiodarone

Amisulpride

Amitriptyline

Amoxapine

Amprenavir

Aprepitant

Aprindine

Arsenic Trioxide

Arsenic Trioxide

Astemizole

Atazanavir

Azimilide

Azithromycin

Belladonna

Belladonna Alkaloids

Bepridil

Betel Nut

Bretylium

Chloral Hydrate

Chloroquine

Chlorpromazine

Chlorpromazine

Cisapride

Clarithromycin

Dalfopristin

Darunavir

Dasatinib

Delavirdine

Desipramine

Dibenzepin

Dirithromycin

Disopyramide

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Efavirenz

Encainide

Enflurane

Erythromycin

Flecainide

Fluconazole

Fluoxetine

Fosamprenavir

Fosaprepitant

Foscarnet

Gemifloxacin

Halofantrine

Haloperidol

Halothane

Hydroquinidine

Hydroquinidine

Ibutilide

Imatinib

Imipramine

Indinavir

Isoflurane

Isradipine

Itraconazole

Kava

Ketoconazole

Lapatinib

Levomethadyl

Lidoflazine

Lithium

Lithospermum

Lorcainide

Lumefantrine

Mefloquine

Mesoridazine

Mesoridazine

Methadone

Miconazole

Moxifloxacin

Nefazodone

Nelfinavir

Nilotinib

Nortriptyline

Octreotide

Ondansetron

Paroxetine

Pentamidine

Phenylalanine

Pirmenol

Pirmenol

Posaconazole

Prajmaline

Prajmaline

Probucol

Procainamide

Procainamide

Prochlorperazine

Prochlorperazine

Propafenone

Protriptyline

Quinidine

Quinupristin

Ranolazine

Rilonacept

Risperidone

Ritonavir

Roxithromycin

Saquinavir

Sematilide

Sertindole

Sertraline

Sotalol

Spiramycin

Sulfamethoxazole

Sultopride

Sunitinib

Tedisamil

Telithromycin

Terfenadine

Tetrabenazine

Thioridazine

Tipranavir

Tramadol

Trifluoperazine

Trifluoperazine

Trimethoprim

Trimipramine

Troleandomycin

Vasopressin

Vitex

Voriconazole

Zileuton

Ziprasidone

Zolmitriptan

Zotepine

3.5.1.A Acecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).
b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.B Ajmaline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because Class Ia antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of pimozide with a drug from this class is contraindicated (Prod Info Orap(R), 1999q; Prod Info Quinaglute Dura-tabs(R), 1999; Stratmann et al, 1985; Chow et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class Ia antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999p).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) Several cases of recurrent irregular ventricular tachycardia also known as torsade de pointes have been reported with conventional doses of disopyramide. This condition is more likely to occur with severe repolarization delay and sinus bradycardia or atrioventricular block, especially when disopyramide therapy is combined with other QT interval prolonging agents (Tzivoni et al, 1981; Commerford & Beck, 1980; Croft & Kennelly, 1981). Others have retrospectively determined that women, irrespective of the presence or absence of other underlying heart conditions, are more at risk than men of developing torsades de pointes, in the setting of prolonged QT interval, following disopyramide therapy (Makkar et al, 1993).

3.5.1.C Ajmaline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999g; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997a).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.D Amiodarone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).
b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.E Amisulpride
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of drugs that potentially prolong the QTc interval, such as amisulpride and pimozide, is contraindicated (Prod Info Solian(R), 1999b; Prod Info Orap(R), 1999ar).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as amisulpride and pimozide, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999l).

3.5.1.F Amitriptyline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT interval
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.G Amoxapine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT interval
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.H Amprenavir
1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Amprenavir is an inhibitor of the isoenzyme cytochrome P450 3A; concomitant use with pimozide may result in inhibition of pimozide metabolism. Elevated pimozide serum concentrations have been associated with an increased risk of cardiotoxicity. The concurrent administration of amprenavir and pimozide is contraindicated (Prod Info AGENERASE(R) Capsules, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of amprenavir and pimozide is contraindicated.
7) Probable Mechanism: increased pimozide serum concentrations due to inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.I Aprepitant
1) Interaction Effect: an increase in pimozide plasma concentrations
2) Summary: Inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by aprepitant could result in elevated pimozide plasma concentrations. The concomitant use of pimozide and aprepitant is contraindicated (Prod Info EMEND(R) oral capsules, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent use of aprepitant and pimozide is contraindicated (Prod Info EMEND (R) oral capsules, 2008).
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated metabolism of pimozide by aprepitant

3.5.1.J Aprindine
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including Class I antiarrhythmic agents, is contraindicated (Prod Info Orap(R) pimozide, 1999a; Prod Info Tambocor(TM), 1998; Prod Info Enkaid(R), 1988; Larochelle et al, 1984).

3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999).

3.5.1.K Arsenic Trioxide
1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. The concurrent administration of pimozide and other agents that can prolong the QT interval, such as arsenic trioxide is contraindicated (Prod Info Trisenox (R), 2001a; Prod Info Orap(R), 1999ak).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QTc prolongation
8) Literature Reports
a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001).

3.5.1.L Arsenic Trioxide
1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes and should not be administered with other drugs that may prolong the QT interval (Prod Info Trisenox(R), 2001c). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999a), haloperidol (O'Brien et al, 1999a), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001b), quetiapine (Owens, 2001f), sultopride (Lande et al, 1992a), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QTc prolongation
8) Literature Reports
a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001b).

3.5.1.M Astemizole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pimozide prolongs the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Orap(R), 1999f). Astemizole alone has caused QT prolongation and torsades de pointes in patients receiving greater than the recommended dose (Prod Info Hismanal(R), 1997). Pimozide is contraindicated in patients taking other drugs which may prolong the

QT interval (Prod Info Orap(R), 1999f).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999e).

3.5.1.N Atazanavir
1) Interaction Effect: an increased risk of cardiac arrhythmias
2) Summary: Coadministration of atazanavir is contraindicated with drugs that are metabolized by cytochrome P450 3A and for which elevated plasma concentrations are associated with serious and/or life threatening events. Side effects may include cardiac arrhythmias (Prod Info Reyataz(TM), 2003).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Coadministration of atazanavir and pimozide is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism by atazanavir

3.5.1.O Azimilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).
b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.P Azithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Azithromycin may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death (Flockhart et al, 1996d). The concurrent administration of azithromycin and pimozide is contraindicated (Prod Info Orap (R), 1999bj).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of pimozide and azithromycin is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.Q Belladonna
1) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination,

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

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

3.5.1.S Bepridil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002a; Agelink et al, 2001; Owens, 2001c; Prod Info Orap(R), 1999o; Prod Info Haldol(R), 1998). In U.S. clinical trials, bepridil increased QT and QTc intervals which was associated with torsades de pointes in approximately 1% of patients. Other drugs that increase the QT interval may exaggerate the prolongation of the QT interval observed with bepridil (Prod Info Vascor(R), 1997). Pimozide is contraindicated in patients taking other drugs which may prolong the QT interval (Prod Info Orap(R), 1999o).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as bepridil, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999n).
b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999a; Ravin & Levenson, 1997a).

3.5.1.T Betel Nut
1) Interaction Effect: increased extrapyramidal side effects of pimozide
2) Summary: Case reports have described increased extrapyramidal side effects when betel nut was chewed by patients taking fluphenazine and fluphenthixol for schizophrenia (Deahl, 1989a). The

extrapyramidal effects were not improved with anticholinergic therapy with procyclidine, and resolved with betel nut discontinuation (Deahl, 1989a). A similar effect may occur if betel nut is chewed with concomitant pimozide therapy. The cholinergic activity of betel nut has been attributed to the arecoline content. When given with peripheral anticholinergics, arecoline increased the heart rate due to central muscarinic agonist activity (Nutt et al, 1978a). Case reports suggest the onset of betel nut activity to be within 3 weeks with resolution within 4 to 7 days after discontinuation (Deahl, 1989a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: It is unclear to what extent the cholinergic effect of betel nut may increase the incidence of extrapyramidal side effects of pimozide, especially if patients are treated with anticholinergic agents to control these side effects. Deterioration in symptoms of patients with Parkinson's disease or other extrapyramidal movement disorders may be expected. Persons who have been chewing betel nut have a characteristic red stain on the teeth which may help the clinician discover betel nut use.

7) Probable Mechanism: cholinergic effect of betel nut

8) Literature Reports

a) Within 3 weeks of initiating betel nut chewing, a 51-year-old Indian man experienced marked rigidity, bradykinesia, and jaw tremor. This patient had been stabilized on fluphenazine decanoate depot 50 milligrams (mg) every 3 weeks for schizophrenia and procyclidine 5 mg twice daily for a mild Parkinsonian tremor for the previous 2 years. Within one week of discontinuation of betel nut chewing, the patient's condition returned to baseline. This report appears to demonstrate decreased anticholinergic effects of procyclidine when coadministered with betel nut (Deahl, 1989).

b) A 45-year-old Indian man developed akathisia, tremor and stiffness following betel nut ingestion which was not affected by dosage escalations of up to 20 mg daily of procyclidine. This patient had been previously stabilized on fluphenthixol 60 mg depot every two weeks for the previous year for schizoaffective disorder without extrapyramidal side effects. His symptoms resolved over 4 days after discontinuing betel nut. It appears that the anticholinergic effects of procyclidine were diminished when betel nut was chewed concomitantly (Deahl, 1989).

c) High doses (5 mg, 10 mg, and 20 mg) of subcutaneous (SC) arecoline given one hour after SC administration of 0.5 mg of the peripheral anticholinergic agent methscopolamine increased the heart rate and blood pressure of six Huntington disease patients. Significant increases in blood pressure occurred at doses of 5 mg, 10 mg (p less than 0.01) and 20 mg (p less than 0.05). Heart rate increased at doses of 5 mg and 20 mg (p less than 0.01), and 10 mg (p less than 0.05). Subjective effects in some patients included tremor, flushing or pallor at the time of peak drug effect and nausea, weakness, and mental changes at the higher doses. No peripheral cholinergic effects were noted. The results indicated a central muscarinic effect for arecoline (Nutt et al, 1978).

d) A low dose (0.5 mg) of arecoline given intravenously 3 minutes after the peripheral anticholinergic agent glycopyrrolate 0.15 mg to 8 patients with major depressive disorder increased their heart rates. The peak heart rate increase in a non-REM portion of the sleep cycle during the 10 minute post-infusion period was 6.75 +/- 12.9 beats per minute for placebo and 25 +/- 10.3 beats per minute for arecoline. The peak heart rates all began 1 to 8 minutes after the arecoline infusion, and the mean heart rate was significantly elevated over placebo from 2 to 10 minutes after arecoline infusion (p less than 0.05) (Abramson et al, 1985).

e) Though chewing betel nut alone does not significantly increase catecholamine levels, a popular betel nut preparation does. Six to eight minutes after chewing betel nut, 4 subjects had only a moderate increase in plasma noradrenaline from 266.2 +/- 105.7 picograms/milliliter (pg/mL) to 313.7 +/- 92.9 pg/mL (p equal to 0.0607). Combining betel nut with lime, catechu and Piper betel flower as is commonly done caused significant elevation of norepinephrine in nine subjects from 292.2 +/- 59.5 pg/mL to 375.1 +/- 130.0 pg/mL (p equal to 0.0244) and epinephrine from 62.5 +/- 23.9 pg/mL to 102.2 +/- 45.0 pg/mL (p equal to 0.0226). In this group dopamine was also elevated in 8 of 9 subjects, but the mean was not significant (Chu, 1995).

3.5.1.U Bretylium

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

2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths

have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).

b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.V Chloral Hydrate

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

2) Summary: Chloral hydrate has been shown to prolong the QTc interval at the recommended therapeutic dose (Young et al, 1986). Even though no formal drug interaction studies have been done, the administration of drugs known to prolong the QTc interval, such as pimozide and chloral hydrate is contraindicated (Prod Info Orap(R), 1999d).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of chloral hydrate and pimozide is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999b).

3.5.1.W Chloroquine

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

2) Summary: Chloroquine has been shown to prolong the QTc interval at the recommended therapeutic dose and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Aralen(R), 1999). Several antipsychotic agents have demonstrated QT prolongation including pimozide (Prod Info Orap(R), 1999x).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide and agents that prolong the QT interval, such as chloroquine is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999d).

