DRUGDEX® Evaluations

HALOPERIDOL

0.0 Overview

1) Class

a) This drug is a member of the following class(es):

Antipsychotic
Butyrophenone
Dopamine Antagonist

2) Dosing Information

a) Haloperidol

1) Adult

a) Gilles de la Tourette's syndrome

1) 0.5 to 2 mg (moderate symptoms) OR 3 to 5 mg (severe symptoms) ORALLY 2 to 3 times daily (Proc Info haloperidol oral tablets, 2008; Prod Info haloperidol oral solution, 2008)

b) Psychotic disorder

1) 0.5 to 2 mg (moderate symptoms) OR 3 to 5 mg (severe symptoms) ORALLY 2 to 3 times daily (Proc Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

c) Schizophrenia

1) 0.5 to 2 mg (moderate symptoms) OR 3 to 5 mg (severe symptoms) ORALLY 2 to 3 times daily (Proc Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

2) Pediatric

a) Not FDA approved in children less than 3 years of age (Prod Info haloperidol oral tablets, 2008; Prod Info haloperidol oral solution, 2008)

1) Gilles de la Tourette's syndrome

a) age 3 to 12 yr (weight range 15 to 40 kg), begin with the lowest possible dose (0.5 mg per day) c weight-based dose (0.05 to 0.075 mg/kg/day) ORALLY in 2 to 3 divided doses, whichever is less; increase by 0.5 mg at 5 to 7 day intervals to therapeutic effect (Prod Info haloperidol oral tablets, 20 Prod Info haloperidol oral solution, 2008)

b) over age 12 years, 0.5 to 2 mg (moderate symptoms) or 3 to 5 mg (severe symptoms) orally 2 to times daily (Prod Info haloperidol oral tablets, 2008; Prod Info haloperidol oral solution, 2008)

2) Hyperactive behavior, (Short-term treatment) after failure to respond to non-antipsychotic medication and psychotherapy

a) 3 to 12 yr (weight range 15 to 40 kg), 0.05 to 0.075 mg/kg/day ORALLY in 2 to 3 divided doses, increase by 0.5 mg at 5 to 7 day intervals to therapeutic effect; MAX daily dose 0.075 mg/kg/day (Pr Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

3) Psychotic disorder

a) 3 to 12 yr (weight range 15 to 40 kg), 0.05 mg/kg/day ORALLY in 2 to 3 divided doses, may increase by 0.5 mg/day at 5 to 7 day intervals to therapeutic effect; MAX daily dose 0.15 mg/kg/day (Prod Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

b) 12 yr and older, 0.5 to 2 mg (moderate symptoms) OR 3 to 5 mg (severe symptoms) ORALLY 2 3 times daily (Prod Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

4) Schizophrenia

a) 3 to 12 yr (weight range 15 to 40 kg), 0.05 mg/kg/day ORALLY in 2 to 3 divided doses, may increase by 0.5 mg/day at 5 to 7 day intervals to therapeutic effect; MAX daily dose 0.15 mg/kg/day (Prod Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

b) 12 yr and older, 0.5 to 2 mg (moderate symptoms) OR 3 to 5 mg (severe symptoms) ORALLY 2 3 times daily (Prod Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

b) Haloperidol Decanoate

1) Adult

a) Chronic schizophrenia

1) stabilized on low daily oral doses (up to 10 mg/day), 10 to 15 times previous daily oral dose IM month or every 4 wks; MAX initial dose 100 mg (Prod Info haloperidol decanoate injection, 2005)

2) stabilized on high daily oral doses, 20 times previous daily oral dose IM for the first month, then 10 to times previous daily oral dose IM monthly or every 4 wks; MAX initial dose 100 mg (Prod Info haloperido decanoate injection, 2005)

2) Pediatric

a) Safety and effectiveness have not been established in children

c) Haloperidol Lactate

1) Adult

a) Gilles de la Tourette's syndrome

1) 2 to 5 mg IM, may repeat every 4 to 8 hr depending on patient response; increase to every 1 hr if needed (Prod Info haloperidol lactate IM injection, 2005)

b) Schizophrenia

1) 2 to 5 mg IM, may repeat every 4 to 8 hr depending on patient response; increase to every 1 hr if needed (Prod Info HALDOL(R) immediate release IM injection, 2008)

2) Pediatric

a) safety and effectiveness have not been established in pediatric patients (Prod Info HALDOL(R) immediate release IM injection, 2008)

3) Contraindications

a) Haloperidol

1) comatose state from any cause (Prod Info haloperidol oral tablets, 2008)
2) hypersensitivity to haloperidol (Prod Info haloperidol oral tablets, 2008)
3) Parkinson's disease (Prod Info haloperidol oral tablets, 2008)
4) toxic central nervous system depression, severe (Prod Info haloperidol oral tablets, 2008)

b) Haloperidol Decanoate

1) comatose state from any cause (Prod Info HALDOL(R) Decanoate IM injection, 2008)
2) hypersensitivity to haloperidol (Prod Info HALDOL(R) Decanoate IM injection, 2008)
3) Parkinson's disease (Prod Info HALDOL(R) Decanoate IM injection, 2008)
4) toxic CNS depression, severe (Prod Info HALDOL(R) Decanoate IM injection, 2008)

c) Haloperidol Lactate

1) comatose state from any cause (Prod Info HALDOL(R) immediate release IM injection, 2008)
2) hypersensitivity to haloperidol lactate (Prod Info HALDOL(R) immediate release IM injection, 2008)
3) Parkinson's disease (Prod Info HALDOL(R) immediate release IM injection, 2008)
4) toxic CNS depression, severe (Prod Info HALDOL(R) immediate release IM injection, 2008)

4) Serious Adverse Effects

a) Haloperidol

1) Agranulocytosis
2) Dead - sudden death
3) Death
4) Neuroleptic malignant syndrome
5) Paralytic ileus
6) Priapism
7) Prolonged QT interval
8) Seizure
9) Sudden cardiac death
10) Tardive dyskinesia
11) Torsades de pointes

b) Haloperidol Decanoate

1) Agranulocytosis
2) Neuroleptic malignant syndrome
3) Paralytic ileus
4) Priapism
5) Prolonged QT interval
6) Seizure
7) Tardive dyskinesia
8) Torsades de pointes

5) Clinical Applications

a) Haloperidol

1) FDA Approved Indications

a) Gilles de la Tourette's syndrome
b) Hyperactive behavior, (Short-term treatment) after failure to respond to non-antipsychotic medication and psychotherapy
c) Psychotic disorder
d) Schizophrenia

b) Haloperidol Decanoate

1) FDA Approved Indications

a) Chronic schizophrenia

c) Haloperidol Lactate

1) FDA Approved Indications

a) Gilles de la Tourette's syndrome
b) Schizophrenia

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
Haloperidol
Haloperidol Decanoate
Haloperidol Lactate

C) Physicochemical Properties

1) Molecular Weight

a) Haloperidol: 375.87 (Prod Info haloperidol oral tablets, 2008); haloperidol decanoate: 530.13 (Prod Info haloperidol decanoate injection, 2005)

2) pH

a) Haloperidol lactate: 3 to 3.6 (Prod Info HALDOL(R) immediate release IM injection, 2008)

3) Solubility

a) Haloperidol decanoate is soluble in most organic solvents and almost insoluble in water (0.01 mg/mL) (Pr Info haloperidol decanoate injection, 2005).

1.2 Storage and Stability

A) Haloperidol Decanoate

1) Preparation

a) Intramuscular route

1) Do not administer haloperidol decanoate intravenously (Prod Info haloperidol decanoate injection, 2005).

2) Haloperidol decanoate should be administered by deep intramuscular injection (21G needle) into the gluteal region. The maximum recommended volume is 3 milliliters per injection site (Prod Info haloperido decanoate injection, 2005).

B) Haloperidol Lactate

1) Preparation

a) General Information

1) Do NOT administer haloperidol lactate intravenously (Prod Info HALDOL(R) immediate release IM injection, 2008).

C) Haloperidol

1) Oral route

a) Tablet

1) Store at controlled room temperature, between 20 and 25 degrees C (68 and 77 degrees F), in a tigh light-resistant container (Prod Info haloperidol oral tablets, 2008).

D) Haloperidol Decanoate

1) Intramuscular route

a) Solution

1) Store at controlled room temperature, between 15 and 30 degrees C (59 and 86 degrees F). Protect from light. Do not refrigerate or freeze (Prod Info HALDOL(R) Decanoate IM injection, 2008).

2) Investigations of the stability of haloperidol decanoate when drawn into plastic syringes have not bee conducted. Preparation of individual doses of medication in disposable plastic syringes may be carried o a few hours prior to administration, provided these are protected from light. Because of unknown stability and because of concern for dosage sterility, such storage for longer periods is not recommended. Stabili in other types of syringes is also unknown (Pers Comm, 1987).

E) Haloperidol Lactate

1) Intramuscular route

a) Solution

1) Store at controlled room temperature, between 15 and 30 degrees C (59 and 86 degrees F). Protect from light. Do not freeze (Prod Info HALDOL(R) immediate release IM injection, 2008).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

Dosage in Other Disease States

1.3.1 Normal Dosage

Important Note

Important Note

Important Note

Haloperidol

Haloperidol Decanoate

Haloperidol Lactate

1.3.1.A Important Note

The US Food and Drug Administration (FDA) issued an alert concerning reports of Torsades de Pointes and prolongation, some with fatal outcomes associated with the use of haloperidol, haloperidol decanoate, and haloperidol lactate, especially when administered intravenously (not an approved route of administration) or i higher doses than recommended. At least 28 published case reports exist, and case-control studies have demonstrated a dose-response relationship between intravenous haloperidol and the development of Torsad de Pointes (US Food and Drug Administration, 2007).

1.3.1.B Important Note

Haloperidol decanoate is in a sesame seed oil base and should not be given intravenously (Prod Info haloperidol decanoate injection, 2005).

The US Food and Drug Administration (FDA) issued an alert concerning reports of Torsades de Pointes and prolongation, some with fatal outcomes associated with the use of haloperidol, haloperidol decanoate, and haloperidol lactate, especially when administered intravenously (not an approved route of administration) or i higher doses than recommended. At least 28 published case reports exist, and case-control studies have demonstrated a dose-response relationship between intravenous haloperidol and the development of Torsad de Pointes (US Food and Drug Administration, 2007).

1.3.1.C Important Note

Haloperidol lactate should NOT be given intravenously (Prod Info HALDOL(R) immediate release IM injectior 2008).

The US Food and Drug Administration (FDA) issued an alert concerning reports of Torsades de Pointes and prolongation, some with fatal outcomes associated with the use of haloperidol, haloperidol decanoate, and haloperidol lactate, especially when administered intravenously (not an approved route of administration) or i higher doses than recommended. At least 28 published case reports exist, and case-control studies have demonstrated a dose-response relationship between intravenous haloperidol and the development of Torsad de Pointes (US Food and Drug Administration, 2007).

1.3.1.D Haloperidol

Intravenous route

Oral route

Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

Hiccoughs

Ocular hypertension

Opioid withdrawal

1.3.1.D.1 Intravenous route

a) CONTINUOUS INTRAVENOUS DOSING

1) An initial bolus dose of 10 milligrams followed by continuous infusion beginning as 10 milligrams per hour is recommended. If control is not achieved, the bolus is repeated every 30 minutes, as well increasing the infusion rate by 5 milligrams per hour. Adjunctive sedative (benzodiazepines) doses should be adjusted as needed or discontinued if possible. After achieving control, infusion rates sho be titrated downward by 50% at each interval, seeking eventual return to bolus dosing. Continuous infusion haloperidol should be considered for patients receiving 80 mg of haloperidol daily (given in or more bolus doses) or who receive more than 10 mg/hour over 5 or more consecutive hours. Continuous dosing is also warranted in patients not effectively managed on other sedatives and in those in whom attempted reversal of the cause of agitation has been unsuccessful (Riker et al, 199

2) Initial infusion doses of 2 to 25 milligrams per hour haloperidol by continuous infusion have been cited in individual cases (Seneff & Mathews, 1995); (Dixon & Craven, 1993)(Fernandez et al, 1988).

3) Maximum infusion rate cited is 40 milligrams per hour (Riker et al, 1994a).

b) INTERMITTENT INTRAVENOUS DOSING

1) Total daily intermittent intravenous haloperidol doses of 80, 285, 130, 460, and 530 milligrams w generally well tolerated (Tesar et al, 1985).

c) SWITCHING FROM INJECTABLE TO ORAL HALOPERIDOL

1) For an initial approximation of the total daily dose required, the parenteral dose administered in t preceding 24 hours may be used; the first oral dose should be given within 12 to 24 hours following last parenteral dose (Prod Info HALDOL(R) injection, 2007).

1.3.1.D.2 Oral route

Behavioral syndrome - Dementia

Gilles de la Tourette's syndrome

Schizophrenia

1.3.1.D.2.a Behavioral syndrome - Dementia

1) A randomized, double-blind, placebo controlled crossover study demonstrated that standard-dos (2 to 3 milligrams (mg) daily) haloperidol was effective and superior to low-dose (0.05 to 0.75 mg da for treating psychosis and disruptive behaviors in patients with Alzheimer's disease. Seventy-one patients were treated with either standard-dose or low-dose haloperidol or placebo for 6 weeks. The patients taking placebo then crossed over to either standard or low- dose haloperidol while the haloperidol patients crossed over to placebo for another 6 weeks. Standard-dose haloperidol was efficacious and superior to low- dose haloperidol and placebo for the 60 patients who completed the first phase of the study. The same results were demonstrated in the second phase. Extrapyramidal side effects were greater with the standard dose however, low- dose haloperidol did not differ from placebo with regard to efficacy (Devanand et al, 1998).

1.3.1.D.2.b Gilles de la Tourette's syndrome

1) Manufacturer dose

a) The recommended dose in adults with moderate symptoms is haloperidol 0.5 to 2 milligrams (mg) orally 2 to 3 times daily, or with severe symptoms 3 to 5 mg orally 2 to 3 times daily (Prod Info haloperidol oral tablets, 2008; Prod Info haloperidol oral solution, 2008).

2) Tourette's syndrome is initially treated with haloperidol 6 to 15 mg/day orally in divided doses. Dosage is gradually increased in 2 mg increments until adverse effects are disabling. When sympto are controlled the dose is tapered to approximately 9 mg/day for maintenance (AMA Department of Drugs, 1980).