3.5.1.X Chlorpromazine

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

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of pimozide warns against its administration with other drugs which are also known to prolong the QTc interval, including phenothiazines (Prod Info Thorazine(R), 2002; Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Orap(R), 1999t). The manufacturers of mesoridazine and thioridazine state that concomitant use is contraindicated with other agents known to prolong the QT interval (Prod Info Mellaril(R), 2002; Prod Info Serentil(R), 2001).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide and other drugs that may prolong the QT interval, such as phenothiazines is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R), 1999s).

3.5.1.Y Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002a; Prod Info Thorazine(R), 2002a). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001e), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.Z Cisapride

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002; Owens, 2001; Prod Info Orap(R), 1999a). Torsades de pointes and QT prolongation have been reported with cisapride (Prod Info Propulsid(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as cisapride, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone (Duenas-Laita et al, 1999; Ravin & Levenson, 1997).

3.5.1.AA Clarithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Clarithromycin may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent (Prod Info Biaxin(R), 2001). Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death (Flockhart et al, 1996b). One patient being treated with therapeutic doses of pimozide for Tourette's syndrome died five days after clarithromycin was prescribed for bronchitis. The patient had toxic plasma levels of pimozide (greater than 50 ng/mL) and a prolonged QTc interval (Flockhart et al, 2000a). A 27-year-old patient being treated with pimozide for Tourette's syndrome was prescribed clarithromycin for bronchopneumonia. The patient died five days later from a cardiac arrhythmia. Blood pimozide concentrations were 50 ng/ml (4-20 ng/ml). The concurrent use of clarithromycin and pimozide is contraindicated (Prod Info Orap(R), 1999ah).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of pimozide and clarithromycin is contraindicated.
7) Probable Mechanism: inhibition by clarithromycin of cytochrome P450 3A-mediated pimozide metabolism
8) Literature Reports

a) In a randomized, double-blind, placebo-controlled crossover design study, twelve healthy volunteers were given a single oral dose of pimozide 6 mg after five days of pretreatment with placebo or clarithromycin 500 mg twice daily. With respect to cytochrome P450 2D6 (CYP2D6) phenotyping, five study subjects were poor metabolizers and seven were extensive metabolizers. All participants had a corrected QTc shorter than 470 ms prior to inclusion in the study. Clarithromycin pretreatment increased the pimozide maximum concentration (Cmax) from 4.4 ng/mL to 6.1 ng/mL and increased the area under the concentration-time curve (AUC) by 113% (146 ng/mL/h vs. 310 ng/mL/h). Pimozide half-life, clearance, and apparent volume of distribution were also significantly increased by clarithromycin. Pimozide prolonged the QT interval in all study subjects, and these increases coincided with plasma concentrations. In the first 20 hours after administration, the clarithromycin group had a more prolonged QTc interval (increased by 15.7 ms) than the placebo group (increased by 13.3 ms). There was no significant effect of CYP2D6 phenotyping or gender on the pharmacodynamics or pharmacokinetics of pimozide. Clarithromycin inhibits cytochrome P450 3A (CYP3A) enzymes, which are responsible for pimozide metabolism. Inhibition of pimozide metabolism leads to cardiotoxicity, which is an effect of the parent drug (Desta et al, 1999).
b) A case report describes a 27-year-old male with a history of Tourette syndrome who experienced sudden cardiac death after being coprescribed pimozide and clarithromycin. The patient was currently taking pimozide 14 mg/day, but due to an increase in the number of tics he was experiencing, it was decided that his dose of pimozide be slowly increased by one 2 mg tablet per day. Two days after the increase in dose, he was diagnosed with bronchopneumonia. Clarithromycin 500 mg per day was prescribed. Four days after he presented to the emergency department he complained of a racing heart and felt a "head rush". He was observed without incident. An ECG showed a corrected QT interval of 0.506 seconds. He was discharged with instructions to follow-up with his neurologist. The following day he was found unconscious, apneic, and unresponsive without the ability to be resuscitated. Blood pimozide concentrations were 50 ng/ml (4-20 ng/ml). Cardiac arrhythmia resulting from an excessive concentration of pimozide was the most likely cause of death (Flockhart et al, 2000).
c) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R), 1999ag).

3.5.1.AB Dalfopristin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Quinupristin/dalfopristin is a major inhibitor of cytochrome P450 3A4 (CYP3A4) isoenzymes, and pimozide is a CYP3A4 substrate. Coadministration of these two agents may likely result in increased plasma concentrations of pimozide, which may lead to QTc interval prolongation and risk of torsades de pointes (Prod Info SYNERCID(R) intravenous injection, 2003; Prod Info ORAP(R) Tablets, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of pimozide and quinupristin/dalfopristin is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated pimozide metabolism

3.5.1.AC Darunavir

1) Interaction Effect: an increased risk of serious and/or life-threatening reactions such as cardiac arrhythmias
2) Summary: The coadministration of darunavir/ritonavir and pimozide is contraindicated as this may result in inhibition of the CYP3A-mediated pimozide metabolism, leading to increased pimozide plasma concentrations and creating the potential for serious and/or life-threatening reactions such as cardiac arrhythmias (Prod Info PREZISTA(TM) oral tablets, 2006).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of darunavir/ritonavir and pimozide is contraindicated.
7) Probable Mechanism: inhibition of CYP3A-mediated pimozide metabolism

3.5.1.AD Dasatinib

1) Interaction Effect: altered pimozide plasma concentrations
2) Summary: Use caution when coadministering dasatinib (a CYP3A4 inhibitor) and pimozide (a CYP3A4 substrate with a narrow therapeutic index), as this may result in altered plasma concentrations of pimozide (Prod Info SPRYCEL(R) oral tablets, 2008). Monitoring patients for pimozide-related adverse effects (cardiotoxicity including QT interval prolongation, torsades de pointes, and cardiac arrest) may be warranted when these drugs are used concomitantly.
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Use caution if dasatinib and pimozide are coadministered (Prod Info SPRYCEL(R) oral tablets, 2008). Consider monitoring the patient for pimozide-related adverse effects (cardiotoxicity including QT interval prolongation, torsades de pointes, and cardiac arrest) when these drugs are used concomitantly.
7) Probable Mechanism: altered CYP3A4-mediated metabolism of pimozide

3.5.1.AE Delavirdine
1) Interaction Effect: an increased risk of cardiotoxicity
2) Summary: Delavirdine and pimozide are both metabolized by the CYP3A4 enzyme system. Competition for this pathway could result in inhibition of pimozide metabolism, creating the potential for pimozide toxicity and cardiac arrhythmias. Concurrent administration of delavirdine and pimozide is contraindicated (Prod Info RESCRIPTOR(R) oral tablets, 2006).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of delavirdine and pimozide is contraindicated due to the potential for serious or life-threatening cardiac arrhythmias.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.AF Desipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT interval
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.AG Dibenzepin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT interval
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.AH Dirithromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Dirithromycin may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concomitant administration of pimozide and dirithromycin is contraindicated (Flockhart et al, 1996; Prod Info Orap(R), 1999l).
3) Severity: contraindicated
4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: Concurrent use of pimozide and dirithromycin is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.AI Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because Class Ia antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of pimozide with a drug from this class is contraindicated (Prod Info Orap(R), 1999q; Prod Info Quinaglute Dura-tabs(R), 1999; Stratmann et al, 1985; Chow et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class Ia antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999p).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) Several cases of recurrent irregular ventricular tachycardia also known as torsade de pointes have been reported with conventional doses of disopyramide. This condition is more likely to occur with severe repolarization delay and sinus bradycardia or atrioventricular block, especially when disopyramide therapy is combined with other QT interval prolonging agents (Tzivoni et al, 1981; Commerford & Beck, 1980; Croft & Kennelly, 1981). Others have retrospectively determined that women, irrespective of the presence or absence of other underlying heart conditions, are more at risk than men of developing torsades de pointes, in the setting of prolonged QT interval, following disopyramide therapy (Makkar et al, 1993).

3.5.1.AJ Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999g; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997a).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.AK Dofetilide

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

2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).

b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.AL Dolasetron

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

2) Summary: Although no formal interaction studies have been conducted, the manufacturer of pimozide considers its coadministration with other drugs when may prolong the QT interval to be contraindicated (Prod Info Orap(R), 1999ax; Prod Info Anzemet(R), 1997a).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as dolasetron and pimozide, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999o).

b) In several studies, dolasetron resulted in significant, dose-related increases in mean PR, QRS, and QTc intervals compared to baseline values. Measured changes in ECG parameters were transient, reversible, and asymptomatic. Increases in PR and QRS intervals may be due to prolongation of maximum upstroke velocity (Vmax) due to binding of dolasetron to fast sodium channels. The cause of QTc interval prolongation appears to be due to prolongation of the QRS interval, increases in heart rate, or both (Prod Info Anzemet(R), 1997; Hunt et al, 1995; Kris et al, 1994).

3.5.1.AM Doxepin

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

2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.

7) Probable Mechanism: additive effects on QT interval

8) Literature Reports

a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and

schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.AN Droperidol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Droperidol has been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of droperidol and other drugs known to prolong the QTc interval, including pimozide, is contraindicated (Prod Info Inapsine(R), 2001; Prod Info Orap(R), 1999w).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as droperidol and pimozide, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999v).

3.5.1.AO Efavirenz

1) Interaction Effect: an increased risk of cardiac arrhythmias
2) Summary: Efavirenz and pimozide are both metabolized by the CYP3A4 enzyme system. Competition for this pathway could result in inhibition of pimozide metabolism, creating the potential for serious and/or life-threatening reactions such as cardiac arrhythmias. Concurrent administration of efavirenz and pimozide is contraindicated (Prod Info SUSTIVA(R) oral capsules, tablets, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The coadministration of efavirenz and pimozide is contraindicated as this may result in competitive inhibition of pimozide metabolism, thereby increasing the risk for serious and/or potentially life-threatening adverse events such as cardiac arrhythmias (Prod Info SUSTIVA(R) oral capsules, tablets, 2008).
7) Probable Mechanism: competition for CYP3A4-mediated pimozide metabolism by efavirenz

3.5.1.AP Encainide

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including Class I antiarrhythmic agents, is contraindicated (Prod Info Orap(R) pimozide, 1999a; Prod Info Tambocor(TM), 1998; Prod Info Enkaid(R), 1988; Larochelle et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999).

3.5.1.AQ Enflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pimozide prolongs the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Orap(R) pimozide, 1999c). Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval, including enflurane (Owens, 2001b).
3) Severity: contraindicated

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999m).

3.5.1.AR Erythromycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997). Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval, including erythromycin (Prod Info Orap(R) pimozide, 1999q).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as erythromycin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999p).
b) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The erythromycin dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean of 15%), compared with an increase of 8% in patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed torsades de pointes attributed to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

3.5.1.AS Flecainide
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including Class I antiarrhythmic agents, is contraindicated (Prod Info Orap(R) pimozide, 1999a; Prod Info Tambocor(TM), 1998; Prod Info Enkaid(R), 1988; Larochelle et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999).

3.5.1.AT Fluconazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Orap(R) pimozide, 1999u). Case reports have described QT prolongation and torsades de pointes associated with fluconazole (Khazan & Mathis, 2002; Wassmann et al, 1999).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as fluconazole, is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.AU Fluoxetine
1) Interaction Effect: bradycardia, somnolence, and potentially increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: One case of bradycardia and somnolence resulting from concomitant fluoxetine and pimozide therapy has been reported (Ahmed et al, 1993). Although a specific interaction study has not been conducted with these agents, due to the potential for additive QT prolongation effects, the concomitant use of fluoxetine and pimozide is contraindicated (Prod Info PROZAC(R) oral capsule, oral pulvule, oral solution, oral tablet, 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Due to the possibility of additive effects on the QT interval, the concurrent administration of fluoxetine and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) One case has been reported in which concurrent use of pimozide 5 mg daily and fluoxetine 20 mg daily in an elderly patient resulted in severe bradycardia and somnolence. The pulse rate gradually returned to normal after discontinuation of pimozide; rechallenge with a lower pimozide dose and a higher fluoxetine dose also resulted in bradycardia (Ahmed et al, 1993).

3.5.1.AV Fosamprenavir
1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Fosamprenavir is an inhibitor of the isoenzyme cytochrome P450 3A; concomitant use with pimozide may result in inhibition of pimozide metabolism. Elevated pimozide serum concentrations have been associated with an increased risk of cardiotoxicity. The concurrent administration of fosamprenavir and pimozide is contraindicated (Prod Info Lexiva(R), 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of fosamprenavir and pimozide is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.AW Fosaprepitant
1) Interaction Effect: increased plasma concentrations of pimozide
2) Summary: Fosaprepitant is a prodrug of aprepitant, which is a moderate CYP3A4 inhibitor. Coadministration with pimozide, a CYP3A4 substrate, could result in elevated plasma pimozide levels and potentially cause serious or life-threatening reactions. The concomitant use of pimozide and fosaprepitant is contraindicated (Prod Info EMEND(R) IV injection, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of fosaprepitant and pimozide is contraindicated (Prod Info EMEND(R) IV injection, 2008).
7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of pimozide by aprepitant

3.5.1.AX Foscarnet
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of drugs that potentially prolong the QTc interval, such as foscarnet and pimozide, is contraindicated (Prod Info Orap(R), 1999az; Prod Info Foscavir(R), 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as foscarnet and pimozide, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999ay).

3.5.1.AY Gemifloxacin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between gemifloxacin and pimozide, which has the potential to prolong the QT interval, have not been performed, gemifloxacin should not be used in patients receiving pimozide (Prod Info Factive(R), 2003; Prod Info Orap(R), 1999i).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of pimozide with other drugs that prolong the QT interval, such as gemifloxacin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AZ Halofantrine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because pimozide may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halofantrine with pimozide is contraindicated (Prod Info Orap(R) pimozide, 1999n; Prod Info Halfan(R), 1998).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential additive effects on the QT interval, the concurrent administration of halofantrine and pimozide is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999m).

3.5.1.BA Haloperidol
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 2003a; Prod Info Haldol(R), 2001). According to the manufacturer, coadministration of pimozide with drugs that potentially prolong the QTc interval, such as haloperidol, is contraindicated (Prod Info Orap(R), 1999bi).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as haloperidol and pimozide, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Numerous case reports have described significant QTc prolongation and torsades de pointes (TdP) associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dose as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, screen patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003).
b) Seven patients developed torsade de pointes after therapeutic use of haloperidol in high doses.

Three patients developed the dysrhythmia after administration of 211 milligrams (mg) to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger & Friedman, 1993; Wilt et al, 1993). Torsades de pointes developed in 8 of 223 critically ill patients in intensive care units. Patients who received intravenous haloperidol greater than 35 mg/day or had a QTc interval prolongation of greater than 500 milliseconds were at greatest risk (Sharma et al, 1998).
c) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg/kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999v).

3.5.1.BB Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pimozide prolongs the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Orap(R), 1999h). Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval, including halothane (Owens, 2001a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999g).

3.5.1.BC Hydroquinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because Class Ia antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of pimozide with a drug from this class is contraindicated (Prod Info Orap(R), 1999q; Prod Info Quinaglute Dura-tabs(R), 1999; Stratmann et al, 1985; Chow et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class Ia antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999p).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) Several cases of recurrent irregular ventricular tachycardia also known as torsade de pointes have been reported with conventional doses of disopyramide. This condition is more likely to occur with severe repolarization delay and sinus bradycardia or atrioventricular block, especially when disopyramide therapy is combined with other QT interval prolonging agents (Tzivoni et al, 1981; Commerford & Beck, 1980; Croft & Kennelly, 1981). Others have retrospectively determined that women, irrespective of the presence or absence of other underlying heart conditions, are more at risk than men of developing torsades de pointes, in the setting of prolonged QT interval, following disopyramide therapy (Makkar et al, 1993).

3.5.1.BD Hydroquinidine

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

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999g; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997a).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BE Ibutilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).
b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.BF Imatinib

1) Interaction Effect: increased plasma levels of pimozide
2) Summary: Plasma concentrations of pimozide may be altered when coadministration with imatinib. Caution should be utilized when administering imatinib with cytochrome P450 3A4 substrates, such as pimozide, that have narrow therapeutic windows (Prod Info Gleevec(TM), 2002).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution is recommended when administering imatinib with pimozide, a cytochrome P450 3A4 substrate with a narrow therapeutic window.
7) Probable Mechanism: inhibition of cytochrome P450 3A4 metabolism of pimozide by imatinib

3.5.1.BG Imipramine

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

2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.

7) Probable Mechanism: additive effects on QT interval

8) Literature Reports

a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.BH Indinavir

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

2) Summary: Indinavir is an inhibitor of cytochrome P450 3A may result in inhibition of pimozide metabolism. Elevated pimozide serum concentrations have been associated with an increased risk of cardiotoxicity. The concurrent administration of indinavir and pimozide is contraindicated (Prod Info Orap(R), 1999u).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concomitant use of pimozide and indinavir is contraindicated.

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

3.5.1.BI Isoflurane

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

2) Summary: Pimozide prolongs the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Orap(R), 1999bf). Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval, including isoflurane (Owens, 2001j).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.

7) Probable Mechanism: additive effect on QT interval

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999be).

3.5.1.BJ Isradipine

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

2) Summary: Coadministration of drugs that potentially prolong the QTc interval, such as isradipine and pimozide, is contraindicated (Prod Info DynaCirc(R), 2000; Prod Info Orap(R), 1999ai).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as isradipine and pimozide, is contraindicated.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One

possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999h).

3.5.1.BK Itraconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Itraconazole may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concurrent use of itraconazole and pimozide is contraindicated (Prod Info Orap(R), 1999af; Prod Info Sporanox(R), 2002).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of itraconazole and pimozide is contraindicated.
7) Probable Mechanism: inhibition by itraconazole of cytochrome P450 3A4-mediated pimozide metabolism

3.5.1.BL Kava

1) Interaction Effect: additive dopamine antagonist effects
2) Summary: Theoretically, kava may add to the effect of dopamine antagonists, increasing the risk for adverse effects. Case reports describe what appears to be dopamine-blocking activity of kava manifested in patients as dystonia, dyskinesias, and Parkinsonism (Spillane et al, 1997a; Schelosky et al, 1995a). Kava extracts antagonized apomorphine-induced hyperreactivity to external stimuli in mice, suggesting dopamine blockade activity (Jamieson et al, 1989).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of kava with dopamine antagonists. The desired effect and/or adverse effects of the dopamine antagonist may be increased or may be variable depending on the time of administration of kava and the quality of the kava product (i.e., whether it contains a standardized amount of kava).
7) Probable Mechanism: dopamine antagonist effect of kava
8) Literature Reports

a) A 27-year-old Aboriginal Australian male presented three times following heavy kava use with symptoms of severe choreoathetosis of the limbs, trunk, neck, and facial musculature, and athetosis of the tongue. Level of consciousness was not impaired. Symptoms resolved within 12 hours of intravenous diazepam on each occasion. Acute rheumatic fever was excluded, cerebrospinal fluid and computed tomography of the brain was normal, and urinary drug screen was negative. The only abnormalities found in hematological and biochemical tests were a serum alkaline phosphatase of 162 international units/liter (IU/L) (normal: 35-135 IU/L) and serum gamma-glutamyltransferase of 426 IU/L (normal less than 60 IU/L). These were attributed to kava use. The patient did not drink alcohol (Spillane et al, 1997).
b) A 76-year-old female with idiopathic Parkinson's disease of 17 years' duration treated for 8 years with levodopa 500 milligrams (mg) and benserazide 125 mg was prescribed kava extract (Kavasporal Forte(R)) 150 mg twice daily for complaints of inner tension. Within 10 days, she noted a pronounced increase in her daily "off" periods both in terms of duration and number. Within 2 days of discontinuing the kava product, symptoms had returned to her normal baseline (Schelosky et al, 1995).
c) A 63-year-old female experienced sudden and acute forceful involuntary oral and lingual dyskinesias on the fourth day of self-initiated therapy with kava extract (Kavasporal Forte(R)) 150 mg three times daily. She was treated successfully in the emergency room with biperiden 5 mg intravenously. She denied taking any other medications in the months preceding this event (Schelosky et al, 1995).
d) A 22-year-old female took kava extract (Laitan(R)) 100 mg once for anxiety and nervousness. Within four hours she experienced oral and lingual dyskinesias, tonic rotation of the head, and painful twisting trunk movements. She was treated successfully with biperiden 2.5 mg intravenously. She denied taking any other medications in the months preceding this event (Schelosky et al, 1995).
e) A 28-year-old male experienced acute involuntary neck extension with forceful upward deviation of the eyes within 90 minutes of taking kava extract (Laitan(R)) 100 mg. Symptoms resolved spontaneously within 40 minutes. This man had a history of acute dystonic reactions following exposure to promethacin (50 mg) and fluspirilene (1.5 mg), which had responded biperiden 5 mg intravenously 9 and 12 years previously (Schelosky et al, 1995).

3.5.1.BM Ketoconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ketoconazole may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse

cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concurrent use of ketoconazole and pimozide is contraindicated (Prod Info Orap(R), 1999ao).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of ketoconazole and pimozide is contraindicated.
7) Probable Mechanism: inhibition by ketoconazole of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.BN Lapatinib
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, caution should be used when lapatinib and drugs that prolong the QT interval are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008). Thirteen patients had either QTcF (corrected QT by the Friedericia method) greater than 480 msec or an increase in QTcF of greater than 60 msec in an uncontrolled, open-label, dose escalation study in advanced cancer patients (n=81) who received lapatinib doses ranging from 175 mg/day to 1800 mg/day, with serial ECGs collected on days 1 and 14 (Prod Info TYKERB oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of lapatinib and drugs that prolong the QT interval may result in additive effects on the QT interval and an increased risk of torsade de pointes. Therefore, caution should be used when these agents are given concomitantly. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008).
7) Probable Mechanism: additive effects on the QT interval

3.5.1.BO Levomethadyl
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as pimozide that prolong the QT interval (Prod Info Orlaam(R), 2001).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Levomethadyl is contraindicated in patients being treated with pimozide as it may precipitate QT prolongation and interact with levomethadyl.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BP Lidoflazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Lidoflazine has been shown to prolong the QTc interval at the recommended therapeutic dose (Hanley & Hampton, 1983). Even though no formal drug interaction studies have been done, the coadministration of lidoflazine with other drugs known to prolong the QTc interval, including pimozide, is contraindicated (Prod Info Orap(R), 1999bc).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as lidoflazine and pimozide, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999t).