1.3.1.D.2.c Schizophrenia

1) SUMMARY

a) The usual daily oral dose range is from 1 to 15 milligrams; doses exceeding 100 milligrams have been used in severely resistant patients. Moderate doses of neuroleptic drugs, defined as between 165 and 375 milligram equivalent of chlorpromazine, were preferred in the maintenanc therapy of chronic psychosis in a meta-analysis of 22 randomized control trials (Bollini et al, 19 The association between dose and clinical effectiveness and side effects was assessed. At dos greater than 375 milligram equivalent of chlorpromazine, there was no incremental clinical improvement seen, and adverse reactions occurred at a significantly higher rate.

2) There is significant variation between patients in the amount of medication required; dosage mus be individualized. The normal dosage range for initiation of therapy for psychiatric indications is 1 to milligrams/day for moderate symptomatology and 6 to 15 milligrams/day for severe symptomatology divided into 2 to 3 doses. Adjustment of the dose up to 100 milligrams/day may be necessary for

severely resistant patients. When switching from parenteral to oral therapy, the first oral dose shoulc be given within 12 to 24 hours. The same oral as parenteral dose may be used with dosage adjustments made based on patient's response (Prod Info Haldol(R), 97a).

3) A 4-week prospective trial demonstrated that patients experiencing first-episode psychosis responded to haloperidol doses that were well below doses commonly prescribed. Patients (n=36) diagnosed with nonaffective psychosis began haloperidol treatment with 2 milligrams (mg) daily. The dose was increased weekly until either significant improvement or the onset of extrapyramidal symptoms occurred. The optimal dose for 42 percent of the patients was 2 mg daily and on average these patients exhibited the greatest improvement (Zhang- Wong et al, 1999).

4) Low dosage (16 milligrams/day) was compared with high dosage (80 milligrams/day) of haloperic in 40 newly admitted schizophrenia patients for 21 days. Upon evaluation on five occasions, the low dosage group showed significantly greater improvement (Winter et al, 1984). Similar results were found in another study (Rifkin et al, 1991).

5) A double-blind study was conducted in 42 patients treated with 10 milligrams, 30 milligrams, and milligrams per day of haloperidol. The researchers found no relationship between neuroleptic dose a outcome of mania, and no differences in side effects. These results suggest that there is no advanta to using more than 10 milligrams per day of haloperidol (Rifkin et al, 1990).

6) Haloperidol doses of 5, 10, and 20 milligrams per day were compared for 4 weeks in 80 newly admitted schizophrenic patients. The results after two weeks showed the 20 milligrams dose to be more effective than the 5 milligrams dose and the same as the 10 milligrams dose. Over the last two week period, the 20 milligrams dose per day did not control the patients. The researchers referred to this as "psychotoxic" side-effects. The researchers recommended 20 milligrams per day for short-ter therapy of psychotic disorders (Van Putten et al, 1990).

1.3.1.D.2.d Mania

1) In a double-blind, randomized study lasting six weeks, three dosage levels of haloperidol (10, 30 80 mg/day) were compared in 47 newly-diagnosed manic inpatients. All patients also received benztropine (2 mg three times per day). There were no significant differences in treatment outcomes side effects among patients at the three dosage levels. The authors concluded that haloperidol dose in excess of 10 mg/day offered no advantage in controlling symptoms of mania (Rifkin et al, 1994).

1.3.1.D.2.e SWITCHING FROM INJECTABLE TO ORAL HALOPERIDOL

1) For an initial approximation of the total daily dose required, the parenteral dose administered in t preceding 24 hours may be used; the first oral dose should be given within 12 to 24 hours following last parenteral dose (Prod Info HALDOL(R) injection, 2007).

1.3.1.D.3 Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

See Drug Consult reference: CHEMOTHERAPY AND RADIOTHERAPY TREATMENT GUIDELINES FO NAUSEA AND VOMITING

1.3.1.D.4 Hiccoughs

See Drug Consult reference: HICCUPS - ETIOLOGY AND TREATMENT

1.3.1.D.5 Ocular hypertension

a) Topical administration of the haloperidol ophthalmic solution (0.125% and 1%) produced modest reductions in intraocular pressure in healthy volunteers, however, reductions were not considered statistically significant (Lavin & Andrews, 1986). These data do not suggest the role for topical haloperido in the treatment of glaucoma.

1.3.1.D.6 Opioid withdrawal

See Drug Consult reference: DRUG THERAPY OF OPIOID WITHDRAWAL

1.3.1.D.7 HIGH DOSE THERAPY

a) A randomized, double-blind study demonstrated that high-dose, long-term treatment with haloperidol may not be justified regardless if supported by clinical judgment (Volavka et al, 2000). Hospitalized patie (n=23) with the diagnosis of schizophrenia or schizoaffective disorder and with haloperidol plasma levels at least 15 nanograms per milliliter (ng/mL) were assigned to an experimental group (n=11) or a control group (n=12). The plasma level for the experimental group was reduced to 10 ng/mL via a gradual dose reduction while the control group was maintained at the original level. Over a period of 16 weeks, both groups demonstrated a slight reduction in symptoms and there were no significant differences in sympto severity. Additionally, the reduction in dose did not result in any apparent side effects. The authors conclude that high-dose therapy may be cautiously questioned since this study was small and biased.

b) Two studies failed to establish that a dosage of 100 milligrams/day was more effective than a dosage 10 milligrams/day in 63 acutely schizophrenic patients (Donlon et al, 1980; Ericksen et al, 1978). Howeve another study concluded that previously nonresponsive chronic schizophrenics may benefit from adequa high doses (median 100 milligrams/day) of haloperidol (Psaras et al, 1980).

c) Intravenous haloperidol ranging from 100 to 480 milligrams over 24 hours plus 36 to 480 milligrams o lorazepam has been shown to be effective in treatment of delirium in the critically ill cancer patient; the combination of haloperidol and lorazepam intravenously in a wide range of doses appears to be safe and effective (Adams et al, 1986).

d) The need for high-dose therapy was demonstrated in some chronic patients. By evaluating 100 patie

it was found that eight patients required more than 15 milligrams per day of haloperidol. When the streng was reduced, the eight patients lapsed back into their original psychiatric state. These authors conclude that dose-responsive patients should be examined on an individual basis (Brotman & McCormick, 1990).
e) High-dose therapy was used in a patient receiving treatment via an intra-aortic balloon pump. The patient was given a 50 milligrams bolus dose of haloperidol and 50 milligrams intravenously every hour thereafter. The patient received a total of 1200 milligrams of haloperidol in the first 24 hour period, and 1100 milligrams during the next 24 hour period. The doses were then decreased daily until day ten, when the pump was removed. No signs of extrapyramidal symptoms were exhibited (Sanders et al, 1991).

1.3.1.E Haloperidol Decanoate

1) ORAL TO DEPOT CONVERSION

a) The recommended initial dose of Haldol(R) decanoate is 10 to 20 times the previous daily dose in oral haloperidol equivalents but no more than a maximum initial dose of 100 milligrams given at monthly intervals. However, if initial conversion doses are more than 100 milligrams, the dose should be administered in 2 injections (ie, a maximum of 100 mg followed by the remaining balance in 3 to 7 days) (Prod Info haloperidol decanoate injection, 2005).
b) Clinical experience with depot injections greater than 450 milligrams/month is limited (Prod Info haloperidol decanoate injection, 2005).
c) The pharmacokinetic properties and therapeutic efficacy of haloperidol decanoate were studied in 21 chronic psychotic inpatients stabilized on oral haloperidol. The intramuscular dose was calculated from the oral dose, using standard equivalencies for those neuroleptics other than haloperidol. The depot form was administered for 4 months, the last 3 months given at one-half the original calculated loading dose. The depot form resulted in less fluctuation in blood levels, with levels approximating those on oral therapy. One third of the patients deteriorated, and there was no significant change in the incidence or severity of side effects. The authors concluded that there was no clinical advantage to the use of haloperidol decanoate over oral forms of therapy (de Cuyper et al, 1986).
d) Intramuscular haloperidol decanoate was compared with oral haloperidol in 30 chronic schizophrenic patients (Nair et al, 1986). Patients were stabilized for 2 weeks on an oral dose, which was then maintained for 2 weeks. Patients were then transferred to an intramuscular dose, stabilized, then continued on the dose for 5 months. Side effects were comparable and minimal. Therapeutic responses were also comparable. The monthly dose of haloperidol decanoate needed to achieve an equivalent therapeutic response was 15 times the daily dose of haloperidol in 17 patients, 10 times the daily oral dose of haloperidol in 7 patients, and ranged from 9.4 to 15 times the daily oral haloperidol dose in all patients. The authors concluded that intramuscular haloperidol decanoate is comparable to oral haloperidol in safety and efficacy and produces lower blood levels with less fluctuation.
e) Oral haloperidol given daily was compared with intramuscular haloperidol decanoate given every 28 days to establish pharmacokinetically and therapeutically equivalent dosages (Nayak et al, 1987). The study involved 20 patients and was of an open design. Results showed that haloperidol decanoate every 28 days required dosages 21.4 times higher than haloperidol given daily to achieve similar blood concentrations, but required dosages only 14.1 times higher to achieve similar clinical results. The authors recommended that dosages of haloperidol decanoate should be lower than what is calculated to achieve therapeutic blood levels. The dose is subsequently titrated upwards to achieve the desired therapeutic response.
f) Eighteen patients who were taking oral haloperidol and then switched to depot haloperidol were studied. The first month's mean haloperidol decanoate dose was 23.1 times the oral haloperidol dose, with a mean plasma concentration level of 3 +/- 1.9 mg/mL. The second month's dosing level regimen was decreased by 27.6 percent, giving a mean plasma concentration of 6.5 +/- 2.6 mg/mL. The patients improved during the conversion. The researchers concluded that haloperidol decanoate has less fluctuation than oral haloperidol because of constant absorption (Ereshefsky et al, 1990).
g) A method was described to convert from oral to depot intramuscular forms of haloperidol using a loading dose strategy (Ereshefsky et al, 1993). The method consisted of using a total dose of 20 times the oral dose, administered in consecutive divided doses of 100 to 200 milligrams every three to seven days. Oral haloperidol was discontinued prior to the first injection, except in cases where the daily haloperidol dose was 40 milligrams or greater where the dose was gradually reduced over two months. The depot dose was reduced, typically by 25% in both the second and third months to avoid excessive accumulation. The long-term maintenance dose was adjusted based on clinical response.

1.3.1.F Haloperidol Lactate

1.3.1.F.1 Intramuscular route

Gilles de la Tourette's syndrome

Schizophrenia

1.3.1.F.1.a Gilles de la Tourette's syndrome

1) The recommended dose for the control of tics and vocal utterances of Tourette's disorder is haloperidol lactate 2 to 5 milligrams intramuscularly. Depending on the clinical effect, the dose may repeated every 1 hour, although a 4- to 8-hour interval may be sufficient (Prod Info haloperidol lacta IM injection, 2005).

1.3.1.F.1.b Schizophrenia

1) In schizophrenic adults who are acutely agitated with moderately severe to very severe symptom the recommended dose is haloperidol lactate 2 to 5 milligrams intramuscularly. Depending on the clinical effect, the dose may be repeated every 1 hour, although a 4- to 8-hour interval may be sufficient (Prod Info HALDOL(R) immediate release IM injection, 2008).

1.3.2 Dosage in Renal Failure

A) Haloperidol

1) No specific dosage adjustment is necessary in patients with renal impairment (Bennett et al, 1994).

B) Haloperidol Decanoate

1) No specific dosage adjustment is necessary in patients with renal impairment (Bennett et al, 1994).

C) Haloperidol Lactate

1) No specific dosage adjustment is necessary in patients with renal impairment (Bennett et al, 1994).

1.3.4 Dosage in Geriatric Patients

A) Haloperidol

1) ORAL

a) Geriatric or debilitated patients may require a higher doses (0.5 to 2 milligrams 2 to 3 times daily) to achieve prompt response in some cases (Prod Info haloperidol oral tablets, 2006; Prod Info haloperidol c solution, 2001).

b) Elderly patients with chronic refractory schizophrenia should be initially treated with 0.5 to 1.5 milligram/day orally. Dosage may be gradually increased to a usual maintenance dose of 2 to 8 milligrams/day (AMA Department of Drugs, 1980).

c) Results of a double-blind, crossover study in 58 nursing-home residents suggest that the efficacy of long-term haloperidol, thioridazine, and lorazepam should be closely monitored and routine attempts at drug withdrawal should be considered (Cohen-Mansfield et al, 1999). The residents participating in the study were older than 70 years and had received haloperidol, thioridazine, or lorazepam for agitation for least 4 weeks. Half of the residents had their medication dose tapered over 3 weeks and then received placebo while the other half continued their usual medication dosage. After 7 weeks, the residents cross over and either titrated back on their medication or titrated off and began placebo for another 7 weeks. Analyses exhibited no effect of drug therapy discontinuation on behavior and withdrawal of medication h no impact on psychiatric symptom scores or agitation levels. More research is warranted to identify effective treatment for agitation and the appropriate duration of effectiveness.

d) Mentally retarded elderly patients with hyperkinesia are initially treated with 1.5 to 6 milligrams/day orally in divided doses. Doses may be gradually increased to a maximum of 15 milligrams/day to achieve control. Doses are then tapered to a minimally effective maintenance dose (AMA Department of Drugs, 1980).

B) Haloperidol Decanoate

1) INTRAMUSCULAR - DEPOT

a) Initial conversion from oral therapy for elderly patients, debilitated patients, or those on stable low dos of oral haloperidol, consists of a dose 10 to 15 times the previous oral daily dose. The dose is given at monthly intervals (Prod Info haloperidol decanoate injection, 2005).

C) Haloperidol Lactate

1) A lower dose may be required in the elderly, and titrated to clinical effect. In elderly women there has bee prevalence of tardive dyskinesia (Prod Info HALDOL(R) immediate release IM injection, 2008).

1.3.5 Dosage Adjustment During Dialysis

A) Haloperidol

1) It is unlikely that dosage adjustment is required during dialysis. Its large volume of distribution and low plasma levels suggest that little drug would be removed by dialysis (Anderson et al, 1976; Bennett et al, 1994

B) Haloperidol Decanoate

1) It is unlikely that dosage adjustment is required during dialysis. Its large volume of distribution and low plasma levels suggest that little drug would be removed by dialysis (Anderson et al, 1976; Bennett et al, 1994

C) Haloperidol Lactate

1) It is unlikely that dosage adjustment is required during dialysis. Its large volume of distribution and low plasma levels suggest that little drug would be removed by dialysis (Anderson et al, 1976; Bennett et al, 1994

1.3.6 Dosage in Other Disease States

A) Haloperidol Decanoate

1) DEBILITATED PATIENTS

a) Initial conversion from oral to depot injection in debilitated patients consists of a dose 10 to 15 times t previous oral daily dose. The dose is given at monthly intervals (Prod Info haloperidol decanoate injectio

2005).

B) Haloperidol Lactate

1) A lower dose may be required in debilitated patients or those with a history of adverse reactions to antipsychotic drugs, and titrated to clinical effect (Prod Info HALDOL(R) immediate release IM injection, 2008

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage Adjustment During Dialysis

1.4.1 Normal Dosage

Important Note

Important Note

Important Note

Haloperidol

Haloperidol Decanoate

Haloperidol Lactate

1.4.1.A Important Note

The US Food and Drug Administration (FDA) issued an alert concerning reports of Torsades de Pointes and prolongation, some with fatal outcomes associated with the use of haloperidol, haloperidol decanoate, and haloperidol lactate, especially when administered intravenously (not an approved route of administration) or i higher doses than recommended. At least 28 published case reports exist, and case-control studies have demonstrated a dose-response relationship between intravenous haloperidol and the development of Torsad de Pointes (US Food and Drug Administration, 2007).

1.4.1.B Important Note

Haloperidol decanoate is in a sesame seed oil base and should not be given intravenously (Prod Info haloperidol decanoate injection, 2005).

The US Food and Drug Administration (FDA) issued an alert concerning reports of Torsades de Pointes and prolongation, some with fatal outcomes associated with the use of haloperidol, haloperidol decanoate, and haloperidol lactate, especially when administered intravenously (not an approved route of administration) or i higher doses than recommended. At least 28 published case reports exist, and case-control studies have demonstrated a dose-response relationship between intravenous haloperidol and the development of Torsad de Pointes (US Food and Drug Administration, 2007).

1.4.1.C Important Note

Haloperidol lactate should NOT be given intravenously (Prod Info HALDOL(R) immediate release IM injectior 2008).

The US Food and Drug Administration (FDA) issued an alert concerning reports of Torsades de Pointes and prolongation, some with fatal outcomes associated with the use of haloperidol, haloperidol decanoate, and haloperidol lactate, especially when administered intravenously (not an approved route of administration) or i higher doses than recommended. At least 28 published case reports exist, and case-control studies have demonstrated a dose-response relationship between intravenous haloperidol and the development of Torsad de Pointes (US Food and Drug Administration, 2007).

1.4.1.D Haloperidol

Oral route

Anorexia nervosa

1.4.1.D.1 Oral route

1.4.1.D.1.a Gilles de la Tourette's syndrome

1) The recommended dose in pediatric patients age 3 to 12 years (weight range 15 to 40 kilograms for the treatment of Tourette's disorder is haloperidol 0.05 to 0.075 milligrams/kilogram/day (mg/kg/day) orally in 2 to 3 divided doses. Begin with the lowest possible dose (0.5 mg per day) or weight-based dose (0.05 to 0.075 mg/kg/day) ORALLY in 2 to 3 divided dose, whichever is less. Increases in dose are recommended at 0.5 mg increments at 5 to 7 day intervals to therapeutic effe to a maximum daily dose of 0.075 mg/kg/day (Prod Info haloperidol oral tablets, 2008; Prod Info haloperidol oral solution, 2008).

2) In children over age 12 years the recommended dose is haloperidol 0.5 to 2 mg (moderate symptoms) or 3 to 5 mg (severe symptoms) orally 2 to 3 times daily (Prod Info haloperidol oral table 2008; Prod Info haloperidol oral solution, 2008).

b) Haloperidol is not recommended for use in children under 3 years old (Prod Info haloperidol oral table 2008; Prod Info haloperidol oral solution, 2008).

1.4.1.D.2 Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

1.4.1.E Haloperidol Decanoate

1.4.1.F Haloperidol Lactate

1) Safety and effectiveness have not been established in pediatric patients (Prod Info HALDOL(R) immediate release IM injection, 2008).

1.4.2 Dosage in Renal Failure

A) Haloperidol

1) No specific dosage adjustment is necessary in patients with renal impairment (Bennett et al, 1994).

B) Haloperidol Decanoate

1) No specific dosage adjustment is necessary in patients with renal impairment (Bennett et al, 1994).

1.4.4 Dosage Adjustment During Dialysis

A) Haloperidol

1) It is unlikely that dosage adjustment is required during dialysis. Its large volume of distribution and lov plasma levels suggest that little drug would be removed by dialysis (Anderson et al, 1976; Bennett et al, 1994).

B) Haloperidol Decanoate

1) It is unlikely that dosage adjustment is required during dialysis. Its large volume of distribution and lov plasma levels suggest that little drug would be removed by dialysis (Anderson et al, 1976; Bennett et al, 1994).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) Sedation, oral: greater than 1 hour (Forsman & Ohman, 1976).

b) Sedation, intravenous: 1 hour (Forsman & Ohman, 1976).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Schizophrenic, schizoaffective and schizophreniform disorders, 5 to 15 ng/mL (Ulrich et al, 1998); (Van Patten et al, 1992)(Extein et al, 1983; Mavroidis et al, 1983; Morselli et al, 1982; Magliozzi et al, 1981).

a) In a 35-study meta-analysis and review, a lower threshold concentration for therapeutic effect was reported of 5.6 mcg/L (range: 3.1 to 8 mcg/L) and an upper threshold concentration of 16.9 mcg/L (range 11 to 26 mcg/L). A target concentration of 10 mcg/L was recommended (Ulrich et al, 1998).

b) A meta-analysis of 18 studies concluded that there was support for the existence of a therapeutic window between 4 and 26 nanograms/milliliter (de Oliveira et al, 1996a).

c) Increasing the haloperidol dose to achieve plasma levels above 18 ng/mL was not associated with improved response in a study of 66 adult inpatients with schizophrenia (Coryell et al, 1998). These result were supported by a study of 95 adults with acute psychosis (schizophrenia and schizoaffective disorder The probability of improvement among initial non-responders was significantly increased among patients titrated to plasma levels of 5 to 18 ng/mL, as opposed to those at lower or higher haloperidol levels (Janicak et al, 1997).

B) Time to Peak Concentration

1) Oral: 2 to 6 hours (Prod Info Haldol(R), 97).

a) The steady-state pharmacokinetics of oral haloperidol varies widely among different patients (Kudo & Ishizaki, 1999).

b) The steady state plasma concentrations of haloperidol and reduced haloperidol were not significantly different among 4 patient subgroups (n= 101) in a study designed to measure the effect of genetic polymorphism of CYP1A2 inducibility on the steady state plasma concentrations of oral haloperidol. Ther were no significant differences between the 4 subgroups, including age and weight, and smoking status not affect the steady state concentrations in the study. This suggests that CYP1A2 activity does not play key role in the steady state pharmacokinetics of haloperidol or reduced haloperidol (Mihara et al, 2000).

2) Intramuscular, haloperidol: 20 minutes (Prod Info Haldol(R), 97).

3) Intramuscular, haloperidol decanoate: 6 days (Prod Info Haldol(R) Decanoate, 2000).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) Oral: 60 to 70% (Prod Info Haldol(R), 97; Cheng et al, 1987; Holley et al, 1983a).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) greater than 90% (Tedeschi, 1981; Forsman & Ohman, 1977).

2) OTHER DISTRIBUTION SITES

a) Hair, less than 0.1% (Matsuno et al, 1990; Sato et al, 1989; Uematsu et al, 1989).

b) Saliva, levels are higher than serum levels and there is a significant correlation (Yamazumi & Muira, 1981).

B) Distribution Kinetics

1) Volume of Distribution

a) 9.5 to 21.7 liters/kilogram (Kudo & Ishizaki, 1999) or 1300 liters (Forsman & Ohman, 1976).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver (Forsman et al, 1977; Forsman & Ohman, 1976).

a) Some evidence indicates extrahepatic metabolism (Forsman & Ohman, 1976; Forsman et al, 1977).

B) Metabolites

1) Hydroxy metabolite of HALOPERIDOL, active (Shostak et al, 1987) (Midha et al, 1989).

a) A significant correlation exists between the percent improvement and the plasma levels of the hydroxymetabolite reduced HALOPERIDOL (Shostak et al, 1987).

2) 4-fluorobenzol-propionic acid (Forsman et al, 1977).

3) 4-fluoro-phenylaceturic acid (Forsman et al, 1977).

4) Reduced haloperidol (Kudo & Ishizaki, 1999).

5) Pyridinium metabolites (Kudo & Ishizaki, 1999).

6) Haloperidol glucuronide (Kudo & Ishizaki, 1999).

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)
a) 33 to 40% (Prod Info Haldol(R), 97; Anderson et al, 1976a).
B) Other
1) Feces, 15% (Johnson et al, 1967).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 21 hours (range: 10 to 38 hours) (Forsman & Ohman, 1976; Cressman et al, 1974a).
1) HALOPERIDOL DECANOATE administered intramuscularly has a half-life of approximately weeks (Reyntjens et al, 1982).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Haloperidol
a) Oral (Tablet)
1) Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with demen related psychosis treated with atypical antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failu sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Haloperidol is not approved for the treatment of patients with dementia-related psychosis (Prod Info haloperidol oral tablets 2008).
2) Haloperidol Decanoate
a) Intramuscular (Injectable)
1) Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with demen related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of sevente placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Haloperidol decanoa is not approved for the treatment of patients with dementia-related psychosis (Prod Info HALDOL(R) Decanoate IM injection, 2008).
3) Haloperidol Lactate
a) Intramuscular (Solution)
Increased Mortality in Elderly Patients with Dementia-Related Psychosis:
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increase risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely i patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 1 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia)

nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increas mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Haloperidol injection is not approved for the treatment of patients with dementia-related psychosis (Prod Info HALDOL(R) immediate release IM injection, 20(

3.1 Contraindications

A) Haloperidol

1) comatose state from any cause (Prod Info haloperidol oral tablets, 2008)
2) hypersensitivity to haloperidol (Prod Info haloperidol oral tablets, 2008)
3) Parkinson's disease (Prod Info haloperidol oral tablets, 2008)
4) toxic central nervous system depression, severe (Prod Info haloperidol oral tablets, 2008)

B) Haloperidol Decanoate

1) comatose state from any cause (Prod Info HALDOL(R) Decanoate IM injection, 2008)
2) hypersensitivity to haloperidol (Prod Info HALDOL(R) Decanoate IM injection, 2008)
3) Parkinson's disease (Prod Info HALDOL(R) Decanoate IM injection, 2008)
4) toxic CNS depression, severe (Prod Info HALDOL(R) Decanoate IM injection, 2008)

C) Haloperidol Lactate

1) comatose state from any cause (Prod Info HALDOL(R) immediate release IM injection, 2008)
2) hypersensitivity to haloperidol lactate (Prod Info HALDOL(R) immediate release IM injection, 2008)
3) Parkinson's disease (Prod Info HALDOL(R) immediate release IM injection, 2008)
4) toxic CNS depression, severe (Prod Info HALDOL(R) immediate release IM injection, 2008)

3.2 Precautions

A) Haloperidol

1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Pr Info haloperidol oral tablets, 2008)
2) allergies or allergic reactions to drugs, known (Prod Info haloperidol oral tablets, 2008)
3) bronchopneumonia, some fatal, have been reported (Prod Info haloperidol oral tablets, 2008)
4) cardiac abnormalities, underlying; increased risk of QT prolongation and torsades de pointes (Prod Info haloperidol oral tablets, 2008)
5) cardiovascular disorders, severe, preexisting; potential for transient hypotension and/or onset of anginal p (Prod Info haloperidol oral tablets, 2008)
6) concomitant lithium use; a few patients have experienced encephalopathic syndrome followed by irreversi brain damage; causality not established (Prod Info haloperidol oral tablets, 2008)
7) concomitant use with anticoagulants, anticholinergics (including antiparkinson drugs), anticonvulsants, an drugs known to prolong the QT interval (Prod Info haloperidol oral tablets, 2008)
8) EEG abnormalities; may increase risk of seizures due to possible lowered convulsive threshold (Prod Info haloperidol oral tablets, 2008)
9) elderly patients, especially elderly women are at increased risk of tardive dyskinesia (Prod Info haloperido oral tablets, 2008)
10) electrolyte imbalance, especially hypokalemia and hypomagnesemia; increased risk of QT prolongation and torsades de pointes (Prod Info haloperidol oral tablets, 2008)
11) hypothyroidism; increased risk of QT prolongation and torsades de pointes (Prod Info haloperidol oral tablets, 2008)
12) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info haloperidol oral tablets, 2008)
13) long QT syndrome, family history; increased risk of QT prolongation and torsades de pointes (Prod Info haloperidol oral tablets, 2008)
14) neuroleptic malignant syndrome, potentially fatal, has been reported; immediately discontinue (Prod Info haloperidol oral tablets, 2008)
15) QT prolongation, history; increased risk of QT prolongation and torsades de pointes (Prod Info haloperid oral tablets, 2008)
16) QT prolongation and torsades de pointes have been reported (Prod Info haloperidol oral tablets, 2008)
17) rapid mood fluctuation toward depression may occur when haloperidol is used for mania in bipolar disorders (Prod Info haloperidol oral tablets, 2008)
18) seizure disorder, history; may increase risk of seizures due to possible lowered convulsive threshold (Pr Info haloperidol oral tablets, 2008)
19) tardive dyskinesia, potentially irreversible, may occur (Prod Info haloperidol oral tablets, 2008)
20) thyrotoxicosis; severe neurotoxicity may occur (Prod Info haloperidol oral tablets, 2008)

B) Haloperidol Decanoate

1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Pr Info HALDOL(R) Decanoate IM injection, 2008)
2) allergies or allergic reactions to drugs, known (Prod Info HALDOL(R) Decanoate IM injection, 2008)
3) bronchopneumonia, some fatal, have been reported (Prod Info HALDOL(R) Decanoate IM injection, 2008
4) cardiac abnormalities, underlying; increased risk of QT prolongation and torsades de pointes(Prod Info