3.5.1.BQ Lithium
1) Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brain damage
2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few patients treated with lithium plus a dopamine-2 antagonist, particularly haloperidol. A causal relationship between these events and the concomitant administration of a dopamine-2 antagonist and lithium has not

been established (Prod Info LITHOBID(R) slow-release oral tablets, 2005). Coadministration of lithium and a number of antipsychotic drugs has caused a wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and dyskinesias in isolated case reports. In most cases, these effects have occurred with therapeutic lithium levels (Amdisen, 1982; Prakash, 1982; Addonizio et al, 1988a). However, many series and trials have reported using such combinations with no severe adverse consequences (Goldney & Spence, 1986). The mechanism is not fully understood, but chronic lithium treatment decreases neostriatal dopaminergic activity, probably through a direct action on the G protein and the capacity of the G proteins, once activated, to stimulate adenyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined phenothiazine and lithium use (Zall et al, 1968).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, especially if high doses of dopamine-2 antagonists, particularly haloperidol, and lithium are used. Serum lithium levels should be monitored periodically. Some clinicians advocate maintaining levels in the low therapeutic range.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant haloperidol and lithium therapy has resulted in symptoms of encephalopathy, confusion, extrapyramidal symptoms, and fever in several patients with mania (Cohen & Cohen, 1974; Loudon & Waring, 1976; Thomas, 1979). Irreversible neurological injuries have been reported (Sandyk & Hurwitz, 1983; Keitner & Rahman, 1984).

b) Seizures, encephalopathy, delirium, and abnormal EEG occurred in four patients during combined lithium and thioridazine therapy (Spring, 1979). Serum lithium levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had previously tolerated lithium in combination with another phenothiazine. Three of these patients developed symptoms within eight days of initiating combination therapy.

c) The addition of lithium to neuroleptic therapy exacerbated extrapyramidal symptoms (EPS) in a small study (Addonizio et al, 1988). The patients had received at least five days of treatment with either oral thiothixene, haloperidol, or fluphenazine in mean doses of 607.5 chlorpromazine equivalents prior to initiation of the lithium and were experiencing drug-induced extrapyramidal symptoms. Oral lithium was added when clinically indicated in sufficient doses to achieve a therapeutic serum concentration. The maximum levels attained were 0.65 to 1.27 mEq/L. The EPS ratings increased in all ten patients following the addition of lithium. However, only three patients developed marked symptoms and no patient developed lithium toxicity. Significantly increased symptoms included gait, shoulder shaking, elbow rigidity, and tremor.

d) Ten patients treated with clozapine and lithium were studied (Blake et al, 1992). Of the ten patients, four experienced significant neurologic effects, including jerking of limbs, facial spasms and tics, tremor of hands and arms, tongue twitching, and stumbling gait. One of these also experienced delirium. These effects reversed when lithium was discontinued or given at a lower dose. On rechallenge, one of two patients suffered recurrence of symptoms. By keeping serum lithium no greater than 0.5 mEq/L, clozapine could be safely coadministered.

e) Chlorpromazine serum levels can be significantly reduced in the presence of lithium treatment. If used concurrently, abrupt cessation of lithium may result in rebound elevation of chlorpromazine levels, resulting in chlorpromazine toxicity. In patients on a lithium-chlorpromazine combination, abrupt withdrawal of the lithium may precipitate chlorpromazine cardiotoxicity. In this report, such toxicity was manifested as sudden ventricular fibrillation associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation (Stevenson et al, 1989).

f) However, other data do not support that such adverse events are frequent or indeed causally related to combination therapy. Combination of dopamine antagonist antipsychotic drugs and lithium have been used successfully in many patients with manic-depressive illness. It has been proposed that the interaction may only become significant with very high doses of one or both drugs or with failure to discontinue dosing in the presence of toxic symptoms (Miller & Menninger, 1987).

g) A 69-year-old patient with oxygen-dependent chronic obstructive pulmonary disorder and a 25-year history of bipolar disorder was started on risperidone 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been maintained on a regimen of lithium (450 mg daily) for more than 10 years. In addition, she was given amantadine (100 mg twice daily) for tremor. Three weeks after the start of risperidone, the patient experienced a decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, polyuria, depression, and visual and auditory hallucinations. She was then admitted to the hospital for delirium. Her lithium serum level was 1.36 mEq/L at the time of the admission. All medications were discontinued. Although her lithium level decreased to 0.41 mEq/L, she continued to experience profound delirium, tremors, lethargy, and hallucinations for almost one week. After she started to respond to commands, she was restarted on lithium (300 mg at bedtime) because of the onset of mild hypomania. Five days later, she was discharged with a regimen of lithium and low-dose lorazepam for treatment of insomnia. It is suggested that delirium could have been caused by the concurrent use of lithium and risperidone. Other factors could also have caused delirium, such as the patient's serum lithium level and the underlying pulmonary pathology. In addition, amantadine, which facilitates the release of presynaptic dopamine and has a mild anticholinergic effect,

may have contributed (Chen & Cardasis, 1996).

3.5.1.BR Lithospermum

1) Interaction Effect: decreased effectiveness of dopamine antagonists
2) Summary: Theoretically, the dopamine agonist activity of lithospermum may oppose that of dopamine antagonists, decreasing their effectiveness. Lithospermum likely decreases prolactin secretion via dopamine stimulation (Sourgens et al, 1982a). Animal data suggest that the effect occurs rapidly within 3 hours after injection, subsiding within 6 to 9 hours (Sourgens et al, 1980a). The magnitude and clinical significance of this phenomenon has yet to be determined in humans. Furthermore, it is not known if the ability to stimulate dopamine receptors is limited to the hypothalamic region or if such an effect will be noted elsewhere (i.e., if patients with psychosis will experience worsening of their condition due to dopamine stimulation secondary to lithospermum). Caution is recommended until the effects on humans and possible implications of a drug-herb interaction with dopamine antagonists can be fully determined.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: If therapy is initiated with lithospermum and a dopamine antagonist, monitor closely for return of symptoms previously controlled by the dopamine antagonist.
7) Probable Mechanism: dopamine agonism of lithospermum may counteract dopamine antagonists
8) Literature Reports
a) Administration of freeze dried extracts (FDE) of Lithospermum officinale (Boraginaceae) by intravenous injection to rats resulted in reduced prolactin serum levels and hypophyseal stores. When administered diluent, prolactin levels decreased from 36 +/- 8 nanograms/milliliter (ng/mL) serum to 10 +/- 4 ng/mL serum (p less than 0.005) when administered Lithospermum officinale FDE (40 milligrams (mg)/100 grams body weight) within 3 hours post intravenous administration. The authors concluded that Lithospermum officinale possibly impacted prolactin secretion at the hypothalamic site via dopamine stimulation (Sourgens et al, 1982).
b) Prolactin levels decreased rapidly below basal values in rats within the first 3 hours following a single intravenous injection of Lithospermum officinale. Prolactin levels returned to control levels within 6 to 9 hours after the injection (Sourgens et al, 1980).

3.5.1.BS Lorcainide

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including Class I antiarrhythmic agents, is contraindicated (Prod Info Orap(R) pimozide, 1999a; Prod Info Tambocor(TM), 1998; Prod Info Enkaid(R), 1988; Larochelle et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999).

3.5.1.BT Lumefantrine

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on QT interval prolongation, concomitant use of artemether/lumefantrine with drugs that prolong the QT interval should be avoided (Prod Info COARTEM(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of artemether/lumefantrine with drugs that prolong the QT interval should be avoided due to the potential for additive effects on QT interval prolongation (Prod Info COARTEM(R) oral tablets, 2009).
7) Probable Mechanism: additive effects on QT interval prolongation
8) Literature Reports
a) Concurrent administration of a single dose of IV quinine 10 mg/kg with the final dose of a 6-dose regimen of artemether/lumfantrine did not alter the systemic exposure to quinine, lumefantrine, or dihydroartemisinin (active metabolite of artemether). Although artemether exposure was decreased, it was not believed to be clinically significant. The effects on QT prolongation were not reported in this

study (Prod Info COARTEM(R) oral tablets, 2009).

3.5.1.BU Mefloquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Orap(R), 1999ae). Mefloquine was associated with significant QT prolongation in a study of 46 healthy subjects (Davis et al, 1996).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as mefloquine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BV Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of pimozide warns against its administration with other drugs which are also known to prolong the QTc interval, including phenothiazines (Prod Info Thorazine(R), 2002; Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Orap(R), 1999t). The manufacturers of mesoridazine and thioridazine state that concomitant use is contraindicated with other agents known to prolong the QT interval (Prod Info Mellaril(R), 2002; Prod Info Serentil(R), 2001).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide and other drugs that may prolong the QT interval, such as phenothiazines is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R), 1999s).

3.5.1.BW Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001a). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999d), haloperidol (O'Brien et al, 1999c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001h), risperidone (Duenas-Laita et al, 1999f), sertindole (Agelink et al, 2001c), sultopride (Lande et al, 1992c), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics and mesoridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BX Methadone

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Cases of QT interval prolongation and serious arrhythmias, including torsade de pointes, have been reported with methadone use (Prod Info DOLOPHINE(R) HYDROCHLORIDE oral tablets, 2006). Treatment with pimozide has also been associated with QTc prolongation (Prod Info ORAP(R) oral tablets, 2005). Concurrent administration of methadone and pimozide is contraindicated due to the potential for additive effects on QTc prolongation (Prod Info ORAP(R) oral tablets, 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of methadone and pimozide is contraindicated due to the potential for additive effects on QT interval prolongation (Prod Info ORAP(R) oral tablets, 2005).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BY Miconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Miconazole may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concurrent use of miconazole and pimozide is contraindicated (Prod Info Orap(R), 1999al).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of miconazole and pimozide is contraindicated.
7) Probable Mechanism: inhibition by miconazole of cytochrome P450 3A4-mediated pimozide metabolism

3.5.1.BZ Moxifloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Prolongation of the QTc interval has occurred with oral and intravenous moxifloxacin (Prod Info AVELOX(R) oral tablets, IV injection, 2005). Treatment with pimozide has also been associated with QTc prolongation. Concurrent administration of moxifloxacin and pimozide is contraindicated due to the potential for additive effects on QTc prolongation (Prod Info ORAP(R) oral tablets, 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of moxifloxacin and pimozide is contraindicated due to the potential for additive effects on QT interval prolongation (Prod Info ORAP(R) oral tablets, 2005).
7) Probable Mechanism: additive cardiac effects

3.5.1.CA Nefazodone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Nefazodone may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concurrent use of nefazodone and pimozide is contraindicated (Prod Info Orap(R), 1999an).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of nefazodone and pimozide is contraindicated.
7) Probable Mechanism: inhibition by nefazodone of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.CB Nelfinavir

1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Nelfinavir is an inhibitor of cytochrome P450 3A may result in inhibition of pimozide metabolism. Elevated pimozide serum concentrations have been associated with an increased risk of cardiotoxicity. The concurrent administration of nelfinavir and pimozide is contraindicated (Prod Info Orap (R), 1999aq).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concomitant use of pimozide and nelfinavir is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.CC Nilotinib

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, concomitant use of nilotinib with drugs that prolong the QT interval should be avoided. However, if concomitant use is required, the patient should be closely monitored for prolongation of the QT interval (Prod Info TASIGNA(R) oral capsules, 2007).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of nilotinib with drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval (Prod Info TASIGNA(R) oral capsules, 2007).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CD Nortriptyline

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

2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.

7) Probable Mechanism: additive effects on QT interval

8) Literature Reports

a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.CE Octreotide

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

2) Summary: Octreotide has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Sandostatin(R), 1999). Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including octreotide, is contraindicated (Prod Info Orap(R) pimozide, 1999s).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as octreotide, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999r).

3.5.1.CF Ondansetron

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

2) Summary: Rarely, and predominantly with the intravenous formulation, transient ECG changes including QT interval prolongation have occurred with ondansetron (Prod Info ZOFRAN(R) oral tablets, oral solution, ZOFRAN ODT(R) orally disintegrating tablets, 2006). Pimozide has been shown to prolong the QTc interval and coadministration with other drugs which prolong the QT interval is contraindicated (Prod Info ORAP(R) oral tablets, 2004).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide and agents that may prolong the QT interval, such as ondansetron, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CG Paroxetine

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

2) Summary: Coadministration of paroxetine and pimozide is contraindicated. A controlled study involving concurrent administration of pimozide and paroxetine to healthy volunteers resulted in a mean increase in AUC and Cmax of 151% and 62%, respectively. The consequence of such an extreme increase of pimozide plasma concentrations may be pimozide toxicity, including risk of QT prolongation leading to torsades de pointes (Prod Info PAXIL CR(R) CONTROLLED-RELEASE TABLETS, 2005).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The concurrent administration of paroxetine and pimozide is contraindicated due to the possibility of significantly increased pimozide plasma concentrations resulting in a dangerous risk of

pimozide toxicity.
7) Probable Mechanism: unknown
8) Literature Reports
a) A group of healthy volunteers in a controlled study received a single dose of 2 mg pimozide after being titrated up to a daily dose of 60 mg of immediate-release paroxetine hydrochloride. The study resulted in a mean increase of pimozide area under the concentration time-curve (AUC) and maximum concentration (Cmax) of 151% and 62%, respectively (Prod Info PAXIL CR(R) CONTROLLED-RELEASE TABLETS, 2005).

3.5.1.CH Pentamidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pentamidine has been shown to prolong the QTc interval at the recommended therapeutic dose (Lindsay et al, 1990). Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including pentamidine, is contraindicated (Prod Info Orap(R), 1999at).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as pentamidine, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999as).