HALDOL(R) Decanoate IM injection, 2008)
5) cardiovascular disorders, severe; potential for transient hypotension and/or onset of anginal pain(Prod Inf
HALDOL(R) Decanoate IM injection, 2008)
6) concomitant use with anticoagulants, anticholinergics (including antiparkinson drugs), anticonvulsants, an
drugs known to prolong the QT interval (Prod Info HALDOL(R) Decanoate IM injection, 2008)
7) EEG abnormalities; may increase risk of seizures due to possible lowered convulsive threshold(Prod Info
HALDOL(R) Decanoate IM injection, 2008)
8) elderly patients, especially elderly women are at increased risk of tardive dyskinesia (Prod Info HALDOL(
Decanoate IM injection, 2008)
9) electrolyte imbalance, especially hypokalemia and hypomagnesemia; increased risk of QT prolongation a
torsades de pointes(Prod Info HALDOL(R) Decanoate IM injection, 2008)
10) hypothyroidism; increased risk of QT prolongation and torsades de pointes(Prod Info HALDOL(R)
Decanoate IM injection, 2008)
11) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod
Info HALDOL(R) Decanoate IM injection, 2008)
12) long QT syndrome, family history; increased risk of QT prolongation and torsades de pointes (Prod Info
HALDOL(R) Decanoate IM injection, 2008)
13) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotic
drugs; immediately discontinue drug (Prod Info HALDOL(R) Decanoate IM injection, 2008)
14) QT prolongation, history; increased risk of QT prolongation and torsades de pointes(Prod Info HALDOL(
Decanoate IM injection, 2008)
15) QT prolongation and torsades de pointes have been reported, especially when administered intravenous
or at doses higher than recommended (Prod Info HALDOL(R) Decanoate IM injection, 2008)
16) rapid mood fluctuation toward depression may occur when risperidone is used for mania in bipolar
disorders (Prod Info HALDOL(R) Decanoate IM injection, 2008)
17) seizure disorder, history; may increase risk of seizures due to possible lowered convulsive threshold(Pro
Info HALDOL(R) Decanoate IM injection, 2008)
18) tardive dyskinesia, potentially irreversible, may occur (Prod Info HALDOL(R) Decanoate IM injection, 20
19) thyrotoxicosis; severe neurotoxicity may occur (Prod Info HALDOL(R) Decanoate IM injection, 2008)

C) Haloperidol Lactate
1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths
were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Pr
Info HALDOL(R) immediate release IM injection, 2008)
2) allergies, known, or with a history of allergic reactions to drugs (Prod Info HALDOL(R) immediate release
injection, 2008)
3) bronchopneumonia, some cases fatal, has been reported (Prod Info HALDOL(R) immediate release IM
injection, 2008)
4) cardiovascular disorders, severe; potential for transient hypotension and/or onset of anginal pain (Prod In
HALDOL(R) immediate release IM injection, 2008)
5) concomitant use with anticoagulants, anticholinergics (including antiparkinson drugs), anticonvulsants, or
lithium (Prod Info HALDOL(R) immediate release IM injection, 2008)
6) EEG abnormalities; may increase risk of seizures due to lowered convulsive threshold (Prod Info HALDO
(R) immediate release IM injection, 2008)
7) elderly patients, especially elderly women, are at increased risk of tardive dyskinesia (Prod Info HALDOL(
immediate release IM injection, 2008)
8) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod I
HALDOL(R) immediate release IM injection, 2008)
9) neuroleptic malignant syndrome, potentially fatal, has been reported; immediately discontinue if
signs/symptoms develop (Prod Info HALDOL(R) immediate release IM injection, 2008)
10) QT prolongation and torsades de pointes have been reported; increased risk in patients with underlying
cardiac abnormalities, familial long QT syndrome, hypothyroidism, electrolyte imbalance (especially
hypokalemia and hypomagnesemia), and with other drugs that prolong the QT interval (Prod Info HALDOL(R
immediate release IM injection, 2008)
11) rapid mood swing toward depression may occur when haloperidol is used for mania in cyclic disorders
(Prod Info HALDOL(R) immediate release IM injection, 2008)
12) seizure, history of; may increase risk of seizures due to lowered convulsive threshold (Prod Info HALDO
(R) immediate release IM injection, 2008)
13) tardive dyskinesia, potentially irreversible, may occur (Prod Info HALDOL(R) immediate release IM
injection, 2008)
14) thyrotoxicosis; severe neurotoxicity may occur (Prod Info HALDOL(R) immediate release IM injection,
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

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Cardiac arrest

Heart block, third degree

Hypertension

Hypotension

Prolonged QT interval

Sudden cardiac death

Tachycardia

Torsades de pointes

Ventricular premature beats

3.3.1.A Cardiac arrest

1) Cases of cardiac arrest secondary to haloperidol administration have been reported. A 49-year-old female with normal vital signs was brought to the emergency department in an acute confusional state a was given 5 milligrams (mg) haloperidol intramuscularly upon admission. She was given 10 mg haloperic intramuscularly 5 hours later due to complaints of feeling sick and anxious. The patient remained disoriented and confused and received another dose of haloperidol 10 mg the next morning. Forty-five minutes later, the patient was found unresponsive, cyanotic, and in asystolic arrest. Electrocardiogram a resuscitation showed no evidence of ischemia or prolongation of corrected QT interval. The patient remained comatose and died one month after being transferred to a long-term care facility. Information l received from her treating psychiatrist revealed the patient had previous admissions for similar incidents confusion and had experienced severe reactions to neuroleptic agents. The authors suggest such patien are candidates for medical alert bracelets (Westlake & Rastegar, 1973). In addition, a 65-year-old male patient twice suffered asystolic cardiac arrest after separate intravenous injections of haloperidol 7.5 mg confusion. The authors suggest that extreme (greater than 50 mg) or intermittent intravenous doses nee to be restricted to those patients in intensive care units with cardiac monitoring facilities (Huyse & Van

Schijndel, 1988).

3.3.1.B Heart block, third degree

1) Intermittent third degree heart block occurred during the highest rate of infusion (40 mg/hour) (Riker e al, 1994).

2) Two patients experienced adverse reactions attributed to continuous infusion haloperidol. Intermittent third-degree heart block and prolonged qt interval with torsade de pointes occurred during the highest ra of infusion (40 mg/hour). Hemodynamically compromising tachycardia requiring cardioversion and lidoca occurred during infusion of 10 mg/hour over 5 days. Finally, extrapyramidal side effects appeared after abrupt discontinuation of benzodiazepine treatment, requiring its reinstatement for resolution (Riker et al 1994).

3.3.1.C Hypertension

1) Hypertension has been reported with haloperidol use, especially if excessive doses are ingested. Haloperidol in therapeutic doses rarely has an effect on blood pressure. Many neuroleptics cause hypotension. In overdosage, patients normally remain normotensive. However, a 22-month-old girl accidentally ingesting 15 to 20 mg haloperidol developed significant hypertension of 146/100 at 8 hours and 164/134 at 10 hours after a baseline level of 136/66 taken on admission. IV hydralazine was require to reduce pressures reaching as high as 180 systolic over the subsequent 5 days. This report substantia 2 other reports of hypertension recently received by the manufacturer (Cummingham & Challapalli, 1979

3.3.1.D Hypotension

1) Transient hypotension may occur. A vasopressor may be necessary to treat the hypotension. Epinephrine should not be the vasopressor selected because haloperidol blocks the vasopressor effects and paradoxical lowering of the blood pressure may occur (Prod Info HALDOL(R) injection, 2007).

3.3.1.E Prolonged QT interval

1) Summary

a) Torsades de Pointes and QT prolongation, including sudden death, have been reported especial when haloperidol is administered intravenously or at doses higher than recommended. Risk factors Torsades de Pointes or QT prolongation include QT-prolonging conditions such as electrolyte imbalance (especially, hypokalemia and hypomagnesemia); underlying cardiac abnormalities; hypothyroidism; familial long QT syndrome; and concomitant drugs that prolong the QT interval. Electrocardiogram monitoring is recommended in patients on intravenous haloperidol (US Food and Drug Administration, 2007).

b) The incidence of long QTc interval syndrome or torsade de pointes with haloperidol is small (Lawrence & Nasraway, 1997). The majority of cases occurred in critically ill patients with a history c cardiovascular disease prescribed more than 50 mg/day. It is recommended that before initiating therapy with haloperidol in critically ill patients that a baseline QTc interval and serum magnesium a potassium concentrations be measured. In cases where the baseline QTc interval is 440 millisecond or longer and they are receiving other drugs that may prolong the QTc interval, or they have an electrolyte disturbance, haloperidol or similar drugs should be used with caution. Electrocardiogram monitoring should be done in critically ill patients once haloperidol is initiated. If the QTc interval lengthens by 25% or more, the haloperidol should be discontinued or the dosage should be reduced

2) The medical literature includes 28 case reports of QT prolongation and Torsades de Pointes, includin cases of death when haloperidol was administered intravenously. Furthermore, a dose-response relationship between intravenous doses and subsequent Torsades de Pointes was demonstrated in case control studies (US Food and Drug Administration, 2007).

3) There were 229 cases of QT prolongation in patients administered injectable or oral haloperidol, including 73 cases of Torsades de Pointes of which 11 were fatal, reported in the manufacturer's worldw safety database received through June 30, 2005. Various doses of intravenous haloperidol were used in of the 11 fatal cases. QT-prolonging or medical conditions may have contributed to the events. A second postmarketing investigation, submitted to the Food and Drug Administration in March 2007, reported 13 Torsades de Points, QT prolongation, ventricular arrhythmias and/or sudden death (US Food and Drug Administration, 2007).

4) QT prolongation has been reported in clinical trials. Predisposed patients (long QT-syndrome, hypokalemia, electrolyte imbalance, drugs known to prolong QT, cardiovascular disease, family history c QT prolongation) or those being treated with high doses may have an increased risk of QT prolongation (Prod Info HALDOL(R) injection, 2007).

5) Two patients experienced adverse reactions attributed to continuous infusion haloperidol. Intermittent third-degree heart block and prolonged qt interval with Torsade de Pointes occurred during the highest ra of infusion (40 mg/hour). Hemodynamically compromising tachycardia requiring cardioversion and lidoca occurred during infusion of 10 mg/hour over 5 days (Riker et al, 1994).

6) Intermittent prolonged QT interval with torsades de pointes occurred during the highest rate of infusio (40 mg/hour) (Riker et al, 1994).

3.3.1.F Sudden cardiac death

1) In a large, retrospective, cohort study that included a primary cohort of 93,300 users of antipsychotic

drugs and 186,600 non-users of antipsychotic drugs, there was an increased risk of sudden cardiac deat in adult participants 30 to 74 years of age (mean age of 45.7 years) who were using haloperidol compare to those who were not using antipsychotic drugs (incidence-rate ratio, 1.61; 95% confidence interval (CI) 1.16 to 2.24; p=0.005). In participants being treated with typical antidepressants (haloperidol, thioridazine the incidence-rate ratio for sudden cardiac death increased from 1.31 (95% CI, 0.91 to 1.39) for those us low doses to 2.42 (95% CI, 1.91 to 3.06) for those using high doses (p less than 0.001) (Ray et al, 2009)

3.3.1.G Tachycardia

1) Hemodynamically compromising tachycardia requiring cardioversion and lidocaine occurred during infusion of 10 mg/hour over 5 days (Riker et al, 1994).

3.3.1.H Torsades de pointes

1) Summary

a) Torsades de Pointes and QT prolongation, including sudden death, have been reported especial when haloperidol is administered intravenously or at doses higher than recommended. Risk factors Torsades de Pointes or QT prolongation include QT-prolonging conditions such as electrolyte imbalance (especially, hypokalemia and hypomagnesemia); underlying cardiac abnormalities; hypothyroidism; familial long QT syndrome; and concomitant drugs that prolong the QT interval. Electrocardiogram monitoring is recommended in patients on intravenous haloperidol (US Food and Drug Administration, 2007).

b) The incidence of long QTc interval syndrome or torsade de pointes with haloperidol is small (Lawrence & Nasraway, 1997). The majority of cases occurred in critically ill patients with a history c cardiovascular disease prescribed more than 50 mg/day. It is recommended that before initiating therapy with haloperidol in critically ill patients that a baseline QTc interval and serum magnesium a potassium concentrations be measured. In cases where the baseline QTc interval is 440 millisecond or longer and they are receiving other drugs that may prolong the QTc interval, or they have an electrolyte disturbance, haloperidol or similar drugs should be used with caution. Electrocardiogram monitoring should be done in critically ill patients once haloperidol is initiated. If the QTc interval lengthens by 25% or more, the haloperidol should be discontinued or the dosage should be reduced

2) The medical literature includes 28 case reports of QT prolongation and Torsades de Pointes, includin cases of death when haloperidol was administered intravenously. Furthermore, a dose-response relationship between intravenous doses and subsequent Torsades de Pointes was demonstrated in case control studies (US Food and Drug Administration, 2007).

3) There were 229 cases of QT prolongation in patients administered injectable or oral haloperidol, including 73 cases of Torsades de Pointes of which 11 were fatal, reported in the manufacturer's worldw safety database received through June 30, 2005. Various doses of intravenous haloperidol were used in of the 11 fatal cases. QT-prolonging or medical conditions may have contributed to the events. A second postmarketing investigation, submitted to the Food and Drug Administration in March 2007, reported 13 Torsades de Points, QT prolongation, ventricular arrhythmias and/or sudden death (US Food and Drug Administration, 2007).

4) A case of haloperidol-induced torsade de pointes was reported in a 41-year-old woman with no predisposing factors. The patient developed torsade de pointes 55 minutes after receiving 80 milligrams (mg) of intravenous haloperidol. The patient was treated and the arrhythmia was controlled. She receive one more 80-mg dose of haloperidol without incident and then it was discontinued. The patient experienc no further arrhythmias (O'Brien et al, 1999t).

5) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (Metzger & Friedman, 1993l; Wilt et al, 1993j). Three patients developed the dysrhythmia after administration of 211 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 readministrati of haloperidol. Four patients developed the dysrhythmia after administration of 170 to 580 mg over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) or respiratory insufficien (1). All 4 patients recovered with no adverse sequelae.

6) A case of torsade de pointes was reported in a 48-year-old woman who ingested 210 mg of haloperic and 1400 mg of orphenadrine. It was concluded that the haloperidol caused this reaction. The patient wa given gastric lavage, 50 grams of activated charcoal and a constant infusion of lidocaine administered at rate of 4 mg per minute. Later, the lidocaine was stopped and replaced by a pacing electrode. The patie was released eight days later in normal condition (Henderson et al, 1991).

7) A case of torsade de pointes caused by haloperidol was reported in a 36-year-old male chronic schizophrenic patient. The patient had been treated with oral haloperidol 20 mg/day for five days, and th 50 mg/day for two more days during hospitalization in a closed psychiatric department. The torsade de pointes was treated with an isoproterenol infusion 2 to 3 mg/minute until the electrocardiogram returned normal (Kriwisky et al, 1990).

8) In another report, the incidence of torsade de pointes was substantial, developing in 8 of 223 critically patients in intensive care units (Sharma et al, 1998f). Patients who received intravenous haloperidol grea than 35 mg/day or had a QTc interval prolongation of greater than 500 ms were at greatest risk.