3.5.1.CI Phenylalanine
1) Interaction Effect: increased incidence of tardive dyskinesia
2) Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dyskinesia (Gardos et al, 1992a). Abnormal phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain and in turn, reduced brain availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines (Gardos et al, 1992a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monitor the patient closely for signs of tardive dyskinesia.
7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with catecholamine synthesis
8) Literature Reports
a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics in an open study. Three groups of patients were studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients with no tardive dyskinesia with current or past exposure to greater than or equal to 100 milligrams (mg) of a chlorpromazine equivalent for at least 3 months (n=10), and (3) patients with no tardive dyskinesia not previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were obtained just prior to phenylalanine administration and 2 hours after administration. Three patients in group 1 (with tardive dyskinesia) had the highest postloading phenylalanine plasma levels, this group as a whole had higher (though nonsignificant) mean phenylalanine levels than the other groups. Tardive dyskinesia score (measured using the Abnormal Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phenylalanine level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading phenylalanine level and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.092; Spearman correlation coefficient 0.679, p less than 0.05). In all patients, phenylalanine loading increased plasma phenylalanine levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of phenylalanine to tyrosine. Plasma levels of competing large neutral amino acids such as tryptophan decreased slightly (Gardos et al, 1992).

3.5.1.CJ Pirmenol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because Class Ia antiarrhythmic agents may also prolong the QT interval and increase the

risk of arrhythmias, the concurrent administration of pimozide with a drug from this class is contraindicated (Prod Info Orap(R), 1999q; Prod Info Quinaglute Dura-tabs(R), 1999; Stratmann et al, 1985; Chow et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class Ia antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999p).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) Several cases of recurrent irregular ventricular tachycardia also known as torsade de pointes have been reported with conventional doses of disopyramide. This condition is more likely to occur with severe repolarization delay and sinus bradycardia or atrioventricular block, especially when disopyramide therapy is combined with other QT interval prolonging agents (Tzivoni et al, 1981; Commerford & Beck, 1980; Croft & Kennelly, 1981). Others have retrospectively determined that women, irrespective of the presence or absence of other underlying heart conditions, are more at risk than men of developing torsades de pointes, in the setting of prolonged QT interval, following disopyramide therapy (Makkar et al, 1993).

3.5.1.CK Pirmenol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999g; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997a).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.CL Posaconazole
1) Interaction Effect: increased risk of QT prolongation and torsade de pointes
2) Summary: Concurrent use of pimozide and posaconazole is contraindicated. Posaconazole is an inhibitor of CYP3A4 enzymes. Coadministration of posaconazole and pimozide, a CYP3A4 substrate, may result in increased pimozide plasma concentrations, thereby leading to QT prolongation and rarely, torsade de pointes (Prod Info NOXAFIL(R) oral suspension, 2006).
3) Severity: contraindicated

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of pimozide and posaconazole may result in increased pimozide plasma concentration and can lead to QT prolongation and rarely, torsade de pointes. Therefore, concurrent use of pimozide and posaconazole is contraindicated (Prod Info NOXAFIL(R) oral suspension, 2006).
7) Probable Mechanism: increased plasma pimozide levels due to inhibition of CYP3A4-mediated pimozide metabolism

3.5.1.CM Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because Class Ia antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of pimozide with a drug from this class is contraindicated (Prod Info Orap(R), 1999q; Prod Info Quinaglute Dura-tabs(R), 1999; Stratmann et al, 1985; Chow et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class Ia antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999p).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) Several cases of recurrent irregular ventricular tachycardia also known as torsade de pointes have been reported with conventional doses of disopyramide. This condition is more likely to occur with severe repolarization delay and sinus bradycardia or atrioventricular block, especially when disopyramide therapy is combined with other QT interval prolonging agents (Tzivoni et al, 1981; Commerford & Beck, 1980; Croft & Kennelly, 1981). Others have retrospectively determined that women, irrespective of the presence or absence of other underlying heart conditions, are more at risk than men of developing torsades de pointes, in the setting of prolonged QT interval, following disopyramide therapy (Makkar et al, 1993).

3.5.1.CN Prajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999g; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997a).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9

ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.CO Probucol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Orap(R), 1999r). Probucol has been shown to prolong the QTc interval (Gohn & Simmons, 1992; Prod Info Lorelco (R), 1991).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as probucol, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CP Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Because Class Ia antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of pimozide with a drug from this class is contraindicated (Prod Info Orap(R), 1999q; Prod Info Quinaglute Dura-tabs(R), 1999; Stratmann et al, 1985; Chow et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class Ia antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999p).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) Several cases of recurrent irregular ventricular tachycardia also known as torsade de pointes have been reported with conventional doses of disopyramide. This condition is more likely to occur with severe repolarization delay and sinus bradycardia or atrioventricular block, especially when disopyramide therapy is combined with other QT interval prolonging agents (Tzivoni et al, 1981; Commerford & Beck, 1980; Croft & Kennelly, 1981). Others have retrospectively determined that women, irrespective of the presence or absence of other underlying heart conditions, are more at risk than men of developing torsades de pointes, in the setting of prolonged QT interval, following disopyramide therapy (Makkar et al, 1993).

3.5.1.CQ Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999g; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997a).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.CR Prochlorperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of pimozide warns against its administration with other drugs which are also known to prolong the QTc interval, including phenothiazines (Prod Info Thorazine(R), 2002; Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Orap(R), 1999t). The manufacturers of mesoridazine and thioridazine state that concomitant use is contraindicated with other agents known to prolong the QT interval (Prod Info Mellaril(R), 2002; Prod Info Serentil(R), 2001).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide and other drugs that may prolong the QT interval, such as phenothiazines is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R), 1999s).

3.5.1.CS Prochlorperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002a; Prod Info Thorazine(R), 2002a). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001e), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.CT Propafenone
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including Class I antiarrhythmic agents, is contraindicated (Prod Info Orap(R) pimozide, 1999a; Prod Info Tambocor(TM), 1998; Prod Info Enkaid(R), 1988; Larochelle et al, 1984).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class I antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999).

3.5.1.CU Protriptyline

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

2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000; Marshall & Forker, 1982).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.

7) Probable Mechanism: additive effects on QT interval

8) Literature Reports

a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.CV Quinidine

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

2) Summary: Because Class Ia antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of pimozide with a drug from this class is contraindicated (Prod Info Orap(R), 1999q; Prod Info Quinaglute Dura-tabs(R), 1999; Stratmann et al, 1985; Chow et al, 1984).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class Ia antiarrhythmic agents, is contraindicated.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999p).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).

c) Several cases of recurrent irregular ventricular tachycardia also known as torsade de pointes have been reported with conventional doses of disopyramide. This condition is more likely to occur with severe repolarization delay and sinus bradycardia or atrioventricular block, especially when disopyramide therapy is combined with other QT interval prolonging agents (Tzivoni et al, 1981; Commerford & Beck, 1980; Croft & Kennelly, 1981). Others have retrospectively determined that women, irrespective of the presence or absence of other underlying heart conditions, are more at risk than men of developing torsades de pointes, in the setting of prolonged QT interval, following disopyramide therapy (Makkar et al, 1993).

3.5.1.CW Quinupristin

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

2) Summary: Quinupristin/dalfopristin is a major inhibitor of cytochrome P450 3A4 (CYP3A4) isoenzymes, and pimozide is a CYP3A4 substrate. Coadministration of these two agents may likely result in increased plasma concentrations of pimozide, which may lead to QTc interval prolongation and risk of torsades de pointes (Prod Info SYNERCID(R) intravenous injection, 2003; Prod Info ORAP(R) Tablets, 2004).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of pimozide and quinupristin/dalfopristin is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated pimozide metabolism

3.5.1.CX Ranolazine
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Pimozide and ranolazine have both been shown to prolong the QT interval. Concurrent administration of pimozide and ranolazine is contraindicated due to the potential for additive effects on QTc prolongation (Prod Info ORAP(R) oral tablets, 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of pimozide and ranolazine is contraindicated due to the potential for additive effects on QT interval prolongation (Prod Info ORAP(R) oral tablets, 2005).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CY Rilonacept
1) Interaction Effect: altered pimozide plasma concentrations
2) Summary: In states of chronic inflammation, the formation of CYP450 enzymes is suppressed by increased levels of cytokines such as interleukin-1 (IL-1). Upon administration of an IL-1 blocker, such as rilonacept, the formation of CYP450 enzymes could be normalized. In patients receiving CYP450 substrates with a narrow therapeutic index concomitantly, such normalization may have a clinically relevant effect on the CYP450 substrate levels. If rilonacept therapy is initiated in a patient being treated with a CYP450 substrate that has a narrow therapeutic index, such as pimozide, the therapeutic effect of pimozide should be monitored and pimozide dose should be adjusted if necessary (Prod Info ARCALYST(TM) subcutaneous injection, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If rilonacept therapy is initiated in a patient being treated with a CYP450 substrate with a narrow therapeutic index, such as pimozide, monitor for therapeutic effect of pimozide and adjust pimozide dose as needed (Prod Info ARCALYST(TM) subcutaneous injection, 2008).
7) Probable Mechanism: interference with CYP450-mediated pimozide metabolism

3.5.1.CZ Risperidone
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of pimozide states that coadministration of pimozide with drugs known to prolong the QTc interval should be approached with caution (Prod Info Orap(R) pimozide, 1999f). Risperidone has been reported to prolong the QTc interval (Prod Info Risperdal(R), 2002).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as pimozide and risperidone, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999z).
b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999b; Ravin & Levenson, 1997b; Gesell & Stephen, 1997; Lo Vecchio et al, 1996; Brown et al, 1993).

3.5.1.DA Ritonavir
1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ritonavir is an inhibitor of cytochrome P450 3A may result in inhibition of pimozide metabolism. Elevated pimozide serum concentrations have been associated with an increased risk of cardiotoxicity. The concurrent administration of ritonavir and pimozide is contraindicated (Prod Info Norvir (R), 2000; Prod Info Orap(R), 1999aj).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concomitant use of pimozide and ritonavir is contraindicated.

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

3.5.1.DB Roxithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Roxithromycin may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concomitant administration of roxithromycin and pimozide is contraindicated (Flockhart et al, 1996a; Prod Info Orap(R), 1999aa).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of pimozide and roxithromycin is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.DC Saquinavir

1) Interaction Effect: an increased risk of cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest)
2) Summary: Saquinavir is an inhibitor of cytochrome P450 3A may result in inhibition of pimozide metabolism. Elevated pimozide serum concentrations have been associated with an increased risk of cardiotoxicity. The concurrent administration of saquinavir and pimozide is contraindicated (Prod Info Orap (R), 1999au).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concomitant use of pimozide and saquinavir is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.DD Sematilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).

b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.DE Sertindole

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although no drug interaction studies have been performed, the manufacturer of pimozide states that coadministration of pimozide with drugs known to prolong the QTc interval should be approached with caution (Prod Info Orap(R), 1999bd). Sertindole has been reported to prolong the QTc interval (Brown & Levin, 1998a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with agents that prolong the QT interval, such as sertindole, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide tablets, 1999).
b) Thirty, otherwise healthy, schizophrenic patients participated in an open, dose titration (4 to 16 milligrams per day (mg/day)) study to determine the cardiovascular effects of sertindole. At the end of the 3-week study it was concluded that resting heart rate and frequency corrected QT times increased in a dose-related manner, while there was no change in PQ-conduction times, autonomic parasympathetic tone, or blood pressure. Conduction times increased an average 3.5% to 6.5% over the dosing range (Agelink et al, 2001e).
c) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4% (Brown & Levin, 1998). The potential risk of developing torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998). Periodic electrocardiographic monitoring is required in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997).

3.5.1.DF Sertraline

1) Interaction Effect: an increase in plasma pimozide levels
2) Summary: Due to the narrow therapeutic index of pimozide and due to the interaction noted at low dose of pimozide, concomitant administration of sertraline and pimozide is contraindicated (Prod Info Zoloft(R), 2002a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of sertraline in patients taking pimozide is contraindicated.
7) Probable Mechanism: unknown
8) Literature Reports
a) In a controlled trial of a single 2 mg dose of pimozide, sertraline 200 mg daily coadministration to steady state was associated with a mean increase in pimozide area under the concentration-time curve (AUC) and maximum plasma concentrations (Cmax) of about 40%, but was not associated with any changes in EKG. Since the highest recommended pimozide dose (10 mg) has not been evaluated in combination with sertraline, the effect on QT interval and pharmacokinetic parameters at higher than 2 mg are not known. Considering the narrow therapeutic index of pimozide and observed interaction data with low doses, the combination should be avoided (Prod Info Zoloft(R), 2002).

3.5.1.DG Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).
b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.DH Spiramycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Spiramycin has been shown to prolong the QTc interval at the recommended therapeutic dose (Stramba-Badiale et al, 1997). Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including spiramycin, is

contraindicated (Prod Info Orap(R) pimozide, 1999j).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential additive effects on the QT interval, the concurrent administration of spiramycin and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999i).

3.5.1.DI Sulfamethoxazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic dose (Lopez et al, 1987). Even though no formal drug interaction studies have been done, the manufacturer of pimozide warns against its administration with other drugs which are also known to prolong the QTc interval, including cotrimoxazole (Prod Info Orap(R), 1999ad).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as cotrimoxazole and pimozide, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999g).

3.5.1.DJ Sultopride
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of drugs that potentially prolong the QTc interval, such as pimozide and sultopride, should be approached with caution (Lande et al, 1992e; Montaz et al, 1992a; Harry, 1997a; Prod Info Orap(R), 1999bb).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide and other agents that prolong the QT interval, such as sultopride, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999ba).
b) Sultopride may induce prolongation of the QT interval and ventricular arrhythmias including torsades de pointes following therapeutic or toxic doses (Lande et al, 1992d; Montaz et al, 1992; Harry, 1997).

3.5.1.DK Sunitinib
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Sunitinib has been associated with prolongation of the QT interval in a dose dependent manner, with torsade de pointes occurring in less than 0.1% patients exposed to sunitinib (Prod Info SUTENT(R) oral capsules, 2008). Pimozide is also known to prolong the QT interval. Due to the potential for additive effects on the QT interval and increased risk for torsade de pointes, the concomitant use of pimozide and other drugs that prolong the QT interval is contraindicated (Prod Info ORAP(R) oral tablets, 2005a).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Concomitant use of pimozide and drugs that prolong the QT interval, such as sunitinib, is contraindicated due to the potential for additive effects on the QT interval and an increased risk of torsade de pointes (Prod Info ORAP(R) oral tablets, 2005a).
7) Probable Mechanism: additive effects on the QT interval

3.5.1.DL Tedisamil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Even though no formal drug interaction studies have been done, the coadministration of pimozide and other drugs known to prolong the QTc interval, including class III antiarrhythmics is contraindicated (Yamreudeewong et al, 2003a; Prod Info Orap(R), 1999k).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pimozide with other agents that can prolong the QT interval, such as Class III antiarrhythmic agents, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999j).
b) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as pimozide, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003).

3.5.1.DM Telithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pimozide prolongs the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Orap(R), 1999ac). Even though no formal drug interaction studies have been done, pimozide should not be coadministered with other drugs which are also known to prolong the QTc interval, including telithromycin (Prod Info Ketek(TM), 2004; Owens, 2001d).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval, including telithromycin.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999ab).

3.5.1.DN Terfenadine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotics have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Geodon(TM), 2002c; Owens, 2001k; Prod Info Orap(R), 1999bh). Even though no formal drug interaction studies have been done, the coadministration of terfenadine and other drugs known to prolong the QTc interval, including antipsychotics, is contraindicated (Anon, 1997).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT interval, such as antipsychotic agents, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included

prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999bg).

3.5.1.DO Tetrabenazine

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, concomitant use of tetrabenazine with drugs that prolong the QT interval should be avoided. However, if concomitant use is required, the patient should be closely monitored for prolongation of the QT interval (Prod Info XENAZINE(R) oral tablets, 2008). In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval (Prod Info XENAZINE(R) oral tablets, 2008).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.DP Thioridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999c), haloperidol (O'Brien et al, 1999b), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001g), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999e), sertindole (Agelink et al, 2001c), sultopride (Lande et al, 1992b), ziprasidone (Prod Info GEODON (R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.DQ Tipranavir

1) Interaction Effect: serious and/or life-threatening reactions such as cardiac arrhythmias
2) Summary: Because of the potential for serious and/or life-threatening cardiac arrhythmias that can occur with increased plasma concentrations of pimozide, the concurrent use of tipranavir and ritonavir with pimozide is contraindicated. Tipranavir, coadministered with 200 milligrams of ritonavir, is a net inhibitor of cytochrome P450 3A. Concomitant administration of tipranavir and ritonavir with pimozide, which is metabolized by cytochrome P450 3A4 enzymes, could result in an increased plasma concentration of pimozide and is contraindicated (Prod Info Aptivus (R) capsules, 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of tipranavir and ritonavir, when coadministered with pimozide is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.DR Tramadol

1) Interaction Effect: an increased risk of seizures
2) Summary: Seizures have been reported in patients using tramadol. The manufacturer of tramadol states that combining neuroleptic medications with tramadol may enhance the risk of seizures (Prod Info Ultram(R), 1998).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution should be used if tramadol is to be administered to patients receiving neuroleptic therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.
7) Probable Mechanism: unknown

3.5.1.DS Trifluoperazine

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

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of pimozide warns against its administration with other drugs which are also known to prolong the QTc interval, including phenothiazines (Prod Info Thorazine(R), 2002; Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Orap(R), 1999t). The manufacturers of mesoridazine and thioridazine state that concomitant use is contraindicated with other agents known to prolong the QT interval (Prod Info Mellaril(R), 2002; Prod Info Serentil(R), 2001).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of pimozide and other drugs that may prolong the QT interval, such as phenothiazines is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R), 1999s).

3.5.1.DT Trifluoperazine

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

2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002a; Prod Info Stelazine(R), 2002a; Prod Info Thorazine(R), 2002a). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001e), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.

7) Probable Mechanism: additive QT prolongation

3.5.1.DU Trimethoprim

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

2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic dose (Lopez et al, 1987). Even though no formal drug interaction studies have been done, the manufacturer of pimozide warns against its administration with other drugs which are also known to prolong the QTc interval, including cotrimoxazole (Prod Info Orap(R), 1999ad).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as cotrimoxazole and pimozide, is contraindicated.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999g).

3.5.1.DV Trimipramine

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

2) Summary: Although citing no data, the manufacturer of pimozide states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Orap(R), 1999ap). Tricyclic antidepressants (TCAs) at therapeutic doses can cause QT prolongation (Prod Info Norpramin(R), 2000;

Marshall & Forker, 1982).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Because of the potential to prolong the QT interval, concurrent administration of a tricyclic antidepressant and pimozide is contraindicated.
7) Probable Mechanism: additive effects on QT interval
8) Literature Reports
a) Electrocardiogram (ECG) changes seen during clinical trials of pimozide in Tourette's syndrome and schizophrenia patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day (Prod Info Orap(R) pimozide, 1999k).

3.5.1.DW Troleandomycin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Troleandomycin may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum concentrations of pimozide have been associated with adverse cardiovascular effects, including QT interval prolongation, cardiac arrhythmias, and sudden death. The concomitant administration of pimozide and troleandomycin is contraindicated (Flockhart et al, 1996c; Prod Info Orap(R), 1999am).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concurrent use of pimozide and troleandomycin is contraindicated.
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.DX Vasopressin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pimozide and vasopressin have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Orap(R), 1999c; Mauro et al, 1988). Even though no formal drug interaction studies have been done, the coadministration of these two drugs, known to prolong the QTc interval, is contraindicated.
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as pimozide and vasopressin, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia.The manufactuer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R), 1999b).

3.5.1.DY Vitex
1) Interaction Effect: decreased effectiveness of dopamine antagonists
2) Summary: Theoretically, the dopamine agonist activity of Vitex may oppose that of dopamine antagonists, decreasing their effectiveness. Vitex has been effective in alleviating luteal phase defects due to hyperprolactinemia and in relieving symptoms related to premenstrual tension syndrome (Milewicz et al, 1993a; Lauritzen et al, 1997a). Vitex reduced prolactin secretion in humans (Milewicz et al, 1993a). In vitro, Vitex inhibited prolactin release by binding to the D2 receptor (Jarry et al, 1994a).
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If therapy is initiated with Vitex and a dopamine antagonist, monitor closely for return of symptoms previously controlled by the dopamine antagonist.
7) Probable Mechanism: dopamine agonism of Vitex may counteract dopamine antagonists
8) Literature Reports
a) Vitex agnus castus (Vitex) effectively normalized prolactin release in a randomized double-blind, placebo-controlled trial of 52 women with luteal phase defects due to latent hyperprolactinemia. Administration of Vitex agnus castus 20 mg daily for three months reduced prolactin release (from 23.7 to 22.5 nanogram (ng)/mL; p equal to 0.23), normalized shortened luteal phases (from 5.5 days to 10.5 days; p less than 0.005), and eliminated deficits in luteal progesterone synthesis (from 2.46 ng/mL to 9.69 ng/mL; p less than 0.001). No side effects were noted (Milewicz et al, 1993).

b) Vitex agnus castus and pyridoxine caused a similar reduction on the premenstrual tension scale (PMTS) in a randomized, controlled trial of 127 women with PMTS. Patients taking Vitex agnus castus (Agnolyt(R)) experienced more relief from breast tenderness, inner tension, headache, edema, constipation, and depression than those taking pyridoxine. Patients in the Vitex agnus castus group receive one capsule of Agnolyt(R) and one placebo capsule daily for 3 menstrual cycles. Patients in the pyridoxine group received one placebo capsule twice daily on days 1-15 of the menstrual cycle and pyridoxine 100 mg twice daily on days 16 to 35 of the menstrual cycle for 3 menstrual cycles. Unspecified gastrointestinal disturbances occurred in the treatment group along with two cases of skin reaction and one transient headache (Lauritzen et al, 1997).
c) In vitro, Vitex (Agnus castus) was found to bind to the D2 receptor in rat pituitary cell cultures. Basal prolactin release was significantly inhibited by 0.5 milligram (mg) and 1 mg of vitex extract/mL culture medium (p less than 0.05). Agnus castus extract doses from 0.125 mg/mL to 1 mg/mL significantly suppressed prolactin release in cells stimulated by thyrothropin releasing hormone (TRH) (p less than 0.05). Dopaminergic action was demonstrated in the rat corpus striatum membrane dopamine receptor assay. Agnus castus extract did not affect basal luteinizing hormone (LH) or follicle-stimulating hormone (FSH), indicating selectivity for prolactin secretion, and not generalized inhibition of pituitary hormone secretion. The effect was not due to a cytotoxic effect as demonstrated by the lack of effect on the MTT-conversion test. The authors concluded that Agnus castus exerted its prolactin inhibiting effect via stimulation of D2 receptors in the pituitary (Jarry et al, 1994).

3.5.1.DZ Voriconazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsade de pointes, cardiac arrest)
2) Summary: The systemic exposure to pimozide may be significantly increased by concomitant administration of voriconazole. The metabolism of pimozide may be inhibited by concomitant administration of voriconazole. Increased plasma concentrations of pimozide can lead to QT prolongation and rare occurrence of torsade de pointes (Prod Info VFEND(R) IV injection, oral tablets, suspension, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of voriconazole and pimozide is contraindicated (Prod Info VFEND(R) IV injection, oral tablets, suspension, 2008).
7) Probable Mechanism: inhibition by voriconazole of cytochrome P450 3A4-mediated pimozide metabolism

3.5.1.EA Zileuton
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Zileuton may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concurrent use of zileuton or any inhibitor of cytochrome P450 3A enzymes and pimozide is not recommended (Prod Info Orap(R), 1999av).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of pimozide with an inhibitor of cytochrome P450 3A enzymes, such as zileuton, should be avoided.
7) Probable Mechanism: inhibition by zileuton of cytochrome P450 3A-mediated pimozide metabolism

3.5.1.EB Ziprasidone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including pimozide (Prod Info Geodon(TM), 2002b).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone and pimozide is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.EC Zolmitriptan
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Pimozide and zolmitriptan have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Zomig(R), 2002; Prod Info Orap(R), 1999y). Even though no formal drug interaction studies have been done, the coadministration of these two drugs, known to prolong the QTc interval, is contraindicated.
3) Severity: contraindicated

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as pimozide and zolmitriptan, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) In experimental studies of conditions other than Tourette's Disorder, sudden, unexpected deaths have occurred. The patients were receiving pimozide dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozide treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Prod Info Orap(R) pimozide, 1999e).