3.3.1.I Ventricular premature beats

1) A patient who received 90 mg the first day and 60 mg the second day of this procedure developed

multifocal, premature ventricular beats after a 10 mg dose on the third day. The frequency of these beats decreased from one half to one tenth over a 3 day drug-free period. When the patient then received thiothixene over a 4 day course, the ECG was normal (Mehta et al, 1979).
2) Rapid neuroleptization with high dose haloperidol has been associated with few serious cardiovascul side effects. A patient who received 90 mg the first day and 60 mg the second day of this procedure developed multifocal, premature ventricular beats after a 10 mg dose on the third day. The frequency of these beats decreased from one half to one tenth over a 3 day drug-free period. When the patient then received thiothixene over a 4 day course, the ECG was normal (Mehta et al, 1979).

3.3.2 Dermatologic Effects

Dermatological finding

Hair finding

Photosensitivity

3.3.2.A Dermatological finding

1) The relationship between haloperidol-induced parkinsonism and development of SEBORRHEIC DERMATITIS was studied. In 42 patients with haloperidol-induced parkinsonism, 59.5% developed seborrheic dermatitis, while in 47 patients without the extrapyramidal reaction, only 15% had seborrheic dermatitis (Binder & Jonelis, 1983).
2) Haloperidol has also been reported to cause maculopapular and acneiform SKIN ERUPTIONS (Prod Info Haldol(R), 97a).
3) Four cases of injection site reactions after using haloperidol decanoate 100 mg/mL were reported. Ea of the four patients had been given 50 mg/mL strength and had no reaction. The researchers first though that the vehicle used in the 100 mg/mL strength was the problem, but the same vehicle is used in the 50 mg/mL injection. The conclusion was the concentration of 100 mg/mL created much local intolerance (Hamann et al, 1990).
4) Eight of 9 patients injected with haloperidol decanoate 100 mg/mL developed raised, firm, warm, erythematous nodules of 3.5 cm. Symptoms dissipated over three weeks, but nodules persisted for two months. The authors noted no similar reactions in patients receiving the 50 mg/mL strength (Reinke & Wiesert, 1992).

3.3.2.B Hair finding

1) A case of ALOPECIA areata was reported, possibly secondary to haloperidol therapy. The patient wa 56-year-old man who had taken haloperidol for one month (5 mg twice daily for one week, then 3 mg dai and began to experience hair loss on the back of his head. Haloperidol was discontinued and the patient switched to perphenazine. After one week, hair loss stopped and after one month hair growth was norma The patient was also receiving amoxapine and biperiden which may have contributed to the alopecia (Kubota et al, 1994).

3.3.2.C Photosensitivity

1) Isolated cases of photosensitivity has been reported (Prod Info HALDOL(R) injection, 2007).

3.3.3 Endocrine/Metabolic Effects

Gynecomastia

Hyperprolactinemia

Hypoglycemia

Metabolic syndrome

Syndrome of inappropriate antidiuretic hormone secretion

3.3.3.A Gynecomastia

1) Gynecomastia has been reported with haloperidol treatment (Prod Info HALDOL(R) Decanoate IM injection, 2008; Prod Info HALDOL(R) immediate release IM injection, 2008).

3.3.3.B Hyperprolactinemia

1) Overview

a) Antipsychotic-induced hyperprolactinemia was reported in 65.6%, 45.1%, and 42.4% of women c childbearing potential, postmenopausal women, and men, respectively, in an open-label, clinical tria 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) followir 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 dos 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 dur chronic administration (Prod Info HALDOL(R) Decanoate IM injection, 2008; Prod Info HALDOL(R) immediate release IM injection, 2008).

3) Haloperidol use has been associated with an increased prolactin secretion. It appears that a correlati exists between haloperidol-induced prolactin secretion and antipsychotic effect, blood levels, and extrapyramidal side effects of haloperidol (Rao et al, 1980). However, there is a large intersubject variab in the timing and amount of prolactin secreted with a specific dose (Rubin & Forster, 1980). Furthermore other factors may influence prolactin secretion, the effect is blunted in cases of idiopathic hyperprolactinemia (Falaschi et al, 1980), and the effect may be diminished with high doses of haloperid (Bjorndal et al, 1980). Length of therapy apparently does not diminish the effect (Ohman, 1980).

4) In 15 subjects, with normal prolactin levels and beginning haloperidol therapy 1 to 10 mg twice daily, prolactin levels rapidly increased during the first 6 to 9 days. Thereafter, the level plateaued and in most subjects remained between 30 and 50 ng/mL for the 18 days that prolactin was measured. The level did not exceed 77 ng/mL (Spitzer et al, 1998).

5) Prolactin blood levels resulting from varying doses of haloperidol were studied. In their study, involvin 37 patients who received haloperidol 0.2 to 20 mg/day, the following findings were made; doses less tha mg did not produce elevation, doses of 5 to 20 mg produced increasing elevations of prolactin, and lithiu did not enhance the prolactin response (Mielke & Gallant, 1982).

6) The prolactin response to intramuscular haloperidol (0.5 mg, 1 mg, and 1.5 mg) was studied in 6 norr premenopausal women during the follicular and luteal phases of their menstrual cycles. These were compared to the prolactin response in normal young men at the same doses of haloperidol. The women had significantly greater prolactin responses to haloperidol 1 mg and 1.5 mg doses than the men. This w most likely due to a potentiating effect of estrogen. However, the prolactin response to haloperidol at the lower dose of 0.5 mg was significantly smaller in women than men. The women did not differ in their prolactin response to haloperidol during the early and late phase of their menstrual cycle, showing that a increase in endogenous estrogen did not augment the prolactin response to haloperidol (Asnis et al, 198

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 ar 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, 200

3.3.3.C Hypoglycemia

1) Hypoglycemia has been reported with haloperidol treatment (Prod Info HALDOL(R) Decanoate IM injection, 2008; Prod Info HALDOL(R) immediate release IM injection, 2008).

3.3.3.D Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.E Syndrome of inappropriate antidiuretic hormone secretion

1) Syndrome of inappropriate antidiuretic hormone secretion (SIADH) developed in a lethargic 54-year-c patient following the administration of haloperidol 10 mg/day orally for 1 month. Serum sodium was 111 mEq/L and plasma and urine osmolalities were 225 and 325 mOsm/L, respectively. Renal, liver, and thyr function tests were normal. The response from an adrenocorticotropic hormone stimulation test was alsc normal. Discontinuation of haloperidol and water restriction resolved symptoms and improved serum sodium concentration. After several weeks had lapsed, haloperidol was reinitiated and after 5 days of therapy, the patient became lethargic and serum sodium was 115 mEq/L. The SIADH resolved following water restriction and discontinuation of haloperidol. The authors postulated two possible mechanisms for SIADH induced by haloperidol. Haloperidol may alter the central osmotic threshold for ADH (antidiuretic

hormone) levels, or haloperidol may act on the kidneys directly to increase their sensitivity to ADH (Peck Shenkman, 1979).
2) A 77-year-old female, receiving haloperidol 6 mg daily for 5 days, then 10 mg per day, developed SIADH on the eighth day. While she was taking digoxin and hydrochlorothiazide/triamterene, the tempor relationship to haloperidol suggested it as the cause (Husband et al, 1981).
3) A 25-year-old patient with a history of schizophrenia and mental retardation developed syndrome of inappropriate antidiuretic hormone secretion (SIADH). Prior to admission, the patient received haloperidc 30 mg/day for 4 months. Upon admission, serum sodium was 118 mEq/L, serum and urine osmolality we 254 and 299 mOsm/kg, respectively, and urine sodium was 23 mEq/L. To rule out other causes of SIADI serum calcium, magnesium, and phosphorus levels were determined, a hemogram, and renal, liver, adrenal, and thyroid function tests were performed, and all were normal. Roentgenograms of the chest a skull, an EEG, and CT and brain scan were also normal. The patient was treated with fluid restriction anc discharged 12 days following admission. The authors failed to state if haloperidol was discontinued or if t dose reduced, nor was a rechallenge with haloperidol performed, so the possibility of psychogenic water intake does exist for the etiology of SIADH in this case (Matuk & Kalyanaraman, 1977).

3.3.4 Gastrointestinal Effects

Constipation

Dysphagia

Gastrointestinal tract finding

Paralytic ileus

Xerostomia

3.3.4.A Constipation
1) Haloperidol has been reported to cause constipation (Prod Info Haldol(R), 97a).

3.3.4.B Dysphagia
See Drug Consult reference: ANTIPSYCHOTIC-INDUCED DYSPHAGIA

3.3.4.C Gastrointestinal tract finding
1) Haloperidol has been reported to cause ANOREXIA, DYSPEPSIA, NAUSEA and VOMITING, CONSTIPATION, DIARRHEA, and hypersalivation (Prod Info Haldol(R), 97a).
2) In one study of reported cases (n=192) of antipsychotic-induced PANCREATITIS, 12% of the cases were associated with the use of haloperidol at a mean daily dose of 8.2 milligrams. In most patients, time onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003c).

3.3.4.D Paralytic ileus
1) Incidence: rare
2) A case of ileus was reported in a 52-year-old female who received a mean dose of 41.4 mg haloperidol/day, raised to a mean dose of 53 mg/day the 5 days prior to onset. The resulting fecal impaction resolved over 6 days with discontinuation of haloperidol, IV fluids, and continuous nasogastric suction (Maltbie et al, 1981).

3.3.4.E Xerostomia
1) Dry mouth has been reported (Prod Info HALDOL(R) injection, 2007).

3.3.5 Hematologic Effects

Agranulocytosis

Leukopenia

3.3.5.A Agranulocytosis
1) Incidence: rare (Prod Info HALDOL(R) injection, 2007)
2) Agranulocytosis has occurred, rarely, in association with haloperidol and other medications (Prod Info HALDOL(R) injection, 2007).

3.3.5.B Leukopenia

1) Moderate doses of haloperidol have been associated with the development of mild and usually transi leukopenia (Prod Info Haldol(R), 97a).

2) A case of leukopenia (from 13,000 cu/mm to 3,200 cu/mm) 15 days after starting haloperidol 10 mg/d was reported. This followed a similar occurrence with thiothixene. The mechanism for this rare adverse effect could not be established, but the white count returned to normal within a few days after discontinuation of the drug, and subsequent treatment with fluphenazine has not caused a recurrence (Cutler & Heiser, 1979).

3.3.6 Hepatic Effects

3.3.6.A Hepatotoxicity

1) Chronic cholestatic LIVER DISEASE occurred in a 15-year-old black male following treatment with haloperidol (6 mg daily) and benztropine (8 mg daily) for 4 weeks. The patient was treated for an acute psychotic episode. At this time, the patient presented with jaundice to his psychiatrist and was admitted t the hospital approximately 2 months later. JAUNDICE and pruritus continued for over 7 months. Twenty- eight months after the occurrence of jaundice, the patient is asymptomatic but had mildly elevated alkalir phosphatase and transaminase levels (Dincsoy & Saelinger, 1982).

3.3.8 Musculoskeletal Effects

Musculoskeletal finding

Myasthenia gravis

Rhabdomyolysis

3.3.8.A Musculoskeletal finding

1) An increased incidence of hip fracture was reported in elderly patients receiving psychotropic agents (Ray et al, 1987). This study was a case-control evaluation of 1021 patients with hip fractures and 5606 controls, and indicated that an increased risk of hip fracture was observed with the use of hypnotic/anxiolytic agents with a long elimination half-life (greater than 24 hours), tricyclic antidepressant and antipsychotic agents. Current users were defined as subjects who had received a prescription in the day period prior to the admission date for index hospitalization. The long half-life hypnotic/anxiolytic ager studied were lorazepam, diazepam, chlordiazepoxide and barbiturates, excluding phenobarbital. The tricyclic antidepressants included amitriptyline, doxepin and imipramine; antipsychotic agents evaluated were thioridazine, haloperidol, chlorpromazine and perphenazine/amitriptyline. In contrast, shorter-acting hypnotic-anxiolytic agents (half-life of 24 hours or less) were not associated with an increased risk of hip fracture in these patients. The most frequently used agents in this category were diphenhydramine, hydroxyzine and chloral hydrate. The increased risk of hip fracture observed in this study was directly related to the doses of the drugs. Analysis for confounding by dementia did not alter the results. Addition studies are needed to confirm these results in this and other populations and to evaluate the effects of other psychotropic drugs that have less sedative effects.

3.3.8.B Myasthenia gravis

See Drug Consult reference: DRUG-INDUCED MYASTHENIA GRAVIS

3.3.8.C Rhabdomyolysis

1) A case of haloperidol-induced rhabdomyolysis in the absence of neuroleptic malignant syndrome was reported in a 6-year-old handicapped boy. Oral haloperidol (0.3 milligrams daily) was initiated to treat involuntary movements. The haloperidol was effective and the dose was increased to 0.8 milligrams twic daily. After haloperidol was begun, the patient's urine became dark brown on occasion and the myoglobi level in his urine increased. Mild rhabdomyolysis was suspected and haloperidol was discontinued. Subsequently, the myoglobin in the urine decreased, creatinine kinase decreased to normal, and the urir no longer become dark brown (Yoshikawa et al, 2000).

2) In a 23-year-old male a dystonic reaction occurred complicated by the occurrence of rhabdomyolysis. Ten hours following administration of haloperidol 5 mg PO TID, the patient experienced a dystonic reacti which was mistaken for psychotic behavior. Tonic activity continued into the second day and Benadryl 5(mg IV had minimal effect; the reaction was finally controlled with benztropine IV. On the third day, rhabdomyolysis was observed, and urinary myoglobin on minimal effect; the reaction was finally controlle with benztropine IV. On the third day, rhabdomyolysis was observed, and urinary myoglobin on day 4 wa 67 mcg/mL. Patient recovered following urinary alkalinization and IV fluid therapy (Cavanaugh & Finlays(1984).

3.3.9 Neurologic Effects

Akathisia

Dementia

Dysphoric mood

Dystonia

Encephalopathy

Extrapyramidal disease

Neuroleptic malignant syndrome

Parkinsonism

Phobia

Seizure

Tardive dyskinesia

Tic

3.3.9.A Akathisia

1) A study compared akathisia induced by haloperidol or thiothixene. The haloperidol group (5 mg as tes dose followed by 10 mg/day) experienced akathisia in 75% of cases. The thiothixene group (0.22 mg/kg test dose followed by 0.44 mg/kg/day) experienced akathisia in 46% of cases (Van Putten et al, 1984a; V Putten et al, 1984b).

3.3.9.B Dementia

1) Dementia, characterized by symptoms of confusion, memory impairment, disorientation, and slowing motor performance, has been reported (Thornton, 1976b; Cohen & Cohen, 1974a).