3.5.1.ED Zotepine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Though no drug interaction studies have been performed, the manufacturer of pimozide states that coadministration pimozide with other drugs that potentially prolong the QTc interval is contraindicated (Prod Info Orap(R), 1999aw). Zotepine can prolong the QTc interval (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of agents that prolong the QT interval, such as zotepine and pimozide, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation

3.5.2 Drug-Food Combinations

3.5.2.A Grapefruit Juice
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Grapefruit juice may inhibit the metabolism of pimozide, resulting in increased serum concentrations of this agent. Elevated serum levels of pimozide have been associated with adverse cardiovascular effects including QT interval prolongation, cardiac arrhythmia, and sudden death. The concurrent use of pimozide and grapefruit juice should be avoided (Prod Info Orap(R), 1999bk).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Counsel patients to avoid grapefruit juice during pimozide therapy. Orange juice may be substituted as it provides the same basic nutrients but is not known to inhibit drug metabolism.
7) Probable Mechanism: inhibition by grapefruit juice of cytochrome P450 3A-mediated pimozide metabolism

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters
A) Therapeutic
1) Physical Findings
a) Decrease in severity or elimination of target psychotic symptoms:
1) Positive psychotic symptoms (delusions, auditory hallucinations, racing thoughts)
2) Negative psychotic symptoms (anhedonia, apathy, amotivation, ambivalence).
b) Improvement in socialization, grooming, and attention to activities of daily living.

B) Toxic
1) Physical Findings
a) An ECG should be performed before initiation of pimozide therapy and periodically thereafter, especially during periods of dose adjustment. The QTc interval should not exceed 0.47 seconds in children or 0.52 seconds in adults, or more than 25% above the patient's original baseline (Prod Info Orap(R), 2003).
b) Abnormal involuntary movement scale (AIMS) examination or similar test for tardive dyskinesia every 6 months.
c) Assessment for extrapyramidal symptoms (EPS) during dose adjustment and every 3 months.

4.2 Patient Instructions

A) Pimozide (By mouth)

Pimozide

Treats symptoms of Tourette's syndrome such as uncontrolled body movements or vocal sounds. It is used when these symptoms are severe.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to pimozide or medicines to treat mental problems such as haloperidol, molindone, loxapine, thiothixene, perphenazine, thioridazine, and others. You should not use this medicine if you are using itraconazole, ketoconazole, ritonavir, saquinavir, indinavir, nelfinavir, nefazodone, or zileuton. You should not use this medicine if you have an irregular heartbeat or if you are using any of these antibiotic medicines: clarithromycin, erythromycin, azithromycin, dirithromycin, or troleandomycin. Pimozide used with certain antibiotics can cause severe heart problems.

How to Use This Medicine:
Tablet
Your doctor will tell you how much medicine to use and how often. You should not use more of the medicine than your doctor ordered.

If a Dose is Missed:
Use the missed dose as soon as possible, unless it is almost time for your next dose.
Skip the missed dose if it is almost time for your next regular dose.
You should not use two doses at the same time.

How to Store and Dispose of This Medicine:
Store the tablets at room temperature, away from heat, moisture, and direct light.
Keep all medicine out of the reach of children.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Tell your doctor if you are also using pemoline (Cylert®), methylphenidate (Ritalin®), or amphetamines (Dexedrine®).
Make sure your doctor knows if you are using other drugs that could make you sleepy, such as sleeping pills, tranquilizers, antidepressants, strong pain killers, or cold or allergy medicine. Avoid drinking alcohol while using this medicine. You may get too drowsy or sedated if you drink alcohol or use medicines that cause drowsiness with pimozide.
Some antidepressants, tranquilizers, and medicines to treat mental problems, emotional problems, or an irregular heartbeat can cause or worsen heart problems if used with pimozide. Talk with your doctor about this.
Do not drink grapefruit juice while using this medicine.

Warnings While Using This Medicine:
Check with your doctor before using pimozide if you have seizures, an enlarged prostate, trouble urinating, glaucoma, or heart, liver, or kidney disease.
If you are pregnant or breastfeeding, talk to your doctor before using this medicine.
This medicine may make you drowsy or dizzy. Be careful if driving or using machinery.
Do not suddenly stop using pimozide without checking with your doctor. You may need to use smaller and smaller doses before completely stopping the medicine.
This medicine may cause side effects that include muscle spasms, twitching in the face and body, and uncontrolled tongue or jaw movement. Talk to your doctor about this.
Your doctor may want to check your heart rhythm while you are using this medicine. Make sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Fast or irregular heartbeat, fast breathing
Fever, severe muscle stiffness

Muscle spasms, twitching, uncontrolled tongue or jaw movement
Restlessness or feeling as if you need to be moving constantly
Spasms or cramps in the neck, face, or back

If you notice these less serious side effects, talk with your doctor:
Constipation
Drowsiness, dizziness, headache
Dry mouth
Vision changes, such as trouble focusing

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

4.3 Place In Therapy

A) Pimozide's primary place in therapy is in the treatment of Tourette's syndrome in patients who are refractory to haloperidol or who develop incapacitating side effects during haloperidol therapy (Shapiro & Shapiro, 1984).
B) Clinical studies have demonstrated no significant advantage of pimozide over other antipsychotic agents in the treatment of chronic schizophrenic patients (Clark et al, 1975). The drug may find usefulness due to its long half-life, when given orally once weekly in chronic schizophrenia as an alternative to intramuscular fluphenazine decanoate given every 2 weeks. The drug should also be considered in patients where sedation is a problem with other antipsychotic agents. Pimozide may prove useful as an adjuvant to maintenance therapy with other antipsychotic agents in chronic schizophrenia. Also, pimozide may be effective in schizophrenic patients unresponsive to other antipsychotic medications.
C) Most controlled studies have indicated that pimozide is equally effective as other antipsychotic agents in the treatment of chronic schizophrenia (Kolivakis et al, 1974; Cesarec et al, 1974; Kenway & Masheter, 1971; Hellon, 1971; Kline et al, 1975; Clark et al, 1975). However, there appears to be an advantage of pimozide over other agents in the treatment of patients with poor social adjustment with symptoms of emotional withdrawal, disturbed thought content, hallucinations and blunted affect (Pinder et al, 1976). Pimozide is less effective than the other antipsychotic agents, in general, for the excited, agitated chronic schizophrenic patient.
D) Pimozide is a useful addition to the formulary of institutions which handle Tourette's syndrome and other difficult-to-treat psychiatric patients.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Pimozide is a potent neuroleptic agent, a diphenylbutylpiperidine derivative, structurally dissimilar from phenothiazines, butyrophenones, and thioxanthenes that elicits antipsychotic effects via central antidopaminergic activity. The drug is effective orally and has a long serum half-life (greater than 50 hours). It has been primarily evaluated in the maintenance treatment of chronic schizophrenia (Andersen et al, 1974; Gross, 1974; Janssen et al, 1972).
2) Pimozide, similar to other neuropsychotic agents, is a central antidopaminergic agent which increases dopamine turnover in the brain, but may be more potent than other agents. The drug concentrates in areas rich in dopaminergic neurons (Janssen et al, 1968; Anden et al, 1970). There is evidence that pimozide exhibits more specific antipsychotic effects than other antipsychotic agents with respect to delusions, autism, emotional withdrawal and apathy in chronic schizophrenia (Janssen et al, 1968; Smythies & Beaton, 1974; Stier et al, 1978).
3) Pimozide has also been effective in the treatment of Gilles de la Tourette syndrome, with benefits being similar to those of haloperidol but producing less sedation (Ross & Moldofsky, 1978). The drug's mechanism of action in Tourette's syndrome is related to its dopaminergic blocking activity. The drug may also produce secondary alterations in central dopamine metabolism and function, accompanying receptor blockade, which may contribute to its therapeutic effects (Prod Info Haldol(R), 1984).

4.5 Therapeutic Uses

Anorexia nervosa

Anxiety

Chronic schizophrenia

Gilles de la Tourette's syndrome

Huntington's disease

Obsessive-compulsive disorder

Trigeminal trophic syndrome

4.5.A Anorexia nervosa

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Unclear efficacy
See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

3) Pediatric:

a) All 10 adolescent anorectic females studied for a period of 20 weeks succeeded in gaining body weight with or without pimozide (Weizman et al, 1985; Plantey, 1977). Five patients were treated by behavior therapy programs and the other 5 were treated with pimozide. Serum prolactin levels were increased in the 5 patients receiving pimozide, while no elevation was observed in patients undergoing behavior therapy.

b) One report has described the successful use of pimozide 4 milligrams orally 3 times daily for one month in anorexia nervosa in a 17-year-old male. Dramatic improvement was observed in 3 weeks with the patient gaining 9 kg. Obsession with weight disappeared at this time as well as bradycardia and overactivity (Plantey, 1977).

4.5.B Anxiety

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

As effective as chlordiazepoxide and diazepam in the treatment of non-psychotic patients with anxiety
However, offers no advantage over benzodiazepines

3) Adult:

a) Pimozide has been shown to be more effective than placebo in anxiety (Van Mierlo, 1972), and as effective as haloperidol (Kenway, 1973a). Pimozide 2 milligrams daily has produced similar effects to diazepam 10 milligrams daily or chlordiazepoxide 40 milligrams daily (Anon, 1972; Reyntjens & Van Mierlo, 1972).

b) The addition of pimozide 2 milligrams daily to chlordiazepoxide 30 to 60 milligrams daily did not result in a more rapid antianxiety effect, enhanced antianxiety effect or reduction of chlordiazepoxide dose, or a decrease in the incidence of side effects (Anon, 1975).

4.5.C Chronic schizophrenia

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Efficacious in chronic SCHIZOPHRENIA (Kline et al, 1977; Donlon et al, 1977; Singh, 1971; Sugarman, 1971; Masheter, 1971; Arfwidsson et al, 1971)
Doses range from 2 to 40 milligrams (mean: 6 milligrams daily)

3) Adult:

a) Pimozide has been reported to be more specific than other antipsychotic agents for autistic patients with emotional withdrawal, delusions, and hallucinations as opposed to agitated or aggressive type patients with chronic schizophrenia (Pinder et al, 1976b; Janssen et al, 1972a). Pimozide may have special usefulness, as opposed to other agents, in improving emotional withdrawal and assisting in resocialization of chronic schizophrenic patients (Gross, 1974b; Kolivakis et al, 1974b; Janssen et al, 1972a; Huber et al, 1971a; Kenway & Masheter, 1971b). However, at least one report has indicated that pimozide was no more effective than chlorpromazine in improving emotional withdrawal and social competence in chronic schizophrenia (Wilson et al, 1982).

b) A significant improvement in negative symptoms, but not positive symptoms was observed with pimozide in schizophrenic patients (Feinberg et al, 1988). The dose of pimozide was started at 4 milligrams/day and increased over 4 weeks to an average dose of 12.6 milligrams/day.

c) Pimozide given intermittently has proven effective in the management of schizophrenia, due to its long half-life (McCreadie et al, 1982b; McCreadie et al, 1980a). The drug has been administered orally once weekly, producing equivalent clinical effects as that of fluphenazine decanoate administered once every 2 weeks (McCreadie et al, 1982b).

d) Pimozide has been successful when used concurrently with maintenance antipsychotic medications on

improving work behavior, work habits, and mental status in chronic schizophrenics following its addition to maintenance therapy (8 milligrams daily) (Nakra & Wickramasinghe, 1980). The drug has been used successfully as replacement therapy in patients unresponsive to other neuroleptic agents, resulting in improvement in apathy and withdrawal in many patients who were unresponsive to other agents prior to pimozide therapy (Stirling, 1979).

e) Pimozide in combination with other antipsychotic medications improved social behavior in chronic schizophrenia (Nakra et al, 1980). Pimozide was administered in oral doses of 8 milligrams daily for 12 weeks to 20 patients receiving other medications (haloperidol, flupenthixol, trifluoperazines, thiothixine, fluphenazine, promazine, or chlorpromazine). Pimozide significantly improved social behavior in terms of work behavior, work habits, and mental status after 8 weeks of treatment.

f) Pimozide was effective as single agent therapy for chronic schizophrenia in patients who were primarily withdrawn. Patients were administered pimozide 8 to 20 milligrams daily after withdrawal of all other medications for a period of one month. General improvement was observed after assessment at 4 and 6 months (Cheadle & Freedman, 1979). Marked improvement was reported in 6 of 12 patients with chronic schizophrenia undergoing acute exacerbations with pimozide in doses up to 16 milligrams daily over a period of 10 weeks. Patients demonstrated improvement with thought disorders, apathy, emotional withdrawal, motor retardation and depression. This study supports the antiautistic and antidelusional effects of pimozide (Stier et al, 1978a).