3.3.9.C Dysphoric mood

1) Dysphoria has been reported in patients treated with haloperidol for Gilles de la Tourette syndrome. C 72 patients being treated for Gilles de la Tourette syndrome, 3 patients developed pronounced and 3 patients developed mild dysphoria. The change in mood was not related to akinesia or other extrapyrami side effects, drowsiness, or cognitive impairment. Improvement was seen when dosage was reduced. Th report confirms 2 other case studies of similar nature (Caine & Polinsky, 1979).

2) Twenty-six cases of dysphoria, 13 of which were severe, were reported in patients being treated with haloperidol for Tourette syndrome. All appeared to have a threshold dose, above which dysphoria occur and below which symptoms subsided. The threshold dose was individualized and ranged from 1 to 30 mg/day (Bruun, 1982).

3.3.9.D Dystonia

1) During the first few days after initiating treatment with an antipsychotic medication, symptoms of dystonia may occur in susceptible individuals. Symptoms may include spasm of neck muscles, which ma progress to tightening of the throat, swallowing difficulty, breathing difficulty, and/or protrusion of the tongue. These symptoms can occur at low doses but most often occur (and occur with a greater severity with high potency and at higher doses of first generation antipsychotic medications. Males and younger a groups appear to be at greater risk for developing acute dystonia (Prod Info HALDOL(R) IM injection, 2008).

2) Extrapyramidal and dystonic reactions have occurred following usual therapeutic doses of haloperido The incidence of dystonias following haloperidol is reported to be as high as 16% (Swett, 1975) and for extrapyramidal symptoms as high as 25% (Anon, 1973a).

3) Laryngeal-pharyngeal dystonia was reported in a patient 16 hours after being treated with a single do of haloperidol 5 mg IM. The reaction was treated with benztropine 2 mg IV, repeated after 2 minutes, whereupon recovery without sequelae occurred in 5 minutes (Menuck, 1981).

4) Sudden death was reported in a woman receiving haloperidol 230 mg over less than 48 hours. The proposed mechanism was laryngeal-pharyngeal dystonia, followed by laryngospasm and cardiac arrest (Modestin et al, 1981). A similar case was reported after a patient received 340 mg over less than 96 hou

(Ketai et al, 1979).
5) Dystonic reactions were reported to persist for several weeks after a single dose of haloperidol in two patients (Anderson et al, 1981).
6) A high incidence of dystonic reactions was reported in cocaine abusers. Of 7 chronic heavy cocaine users, administration of intramuscular haloperidol (8 mg on 2 consecutive days) resulted in the occurrenc of acute dystonic reactions in 6; the onset of dystonia was approximately 22 hours following the first dos 4 patients and 3 hours following the second dose in 2 others. Diphenhydramine or benztropine was effective in alleviating dystonia in all patients. These data suggest a higher incidence of dystonic reactior in cocaine abusers treated with neuroleptic agents. However, controlled studies are required to confirm these findings, using a cocaine naive control group (Kumor et al, 1986).

3.3.9.E Encephalopathy
1) A case of post-surgical toxic encephalopathy has been attributed to high-dose haloperidol in a 54-yea old African-American male. The patient had a history of bipolar disorder, hypertension and a cerebrovascular accident. Despite increasing doses of haloperidol (up to 270 milligrams intravenously ov 24 hours) to treat agitation, mental status continued to worsen to the point of obtundation, with toxic encephalopathy diagnosed on day 14 after surgery. After haloperidol discontinuation, encephalopathy completely resolved within 8 days (Maxa et al, 1997).
2) An encephalopathic syndrome with irreversible brain syndrome has been reported (Thornton, 1976b; Cohen & Cohen, 1974a).

3.3.9.F Extrapyramidal disease
1) Incidence: frequent (Prod Info HALDOL(R) injection, 2007)
2) Extrapyramidal symptoms occur frequently. Parkinson-like symptoms, akathisia or dystonia may occu typically within the first few days of starting haloperidol. There is a greater association with higher doses. Dose reductions may alleviate symptoms. Antiparkinson drugs (such as benztropine mesylate or trihexyphenidyl hydrochloride) may be useful. Discontinuation of haloperidol may be necessary in patient with persistent extrapyramidal symptoms (Prod Info HALDOL(R) injection, 2007).
3) Extrapyramidal and dystonic reactions have occurred following usual therapeutic doses of haloperido The incidence of dystonias following haloperidol is reported to be as high as 16% (Swett, 1975) and for extrapyramidal symptoms as high as 25% (Anon, 1973a).
4) Extrapyramidal disturbances can present as mild to severe dyskinetic and dystonic reactions includin oculogyric crises, forced opening of the mouth, protrusion of tongue, spasm of facial muscles, opisthotor and scoliotic positioning, general muscle rigidity, cogwheel phenomenon, coarse tremors, oral dyskinesia restlessness, dystonic spasms and posturings of the neck, trunk, and limbs, aphonia and dysphagia (Ge et al, 1972; Walinder & Carlsson, 1973; Simpson, 1973; Lake & Fann, 1973; Yosselson & Kaplan, 1975; Shields & Bray, 1976; Loudon & Waring, 1976; Rice, 1977). Although a number of agents have been reported to be effective in treating these extrapyramidal disturbances including apomorphine, biperiden, procyclidine, and propranolol, conventional agents such as diphenhydramine, trihexyphenidyl, or benztropine may not always result in improvement of the dystonic reactions (Shields & Bray, 1976). Thes neurotoxic reactions have been reported in patients with thyrotoxicosis (Lake & Fann, 1973; Yosselson & Kaplan, 1975) as well as pediatric patients (Shields & Bray, 1976). Some reports indicate that concomita drug therapy such as with lithium may aggravate extrapyramidal reactions (Loudon & Waring, 1976). Son data suggests that, particularly in elderly patients, parkinsonism reactions induced by haloperidol may persist for up to 2 weeks (Rice, 1977). Parkinsonism-like symptoms (sialorrhea, dystonia, torticollis, and trismus) have occurred following discontinuation of haloperidol therapy (De Maio, 1973). Rigidity occurre in association with dyspnea, cyanosis, and dehydration in a thyrotoxic, 74-year-old female (Hamadah & Teggin, 1974).
5) The extrapyramidal side effects of haloperidol were shown to be lessened by joint administration of imipramine-like drugs (Butterworth, 1972).
6) The incidence of extrapyramidal reactions was lower in patients receiving intravenous as opposed to oral haloperidol (Menza et al, 1987). More studies are required to fully evaluate the potential mechanism for a lower incidence of EPS with the intravenous route. In addition, this study only involved 10 patients (received intravenous haloperidol, 6 received oral haloperidol) and more studies involving larger patient populations are necessary to confirm significant differences.
7) Four cases of severe muscle rigidity were reported in burn patients receiving haloperidol for the neuropsychiatric complications of thermal injury. The authors postulated that the seemingly high incidenc (greater than 30%) of this reaction could have resulted from an increased sensitivity of the neuromuscula receptors to acetylcholine, which is present in greater concentrations after haloperidol treatment (Huang al, 1987).
8) A 5-year-old female with Sydenham's chorea treated with doses of 0.5 to 0.7 mg orally 4 times daily c haloperidol developed side effects of dysphagia, aphonia, and dystonic posturing(Shields & Bray, 1976). Seven weeks later the patient was hospitalized and was noted to have abnormal head posture, left arm extension with fist clinched, inability to walk without falling frequently, and placement of her right thumb in the roof of her mouth causing pressure against the gingiva resulting in the exposure of 2 teeth's roots. Th haloperidol was discontinued and various drugs including diphenhydramine, benztropine, and levodopa were given without effect. The patient's condition deteriorated requiring frequent tube feeding with the patient being unable to walk and often assuming a fixed extensor posture. Due to circumstantial evidenc

the choreiform movements and dystonias were believed to be resulted to the haloperidol ingestion.
9) A 23-year-old woman receiving Lugol's solution, propylthiouracil (PTU), trihexyphenidyl, and haloperi developed facial rigidity, a fixed grin, aphasia, an inability to walk, severe weakness, diarrhea, and dryne of the lips and tongue. Four days prior to hospital admission when diarrhea developed, all drugs were discontinued except haloperidol. After 4 days, some improvement in her symptoms were noted. The authors suggested that this type of reaction is not necessarily idiosyncratic but expected in thyrotoxic patients (Yosselson & Kaplan, 1975).
10) A 32-year-old woman developed haloperidol toxicity because of manganese toxicity. The Parkinsonism-like neurotoxicity may be due to the free-radical formation in the presence of ionic manganese in the neuromelanin-containing regions of the brain (Mehta & Reilly, 1990).
11) The incidence and severity of tardive dyskinesia and extrapyramidal side effects was evaluated in 5 outpatients receiving either fluphenazine decanoate or haloperidol decanoate. Twenty-one patients had probable movement disorders based on the Involuntary Movement Scale and the Simpson-Angus Extrapyramidal symptoms (EPS) Rating Scale. Of these, only six had been previously identified by standard observational means. Frequency was higher with haloperidol decanoate, but these patients we also receiving higher doses (Bransgrove & Kelly, 1994).

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.G Neuroleptic malignant syndrome

1) Incidence: rare
2) Neuroleptic malignant syndrome occurred in a 26-year-old male receiving 20 mg haloperidol TID for hypomania (Town, 1982). This patient developed profound rigidity and dystonia, tachycardia, hypertensi sweating, fever, confusion, depressed level of consciousness, incontinence, elevated CPK and leucocytosis. Withdrawal of the drug and treatment with anti-Parkinsonism drugs resulted in improvemer
3) Neuroleptic malignant syndrome was reported in 3 adults during haloperidol therapy of psychotic stat Discontinuation of haloperidol and institution of antiparkinson medications reversed the adverse effect (Cruz et al, 1983; Dosani, 1983; Henderson & Wooten, 1981). One proposed mechanism attributed dopamine receptor blockade in the striatum increasing thermogenesis and in the hypothalamus impairin heat dissipation (Henderson & Wooten, 1981).
4) Two cases of adverse reactions resembling neuroleptic malignant syndrome were reported in childre treated with haloperidol for psychiatric disorders. Therapy consisted of discontinuing haloperidol and administering fluids and antiparkinson medication (Geller & Greydanus, 1979).
5) Amantadine was used successfully to treat a case of neuroleptic malignant syndrome in a 19-year-ol female patient treated with haloperidol. The proposed mechanism for amantadine was dopaminergic agonist activity (Amdurski et al, 1983).
6) Neuroleptic malignant syndrome (NMS) was reported in a head injury patient treated with haloperidol control agitation. NMS began to develop by the third day and haloperidol was discontinued on the elever day. Improvement began to occur by the fourth day after discontinuation of haloperidol (Vincent et al, 1986).
7) Neuroleptic malignant syndrome (NMS) occurred in a chronic schizophrenic treated with haloperidol. The patient, having been treated with haloperidol for 10 years, was given 2 intramuscular doses to contr an abrupt increase in agitation accompanied by other mental changes. Characteristic signs and sympton of NMS occurred. These improved by the fourth day after haloperidol was discontinued, but recurred wh haloperidol was reinstituted on the twelfth day (Matthews & Cersosimo, 1986).
8) A fatal case of neuroleptic malignant syndrome was reported in an 84-year-old male being treated wi haloperidol for agitation associated with dementia. The patient had been taking haloperidol 6 mg/day, bu the dosage was rapidly increased by the family of the patient without informing the physician. Within 8 da the patient developed neuroleptic malignant syndrome. The authors postulated that the rapid increase in haloperidol dosage may have contributed to the severity of the case (Osser & Stewart, 1988).
9) Neuroleptic malignant syndrome (NMS) was reported in a 67-year-old female with parkinsonism bein treated with haloperidol for agitation. The patient having been treated with haloperidol 1 mg at bedtime fo five months was given a total of 12 mg haloperidol intramuscularly, with an additional 13 mg over the ensuing 48 hours. Within 2 days characteristic signs and symptoms of NMS occurred. Withdrawal of haloperidol and treatment with anti-Parkinsonism drugs resulted in improvement (Ryken & Merrell, 1989)
10) Neuroleptic malignant syndrome was reported in a 25-year-old male head injury patient being treate with haloperidol for agitation. Withdrawal of the haloperidol and treatment with dantrolene and bromocriptine resulted in improvement (Heird et al, 1989).
11) Neuroleptic malignant syndrome (NMS) secondary to haloperidol and subsequent to amantadine withdrawal occurred in a 75-year-old male with "senile" dementia and Parkinsonian symptoms (Hermesh al, 1984). The patient developed NMS approximately 2 days after initiation of therapy with haloperidol 0.5 mg orally 3 times daily to control delusions and aggressive behavior. Haloperidol was discontinued and therapy with amantadine 200 mg twice daily was initiated due to suspected NMS, resulting in subsidence NMS symptoms. Amantadine was withdrawn after approximately 1 month of treatment due to exacerbati of delusions, and NMS symptoms recurred approximately 2 days later. Amantadine and levodopa were given, resulting in abatement of NMS symptoms within several days. It is suggested that NMS occurred i this patient secondary to amantadine withdrawal as a result of decreased central dopamine activity, the same mechanism was implicated in the haloperidol induced NMS. It is speculated that Parkinson's disea may have increased this patient's vulnerability to further diminution of dopamine activity.

3.3.9.H 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) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar ris 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 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 like 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 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 thc prescribed a low-dose atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patier 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.I Phobia

1) Phobia was triggered by use of haloperidol. After a psychotic depressive episode successfully treatec with haloperidol, the patient experienced severe anxiety when placed in stressful driving circumstances. Her symptoms resulted in her taking unusual precautions to avoid these situations. After five years of thi phobic situation, the symptoms gradually disappeared after haloperidol was discontinued (Bristol, 1982). Other similar cases have been reported (Mikkelson et al, 1981).

3.3.9.J Seizure

1) Incidence: rare

2) Convulsions, in association with parkinsonism symptoms, have occurred in pediatric patients treated with 1.5 to 2.5 mg of haloperidol or following a 6 mg overdose. Treatment with or without antiparkinsonis drugs was reported to result in complete recovery within a few days in all patients (Debray & Galland, 1970).

See Drug Consult reference: ANTIPSYCHOTICS - EFFECT ON SEIZURE THRESHOLD

3.3.9.K Tardive dyskinesia

1) Several cases of tardive dyskinesia or worsening of tardive dyskinesia have been reported, at doses ranging from 3 to 18 mg/day. Although features of the dyskinesias were different in each case, including onset, manifestations, concurrent therapy, and duration, all authors described a causal relationship with haloperidol (Kiloh et al, 1973; Moline, 1975); (Petty, 1980)(Faheem et al, 1982; Peabody et al, 1987).

2) The incidence of dyskinesias induced by neuroleptic agents was studied in 58 autistic children. Daily doses of haloperidol ranged from 0.02 to 0.22 mg/kg. Thirteen (22%) developed dyskinesias. There appeared to be no relationship between onset of symptoms and dose or administration schedule (Perry (al, 1985).

3) Molindone was compared with haloperidol with regard to their ability to mask neuroleptic withdrawal-exacerbated tardive dyskinesia, using the theoretical proposition that agents less able to mask are less dyskinetogenic. In a parallel, double-blind study, 11 patients were given either molindone or haloperidol following discontinuation of previous neuroleptic therapy and at a point where involuntary movements showed a significant increase. Doses were based on standard relative potency assignments calculated from previous neuroleptic medications and ranged from 50% to 200% dose equivalency as compared to previous neuroleptics. Molindone was shown to be less effective than haloperidol in masking tardive dyskinesia, thereby suggesting lower dyskinetogenic potential (Glazer et al, 1985a).

3.3.9.L Tic

1) Nondystonic, nonakathisic TICs were reported in a hyperactive child. The reaction was similar to that seen when the boy was treated with amphetamine on one occasion and carbamazepine on another (Gualtieri & Patterson, 1986).

3.3.10 Ophthalmic Effects

Blurred vision

Eye / vision finding

3.3.10.A Blurred vision

1) Blurred vision has been reported (Prod Info HALDOL(R) injection, 2007).

3.3.10.B Eye / vision finding

1) A study was conducted in cooperation with Group Health Cooperative of Puget Sound using men and women born before 1931 to evaluate the risk of cataracts from exposure to phenothiazine drugs. A total 45,301 individuals were identified as potential patients in an effort to study a large population. A list of criteria was used to evaluate these patients, and the group was then whittled to 4,674 individuals. The results of the study showed there is no significant increase in risk of cataract extraction in patients who used haloperidol in either short or long-term cases (Isaac et al, 1991).

2) OCULOGYRIC CRISIS has been reported following the use of haloperidol (Dukes, 1975).

3.3.12 Psychiatric Effects

3.3.12.A Psychotic disorder

1) Psychotic exacerbation has been reported. Deterioration was correlated with dosage increase. An acutely psychotic patient, treated with haloperidol 30 mg/day for 10 days with no improvement, deteriora further over a 3 day period when the dose of haloperidol was increased to 60 mg/day. Upon reduction of the haloperidol dose, the patient gradually improved. When fluphenazine replaced haloperidol, the patier showed a gradual but dramatic recovery (Tornatore et al, 1981).

3.3.14 Reproductive Effects

3.3.14.A Priapism

1) Incidence: rare

2) PRIAPISM has been reported (Greenberg & Lee, 1987; Gomez, 1985).

3.3.15 Respiratory Effects

Pulmonary embolism

Respiratory finding

3.3.15.A Pulmonary embolism

1) The use of psychotropic medications has been linked to an increased risk of fatal pulmonary embolis In a case-control study including 62 cases of fatal pulmonary embolism and 243 matched controls, researchers found that compared to non-use, the current use of conventional antipsychotic medications (thioridazine and haloperidol) was associated with an increased risk of fatal pulmonary embolism (adjuste odds ratio, 13.3; 95% CI, 2.3 to 76.3). In addition, low potency antipsychotics, such as thioridazine, were associated with the highest risk, with an odds ratio of 20.8 (95% CI, 1.7 to 259). The current use of antidepressants was also associated with an increased risk of fatal pulmonary embolism (adjusted odds ratio, 4.9; 95% CI, 1.1 to 22.5); however, current or past use of other psychotropic drugs was not associated with an increased risk (adjusted odds ratio, 1.4; 95% CI, 0.3 to 5.8). (Parkin et al, 2003).

3.3.15.B Respiratory finding

1) A case of acute laryngeal dystonia was reported in a 26-year-old woman receiving haloperidol (no do reported) for management of schizophrenia. The patient received both diphenhydramine and lorazepam intravenously with subsequent resolution of symptoms. Haloperidol was discontinued and the patient wa discharged on oral diphenhydramine 24 hours later (Fines et al, 1999).

2) A 53-year-old female with a 25 year history of psychiatric illness was admitted to the ER after having discontinued all of her medications three weeks earlier. She had been taking trifluoperazine 5 mg daily, benztropine 2 mg daily and lithium in alternating daily doses of 600 and 900 mg. She had no known allergies. She was subsequently admitted to the psychiatric crisis unit where she was put on haloperidol mg every 8 hours. Two hours after the second dose, she experienced shortness of breath with audible wheezing. Physical examination findings included sinus tachycardia and auscultation of the chest reveal poor air entry with diffuse high pitched wheezing. There were no other adverse effects detected and she remained afebrile. The bronchospasm was treated and her breathing returned to normal within 30 minute Two hours later, she developed laryngeal stridor for which she was treated with benztropine. The haloperidol was discontinued and the patient was restarted on trifluoperazine. Allergy tests were done, b

skin testing revealed no significant wheal and flare responses. A tartrazine test was also done, but the results were negative. The cause and mechanism of the haloperidol induced bronchospasm remained unclear (Sethna et al, 1991).

3.3.16 Other

Dead - sudden death

Death

Drug dependence

Extrapyramidal disease

Hyperpyrexia

Withdrawal sign or symptom

3.3.16.A Dead - sudden death

1) Cases of sudden death have been reported in association with haloperidol treatment. Causality has n been determined; however, haloperidol cannot be ruled out. Sudden and unexpected death can occur in psychotic patients who may or may not be receiving treatment with other antipsychotic drugs (Prod Info HALDOL(R) injection, 2007).

2) A 59-year-old man admitted for an acute recurrence of a paranoid disorder died after admission (Turbott, 1984). Prior to admission, the patient had not received any neuroleptic medication. The patient was taking pindolol, hydrochlorothiazide, and amiloride for hypertension. The patient was also taking chlordiazepoxide and allopurinol. Physical examination was normal on admission. The patient received t 10-milligram doses of haloperidol orally three hours apart. Following the second dose, an ECG revealed normal sinus rhythm with a rate of 100 beats/minute, a QT interval of 0.42 seconds, and slight T-wave flattening. Shortly after the ECG, the patient was found cyanotic on the floor. A repeat ECG showed asystole, resuscitation efforts were unsuccessful. Autopsy revealed moderate left ventricular hypertrophy and 80% blockage of the right coronary artery and 70% blockage of the anterior descending left coronary artery. No other abnormalities were noted.

3) A 30-year-old male with a long history of multiple drug abuse died after receiving haloperidol (Mahutte 1982). Upon hospital admission, physical examination, routine laboratories and ECG were normal. Multip drug screens were negative. The patient's course over the next three weeks was varied. The patient was taking desipramine 100 milligrams (mg) each day and haloperidol 10 mg orally as needed for agitation. C the three days prior to his death, the patient received haloperidol 50 mg/day, 50 mg/day and 40 mg/day, respectively. After the last haloperidol dose, he was noted to be in respiratory distress, and bloody sputu was suctioned from the patient. The blood pressure at this time was 56/24 mmHg. Cardiac arrest followe and the patient expired. Autopsy revealed grossly congested lungs with diffuse alveolar hemorrhages. There was no evidence of pulmonary emboli, aspiration, or pneumonia. There was no evidence of significant cardiac disease or injury. The cause of death was thought to be transient pulmonary hypertension.

4) A 44-year-old woman with chronic paranoid schizophrenia, myopia, and obesity died 2 hours after a haloperidol dose (Modestin et al, 1981). All previous laboratories and ECGs were normal. The patient ha taken no medications for 6 weeks prior to admission. During the next two days the patient received 60 milligrams (mg) haloperidol intramuscularly and 160 mg orally. The patient experienced two dyskinetic episodes which were successfully treated by biperiden 2 mg. The patient's last dose of biperiden was tak the morning of the second day. Two hours after the patient's last dose of haloperidol (90 mg), vital signs were pulse regular at 84 beats/minute, blood pressure 120/80 mmHg, and respirations normal. Shortly thereafter, the patient cried out and was found unresponsive. The patient's pulse was not palpable and h breathing was labored, but she was not cyanotic. Her mouth was distorted and she bit her lower lip. Cardiopulmonary resuscitation was unsuccessful. Significant findings at autopsy were mild congestion of pulmonary and systemic circulation and large amounts of viscous mucus just above and below the epiglottis. The proposed mechanism was laryngeal-pharyngeal dystonia, followed by laryngospasm and cardiac arrest.

5) A 35-year-old woman with no prior psychiatric problems or significant medical history died in her slee hours after a total oral dose of haloperidol 80 milligrams (mg) (Ketai et al, 1979). In the previous 65 hours she had received haloperidol 260 mg orally. In response to a dystonic reaction 8 hours prior to her death the patient was given 2 mg of benztropine and started on 1 mg twice daily. The only significant finding or autopsy was mild, nonspecific edema of the lungs, brain and liver. This was thought due to attempts at cardiopulmonary resuscitation.

3.3.16.B 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 antipsychot 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 n 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. 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 ever greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the communit 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 confound 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 great 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-c all-cause mortality. A set of potential confounders was measured based on healthcare utilization data wit 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,8 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death 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 rat 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 (mortalit 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 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 leas likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of ag 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 tim points studied after beginning therapy (within 180 days: RR, 1.37; 95% CI, 1.27 to 1.49; less than 40 day 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. 95% CI, 1.15 to 1.45), without dementia (RR, 1.45; 95% CI, 1.3 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 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.C Drug dependence

1) Several cases of intentional haloperidol ABUSE have been reported. Five patients treated for haloperidol toxicity had taken the drug for recreational purposes. All experienced severe extrapyramidal side effects. No reason was given for the choice of this agent for recreational use (Doenecke & Heuermann, 1980).

3.3.16.D Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.E Hyperpyrexia

1) Hyperpyrexia has been reported with haloperidol treatment (Prod Info HALDOL(R) Decanoate IM injection, 2008; Prod Info HALDOL(R) immediate release IM injection, 2008). A case report described hyperpyrexia in a patient treated with haloperidol 2 mg four times daily. The patient was also receiving benztropine concomitantly (Westlake & Rastegar, 1973). The incidence of hyperthermia (37 to 37.9 C)

ranged from 3 to 13% following haloperidol doses of 10 to 15 mg/day (Harder et al, 1971).

3.3.16.F Withdrawal sign or symptom

1) Sudden discontinuation of haloperidol has been associated with a withdrawal syndrome. Tachycardia hypertension, restlessness, and abdominal distress occurred in a patient upon sudden discontinuation of haloperidol 40 mg/day and doxepin 150 mg/day (Pary et al, 1980). This was postulated to be due either cholinergic rebound or a hyperdopaminergic state (Gardos, 1980).

2) Physical agitation, epigastric distress with vomiting, pallor, diaphoresis, and other symptoms occurred days after discontinuation of haloperidol and benztropine. These symptoms persisted until the fifth day, when benztropine alleviated them (Lieberman, 1981).

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 HALDOL(R) injection, 2007) (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: C(Australian Drug Evaluation Committee, 199

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) Although the teratogenicity of haloperidol has not been proven, its use during pregnancy is discourag It is suggested that haloperidol use during pregnancy be limited to psychotic patients requiring long-term therapy (Berkowitz et al, 1981). If use during pregnancy cannot be avoided, ultrasound with particular attention to limb formation should be considered in first trimester exposures (Diav-Citrin et al, 2005).

5) Literature Reports

a) A prospective, observational study of 54 women (mean age, 30.7 years), recruited from the Emory Women's Mental Health program exposed to antipsychotic medication during pregnancy, showed permeability of the placental barrier. Outcomes were determined by maternal and umbilical cord blood samples taken at delivery and through data collected from maternal reports and medical records. Placen passage ratios (defined as the ratio of umbilical cord to maternal plasma concentrations) showed a significant difference between antipsychotic medications, with olanzapine 72.1% (95% CI, 46.8%-97.5%) being the highest, followed by haloperidol 65.5% (95% CI, 40.3%-90.7%), risperidone 49.2% (95% CI, 13.6%-84.8%), and quetiapine 24.1% (95% CI, 18.7%-29.5%), showing the lowest placental passage rat There was a greater frequency of pre-term deliveries (21.4%, p=less than 0.23), low birth weights (30.8% p=less than 0.07), and neonatal intensive care admission (30.8%, p=less than 0.09) in infants exposed t olanzapine (Newport et al, 2007).

b) A multicenter, prospective, controlled study found no difference in the rate of congenital abnormalities the drug-exposed group and the control group. Haloperidol exposure occurred in 188 pregnancies and penfluridol in 27, with 161 of these known to be in the first trimester. The control group consisted of 631 pregnancies exposed to nonteratogens from 4 participating ENTIS (European Network of Teratology Information Services) centers. Other results include a higher rate of elective pregnancy terminations, hig rate of preterm birth, lower median birth rate and lower median birth weight of full-term infants in the drug exposed group. There were no significant differences in the rate of miscarriages, ectopic pregnancies or stillbirths between the control and haloperidol- or penfluridol-exposed groups(Diav-Citrin et al, 2005).

c) One case report describes a full-term, 3880 gram infant exposed to haloperidol in utero, who experienced "jitteriness" at birth. The mother, a 35-year-old woman with schizoaffective disorder, was maintained on haloperidol decanoate 200 mg every two weeks throughout pregnancy. The last dose was administered 3 weeks prior to delivery. By day 8 of life, the infant became increasingly irritable and experienced an episode of tonic-clonic movements in all extremities with tongue thrusting and torticollis. These episodes continued, but with treatment of clonazepam 0.02mg/kg/day, the tonic-clonic movement began to resolve by day 12. The infant was discharged following resolution of movement disorders and weaning of the clonazepam (Collins & Comer, 2003).

d) A 34-year-old pregnant woman ingested 300 mg haloperidol at 34 weeks gestation and presented CN depression, hypotonia, and involuntary spasms of the extremities. A biophysical profile of the fetus on admission was 2 of 10 (two points for amniotic fluid, no evidence of fetal movement, flexion-extension or fetal breathing, fetal heart rate 150 beats/minute, nonreactive with minimal long-term and short-term variability). The mother appeared fully recovered by 48 hours after admission, but a biophysical profile of was not achieved for the fetus until 5 days after admission. A healthy girl was delivered at 39 weeks gestation and she had normal developmental milestones and growth at 18 months of age (Hansen et al, 1997).

e) Although there are isolated cases of teratogenicity associated with haloperidol (McCullar & Heggenes 1975), no cause-effect relationship has been established. Haloperidol is transferred to the fetus via the placenta (Uematsu et al, 1991). Two cases of limb malformations have occurred in infants born to wome

given haloperidol with other potentially teratogenic drugs during the first trimester of pregnancy (Kopelma et al, 1975). Haloperidol has been used in the second and third trimesters, and during labor, without causing neonatal depression or other effects on the newborn (Ayd, 1976).