4.5.D Gilles de la Tourette's syndrome

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (12 years and older)
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective Gilles de la Tourette syndrome
Effective in patients who were unable to tolerate or were unresponsive to haloperidol (Shapiro & Shapiro, 1984; Shapiro et al, 1983)

3) Adult:

a) Haloperidol has been the drug of choice in Gilles de la Tourette syndrome, its efficacy being related to dopamine receptor blocking activity in the CNS. Pimozide is a more specific antidopaminergic agent. Although effective, superiority of pimozide over haloperidol has not been adequately demonstrated (Colvin & Tankanow, 1985a). The drug is indicated as reserve therapy for Tourette's syndrome in patients who have not responded to haloperidol or who cannot tolerate toxicity of haloperidol. A review of the efficacy and toxicity of pimozide in the treatment of tic and Tourette disorders is available (Shapiro et al, 1987).

b) In 9 patients with Gilles de la Tourette syndrome both haloperidol and pimozide were effective (Ross & Moldofsky, 1978b). In this double-blind study, patients were assigned to pimozide or haloperidol, each in doses of 2 milligrams initially every morning, increasing by 2 milligrams every second day until symptoms disappeared or until side effects were observed or until maximum doses of 12 milligrams daily were obtained. A follow-up period of 420 months was undertaken. Both pimozide and haloperidol significantly reduced mean 5-minute tic counts, with no significant difference between the 2 drugs. Both haloperidol and pimozide were more effective than placebo. Follow-up at 4 to 20 months indicated that 6 of 7 patients continuing on pimozide and one of 2 patients continuing on haloperidol had a greater than 75% improvement in symptoms. Significantly fewer days of lethargy or tiredness was associated with pimozide than haloperidol. Anticholinergic and extrapyramidal effects were similar with both agents. Pimozide is an effective alternative to haloperidol in Gilles de la Tourette syndrome, particularly in haloperidol nonresponders or patients receiving haloperidol but developing incapacitating side effects.

4.5.E Huntington's disease

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in the treatment of Huntington's chorea (Siegmund et al, 1982; Fog & Pakkenberg, 1970)

3) Adult:

a) Oral pimozide 16 milligrams daily (in 3 to 4 divided doses; maximum 40 milligrams daily) produced good long-term results in 9 of 11 patients with Huntington's chorea, with significant improvement in hyperkinesia. These patients were discharged from the hospital indicating therapy may permit social reintegration and improved quality of life for Huntington's patients. However, both haloperidol and chlorpromazine have been utilized with some degree of success in Huntington's chorea (Pinder et al, 1976b) and controlled studies are required to determine any benefits of pimozide.

4.5.F Obsessive-compulsive disorder

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Useful in treating some subtypes of obsessive compulsive disorder

3) Adult:

a) The addition of pimozide was useful in treating a possible subtype of obsessive compulsive disorder (OCD) in a patient with a dual diagnosis of OCD and chronic multiple tics or Tourette's Syndrome. A 25-year-old man with a history of Tourette's Syndrome presented for treatment of OCD symptoms (Delgado et al, 1990). Fluvoxamine alone appeared to exacerbate tics leading to the onset of coprolalia, without improving OCD symptoms. Pimozide alone reduced tics very slightly. In this patient, the combination of fluvoxamine (150 to 250 milligram/day) and pimozide (1 milligram/day) appeared to be necessary for clinical improvement of OCD symptoms, suggesting that both the dopamine and serotonin systems were involved in the near remission of OCD symptoms and the reduction of tics.

b) Pimozide was used successfully for 7 months in ONYCHOTILLOMANIA. The condition was reported to be a manifestation of obsessive compulsive disorder (Hamann, 1982).

4.5.G Trigeminal trophic syndrome

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

In one case, successfully treated severe trigeminal neurotrophic ulceration

3) Adult:

a) A rare case was described of an 82-year-old woman with severe trigeminal neurotrophic ulceration which improved substantially with pimozide, given for treatment of unrelated paranoid symptoms. The established use of pimozide in delusional parasitosis in relationship to this case was discussed (Mayer & Smith, 1993).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Chlorpromazine

Fluphenazine

Haloperidol

Levosulpiride

Trifluoperazine

4.6.A Chlorpromazine

Mania

Schizophrenia

4.6.A.1 Mania

a) SUMMARY: Pimozide is at least as effective as chlorpromazine in the treatment of mania (Cookson et al, 1979; Cookson et al, 1981; Cookson et al, 1980a). In a double-blind, randomized fashion, 23 mania patients received either pimozide 2 milligrams (mg) or chlorpromazine 100 milligrams (mg), with adjustments to a maximum of 32 mg/day and 1600 mg/day, respectively. The patients were evaluated for 14 days using two scales, the Mania Rating Scale (MRS) and the Petterson Rating Scale (PRS). MRS evaluation demonstrated chlorpromazine to be more effective than pimozide, probable due to greater sedative effects (Cookson et al, 1981).

4.6.A.2 Schizophrenia

a) Similar clinical effects were reported with pimozide (mean dose, 7 milligrams (mg) daily) and chlorpromazine sustained-release (mean dose, 216 mg daily) in the treatment of chronic schizophrenia (Kolivakis et al, 1974a). Similar results were observed in chronic schizophrenic patients in a double-blind study over 52 weeks (Wilson et al, 1982a). Average daily doses of pimozide 7.3 mg were as effective as chlorpromazine 381 mg. There was no significant difference in improvement or side effects between the two drug treatment groups except for a higher incidence of skin reactions with chlorpromazine. However, the authors were unable to replicate previous data indicating the special utility of pimozide for improvement of emotional withdrawal and social competence in schizophrenia in this long-term study. All patients in this study were stable, compliant patients which may not be the optimal group for the evaluation of these effects.

4.6.B Fluphenazine

4.6.B.1 Schizophrenia

a) SUMMARY: Clinical studies have reported the equivalent effects of fluphenazine and pimozide in chronic schizophrenia (Cesarec et al, 1974a; Chouinard et al, 1970; Kenway & Masheter, 1971a; Lapierre & Lavellee, 1975; Donlon et al, 1977; Morris et al, 1970; Shepherd, 1979).
b) The comparative efficacy of fluphenazine HCl (12.5 milligrams daily, average) and pimozide (9.6 milligrams daily, average) were reported in the treatment of chronic schizophrenia in a 12-month study. Both drugs were equally effective in maintaining control of symptomatology at a better level than previous medication (Donlon et al, 1977).
c) Other reports have reported the comparability of long-acting fluphenazine and pimozide. There was equivalent efficacy with fluphenazine decanoate given biweekly and pimozide 4 days each week (McCreadie et al, 1980). In a subsequent report, pimozide once weekly (in doses up to 60 milligrams) and fluphenazine decanoate (up to 50 milligrams every 2 weeks) were equally effective in the management of chronic schizophrenia (McCreadie et al, 1982). Tardive dyskinesia was more frequent in pimozide patients. Pimozide may be considered an alternative to intramuscular fluphenazine for chronic schizophrenia.
d) Depot fluphenazine decanoate and oral pimozide were compared in 36 schizophrenic outpatients over 1 year in a double-blind, placebo-controlled trial. Analyses of Social Behavior Assessment Schedule (SBAS) data from pre-trial and end of study assessments revealed no significant advantage for either of the treatments (Barnes et al, 1983).

4.6.C Haloperidol

Gilles de la Tourette's syndrome

Schizophrenia

4.6.C.1 Gilles de la Tourette's syndrome

a) The efficacy of pimozide in Tourette's syndrome was evaluated (Colvin & Tankanow, 1985). Although effective, superiority of the drug over haloperidol has not been adequately demonstrated. The drug is indicated as reserve therapy for Tourette's syndrome in patients who have not responded to haloperidol or who cannot tolerate toxicity of haloperidol.
b) In a 6-month, controlled crossover trial of children and adolescents (n=22) with Tourette's syndrome, only pimozide demonstrated statistical improvement over placebo on the global rating scale (p less than 0.05). However, pimozide and haloperidol did not differ statistically in efficacy from each other. Overall, 64% of subjects attained the goal of 70% tic reduction with active therapy as compared to only 23% with placebo. The mean effective doses of pimozide and haloperidol were equivalent (3.4 and 3.5 milligrams daily, respectively). Haloperidol was associated with a greater incidence of extrapyramidal symptoms (Sallee et al, 1997).
c) Haloperidol was compared with pimozide in 9 patients with Gilles de la Tourette syndrome (Ross & Moldofsky, 1978a). In this double-blind study, patients were assigned to pimozide or haloperidol, each in doses of 2 milligrams (mg) initially every morning, increasing by 2 mg every second day until symptoms disappeared or until side effects were observed or until maximum doses of 12 mg daily were obtained. A follow-up period of 420 months was undertaken. Both pimozide and haloperidol significantly reduced mean 5-minute tic counts, with no significant difference between the 2 drugs. Both haloperidol and pimozide were more effective than placebo. Follow-up at 4 to 20 months indicated that 6 of 7 patients continuing on pimozide and one of 2 patients continuing on haloperidol had a greater than 75% improvement in symptoms. Significantly fewer days of lethargy or tiredness was associated with pimozide than haloperidol. Anticholinergic and extrapyramidal effects were similar with both agents. Pimozide may be an effective alternative to haloperidol in Gilles de la Tourette syndrome, particularly in haloperidol non-responders or patients receiving haloperidol but developing incapacitating side effects.
d) Haloperidol was compared with pimozide in a double-blind, parallel, crossover study lasting 6 weeks in 57 patients with Tourette's syndrome. The maximum dose of haloperidol was 10 milligrams (mg)/day, and for pimozide it was 20 mg/day. Haloperidol was slightly more effective than pimozide in the treatment of

Tourette's syndrome. Adverse effects of haloperidol were not significantly different than those of pimozide. Clinically significant cardiac effects did not occur. However, due to the potential of pimozide prolonging QTC intervals, haloperidol is the drug of choice for initial treatment of Tourette's syndrome (Shapiro et al, 1989).

4.6.C.2 Schizophrenia

a) SUMMARY: Pimozide is at least as effective as haloperidol in the treatment of chronic schizophrenia.
b) Pimozide was compared with haloperidol (5 to 50 milligrams/day (mg/day) of either) in relation to dopaminergic blockade and clinical response in 22 patients with schizophrenia. The drugs were equally effective. There was no correlation between either dopaminergic blockade or blood level and therapeutic response (Silverstone et al, 1984).
c) Pimozide 306 mg daily was superior to haloperidol 7 to 14 mg daily in chronic schizophrenia in a small double-blind study. A subsequent report has indicated the equivalent efficacy of pimozide 10 to 60 mg daily and haloperidol 10 to 60 mg daily in acute schizophrenia (Haas & Beckmann, 1982). In this study, however, extrapyramidal effects were more pronounced in patients using pimozide (Gowardman et al, 1973).

4.6.D Levosulpiride

4.6.D.1 Schizophrenia

a) A single-blind, randomized clinical study compared the therapeutic efficacy of levosulpiride and pimozide in the treatment of schizophrenic patients with negative symptoms not relieved by haloperidol. Following Andreasen's diagnostic criteria based on the Scale of Assessment of Positive Symptoms and the Scale of Assessment of Negative Symptoms, the study showed that the therapeutic activity of low doses of levosulpiride (200 milligrams/day (mg/day) orally) was higher than pimozide 4 mg/day orally (De Ronchi et al, 1996).

4.6.E Trifluoperazine

4.6.E.1 Schizophrenia

a) Comparative studies have reported the similarity of trifluoperazine (5 to 30 milligrams daily) and pimozide (2 to 80 milligrams daily) in the management of chronic schizophrenia (Claghorn, 1974; Kline et al, 1975a). Other reports have indicated the superiority of pimozide over trifluoperazine for retardation, emotional withdrawal and unusual thought content in chronic schizophrenia (Andersen et al, 1971; Andersen et al, 1974a; Gross, 1974a). A more recent report has confirmed these observations (Kline et al, 1977), with pimozide being reported superior to trifluoperazine in improving anxiety, motor retardation, suspiciousness and emotional adjustment, indicating its preferability in certain apathic schizophrenic patients.

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