B) Breastfeeding

1) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may be of concern. (Anon, 2001)

2) World Health Organization Rating: Avoid breastfeeding if possible. Monitor infant for side effects. (Anon, 2002)

3) 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.

4) Clinical Management

a) Haloperidol is excreted into human breastmilk, with a milk to plasma ratio estimated at 0.6 to 0.7 (Whalley et al, 1981). One group reported that the nursing infant receives a dose approximately equivalent to 3% of the maternal dose (Yoshida et al, 1998). It is suggested that when the maternal dose is high, the infant's exposure to the drug may be minimized by limiting the number of feeds per day. There has been a clear association between the small quantities of haloperidol in breastmilk and adverse effects in the exposed newborns (Whalley et al, 1981; Stewart et al, 1980), although a decline in developmental scores has been reported (Anon, 2001).

5) Literature Reports

a) Animal studies have demonstrated that offspring exposed to haloperidol through breast milk experience drowsiness and impairment of motor activity (Iqbal et al, 2001).

b) A wide variation of haloperidol excretion into breast milk has been reported. This is most likely due to the different maternal doses and inter-individual variation in drug metabolism (Chisholm & Kuller, 1997). One study reported a breast milk concentration of 23.5 ng/mL following the administration of haloperidol milligrams twice daily (Whalley et al, 1981). The antipsychotic dose of haloperidol in children ranges from 0.02 to 0.07 milligrams/kilogram/day (Serrano, 1981). Assuming a newborn infant (3 kg) ingests 150 mL/kg/day of breast milk, the maximum dose received would be 0.01 milligram or one-sixth the therapeutic dose. Another author reported a breast milk concentration of only 2 to 5 ng/mL following a maternal haloperidol dose of 12 to 30 mg/day (Stewart et al, 1980).

3.5 Drug Interactions

Drug-Drug Combinations

Intravenous Admixtures

3.5.1 Drug-Drug Combinations

Acecainide

Ajmaline

Amiodarone

Amisulpride

Amitriptyline

Amoxapine

Aprindine

Arsenic Trioxide

Astemizole

Azimilide

Belladonna

Belladonna Alkaloids

Benztropine

Bepridil

Betel Nut

Bretylium

Bupropion

Cabergoline

Carbamazepine

Chloral Hydrate

Chloroquine

Chlorpromazine

Cisapride

Clarithromycin

Dalfopristin

Dehydroepiandrosterone

Desipramine

Dextromethorphan

Dibenzepin

Dicumarol

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Encainide

Enflurane

Erythromycin

Flecainide

Fluconazole

Fluoxetine

Fluvoxamine

Foscarnet

Gemifloxacin

Halofantrine

Halothane

Hydroquinidine

Ibutilide

Imipramine

Isoflurane

Isradipine

Kava

Levodopa

Levomethadyl

Lidoflazine

Lithium

Lithospermum

Lorcainide

Mefloquine

Mesoridazine

Methyldopa

Nefazodone

Nortriptyline

Octreotide

Olanzapine

Pentamidine

Phenylalanine

Pimozide

Pirmenol

Prajmaline

Probucol

Procainamide

Prochlorperazine

Procyclidine

Propafenone

Propranolol

Protriptyline

Quetiapine

Quinupristin

Rifampin

Rifapentine

Risperidone

Sematilide

Sertindole

Sotalol

Sparfloxacin

Spiramycin

Sulfamethoxazole

Sultopride

Tacrine

Tedisamil

Telithromycin

Terfenadine

Tetrabenazine

Thioridazine

Tramadol

Trifluoperazine

Trihexyphenidyl

Trimethoprim

Trimipramine

Vasopressin

Venlafaxine

Vitex

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: Concurrent use of acecainide and haloperidol is not recommended due to the risk of additi effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin is advised (Yamreudeewong et al, 2003a).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of acecainide and haloperidol is not recommend due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o Class III antiarrhythmic agents such as acecainide and haloperidol may have additive effects on the QT interval and is not recommended (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: 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), 1999z; O'Brien et al, 1999r; Pro Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001z; Duenas-Laita et al, 1999y; Agelin et al, 2001x; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increas 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 antipsychoti 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), 1997).
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 show an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and tir to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that tissue binding mechanism is more likely responsible for the plasma level changes than an eliminatio alteration (Young et al, 1993).

3.5.1.C Amiodarone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of amiodarone and haloperidol is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of amiodarone and haloperidol is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Patients who received concurrent administration of amiodarone and haloperidol experienced a potentially significant QTc interval prolongation. All adult patients admitted to a tertiary teaching hospital between January 2005 and December 2006 who received both amiodarone and haloperido were included in a retrospective analysis of data collected to assess patients' risk, cardiac effects, a baseline statistics to determine change in QT interval. Of the 49 patients (age, 68 +/- 10 years) who met inclusion criteria, there were 381 amiodarone and haloperidol distinct exposures, of which 36.2 (138 of 381) exposures included at least one additional QT-interval prolonging drug. Duration of concomitant amiodarone-haloperidol exposure per patient averaged 3 days (range, 1 to 17 days), a the daily dose of haloperidol was 11 +/- 12 mg (range, 1 to 65 mg). There was no apparent affiliatior between longer QTc intervals and the increased number of concomitant QT-interval prolonging drug but QTc intervals were longer with higher daily doses on average. Nearly 55% of patients receiving amiodarone alone had a QTc interval greater than 450 msec and 38% patients had a QTc interval greater than 500 msec. The mean increase in QTc interval following exposure to haloperidol was 9.8 msec (95% CI, 0.6 to 19 msec). Notably, no ventricular arrhythmia was observed (Bush et al, 2008).
b) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o Class III antiarrhythmic agents such as amiodarone and haloperidol may have additive effects on th QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.D Amisulpride
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003c; Prod Info Haldol(R), 2001a). Amisulpride has rarely caused QT prolongation (Prod Info Solian(R) 1999e). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if haloperidol and amisulpride are used concomitantly. Scre patients for conditions that may predispose to QT prolongation and torsade de pointes (i.e. cardiomyopathy, alcohol abuse, hypothyroidism). Monitor the ECG and electrolytes at baseline and throughout therapy.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc 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 dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre

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, 2003b).

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 episode but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger & Friedman, 1993b; Wilt et al, 1993a). Torsades de pointes developed in 8 of 223 critically ill patients i 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

3.5.1.E Amitriptyline

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 (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratio a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsh & Forker, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychoti not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include 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).

3.5.1.F Amoxapine

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 (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratio a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsh & Forker, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychoti not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include 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).

3.5.1.G Aprindine

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

2) Summary: Coadministration of haloperidol with other drugs that potentially prolong the QTc interval, such as aprindine, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001f; Prod Info Haldol(R), 1998b; Larochelle et al, 1984).

3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of aprindine and haloperidol is not recommende due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.H 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 ventricul 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), 2001a). Several antipsychotic agents hav demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999o), haloperidol (O'Brien e al, 1999j), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duena Laita et al, 1999p), sertindole (Agelink et al, 2001m), quetiapine (Owens, 2001p), sultopride (Lande et al 1992o), 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 mse Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and th 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.I Astemizole

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 (Prod Info Solian(R), 1999n), haloperidol (O'Brien et al, 1999i), quetiapine (Owens, 2001o), risperidone (Duenas-Laita et al, 1999m; Prod Info Risperdal(R) risperidone, 2002a), sertindole (Agelink et al, 2001l), sultopride (Lande et al, 1992l), and zotepine (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration of astemizole and other drugs known to prolong the QTc interval, including antipsychotics, is not recommended (Prod Info Hismanal(R), 1996).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of astemizole and agents that prolong the QT interval, such as antipsychotics, is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high dos (Metzger & Friedman, 1993g; Wilt et al, 1993e). Three patients developed the dysrhythmia after administration of 211 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. Four patients developed the dysrhythmia after administration of 170 580 mg over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) respiratory insufficiency (1). All 4 patients recovered with no adverse sequelae.

3.5.1.J Azimilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of azimilide and haloperidol is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of azimilide and haloperidol is not recommende due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio

dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o Class III antiarrhythmic agents such as azimilide and haloperidol may have additive effects on the Q interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.K 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 th patient to excessive anticholinergic activity if taken with haloperidol. 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 roo (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with haloperidol 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, constipatio 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.L 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 th patient to excessive anticholinergic activity if taken with haloperidol. 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 roo (Blumenthal et al, 1998). Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with haloperidol 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, constipatio 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.M Benztropine
1) Interaction Effect: excessive anticholinergic effects (sedation, constipation, dry mouth)
2) Summary: Combined use of haloperidol and anticholinergics may result in excessive anticholinergic effects (Prod Info Haldol(R), 2000a). In a number of case reports, the use of haloperidol with benztropine trihexyphenidyl, or procyclidine, has resulted in a worsening of schizophrenic symptoms. In addition, whe anticholinergics are used with phenothiazines or haloperidol, there may be an increased incidence of tardive dyskinesia (Linnoila et al, 1980a; Singh & Kay, 1979a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor signs of excessive anticholinergic effects. Adjust the doses or discontir the medications as needed.
7) Probable Mechanism: additive anticholinergic effects
8) Literature Reports
a) Concomitant haloperidol and benztropine therapy has been reported to result in inhibition of antipsychotic effects of haloperidol and increased "social avoidance" behavior in several schizophre patients (Singh & Smith, 1973; Prod Info Cogentin(R), 1994).
b) Routine use of antiparkinson medication with neuroleptic agents is controversial and there is evidence that these agents should only be administered at the occurrence of extrapyramidal symptoms, and then only for a short period of time thereafter. This interaction, although not well-documented, supports recommendations by many investigators that routine use of anticholinergic

medications with phenothiazines and haloperidol is not warranted and may be deleterious (Perry et 1991).

c) In a study to evaluate the prophylactic use of benztropine in haloperidol-induced dystonic reactio 29 psychotic patients were treated with haloperidol and either benztropine or a placebo. The results showed no significant difference in side-effects between benztropine or the placebo, except increas dry mouth with benztropine. The occurrence of dystonic reactions with the use of benztropine dropp from 33% to 14%. The researchers conclude that the increased side-effects of benztropine are of litt consequence when compared to the positive effects of the drug (Goff et al, 1991b).

d) Acute intestinal pseudo-obstruction may occur in patients receiving benztropine and haloperidol concomitantly. A 68-year-old female with mild multi-infarct dementia developed acute intestinal pseudo-obstruction after receiving 2 doses of benztropine to treat extrapyramidal symptoms associated with haloperidol therapy. Treatment with haloperidol 0.5 mg 3 times daily was initiated af the patient developed psychotic behavior and agitation. She was hospitalized three days later with extrapyramidal symptoms and was treated with intravenous benztropine. Her abdomen became significantly distended within 3-4 hours. Upon examination, she was dehydrated and had reduced bowel sounds. Dilation of her large bowel and some distention of her small bowel loops were appare on x-ray. Haloperidol and benztropine were discontinued and supportive therapy was initiated. Her abdominal distention had resolved within 24 hours. Benztropine may acutely potentiate the effect of haloperidol, causing acute pseudo-obstruction (Sheikh, 2001).

3.5.1.N 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), 200 Agelink et al, 2001c; Owens, 2001d; Prod Info Orap(R), 1999b; Prod Info Haldol(R), 1998a). In U.S. clini 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 prolongatio the QT interval observed with bepridil (Prod Info Vascor(R), 1997). Pimozide is contraindicated in patient taking other drugs which may prolong the QT interval (Prod Info Orap(R), 1999b).

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 wh 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 include 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), 1999a).

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

3.5.1.O Betel Nut

1) Interaction Effect: increased extrapyramidal side effects of haloperidol (difficulty with movement or abnormal movement of muscles)

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 wit betel nut discontinuation (Deahl, 1989a). A similar effect may occur if betel nut is chewed with concomita haloperidol therapy. The cholinergic activity of betel nut has been attributed to the arecoline content. Wh given with peripheral anticholinergics, arecoline increased the heart rate due to central muscarinic agoni 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 haloperidol, especially if patients are treated with anticholiner agents to control these side effects. Deterioration in symptoms of patients with Parkinson's disease or ot extrapyramidal movement disorders may be expected. Persons who have been chewing betel nut have 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 for the previous 2 years on fluphenazine decanoate depot 50 milligrams (mg) every 3 weeks for schizophrenia and procyclidine mg twice daily for a mild Parkinsonian tremor. Within one week of discontinuation of betel nut chewi 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) Following betel nut ingestion, a 45-year-old Indian man developed akathisia, tremor and stiffness 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 afte discontinuing betel nut. It appears that the anticholinergic effects of procyclidine were diminished wh 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 hea rate and blood pressure of six patients with Huntington's disease. 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 ra 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 nause weakness, and mental changes at the higher doses. No peripheral cholinergic effects were noted. T 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 anticholinergi 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 les 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. +/- 92.9 pg/mL (p equal to 0.0607). Combining betel nut with lime, catechu and Piper betel flower as 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 10 +/- 45.0 pg/mL (p equal to 0.0226). In this group dopamine was also elevated in 8 of 9 subjects, but mean was not significant (Chu, 1995).

3.5.1.P Bretylium

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

2) Summary: Concurrent use of bretylium and haloperidol is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin is advised (Yamreudeewong et al, 2003a).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of bretylium and haloperidol is not recommende due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o Class III antiarrhythmic agents such as bretylium and haloperidol may have additive effects on the C interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.Q Bupropion

1) Interaction Effect: increased plasma levels of haloperidol

2) Summary: It is recommended that haloperidol, an antipsychotic metabolized by the cytochrome P450 2D6 isoenzyme, be initiated at the lower end of the dose range when administered concomitantly with bupropion (Prod Info Wellbutrin XL(TM), 2003; Prod Info Zyban(R), 2000).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of bupropion and haloperidol should be approached with caution and should be initiated at the lower end of the dose range of haloperidol. If bupropion is added tc the treatment regimen of a patient already receiving haloperidol, consider decreasing the dose of

haloperidol.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated haloperidol metabolism

3.5.1.R Cabergoline
1) Interaction Effect: the decreased therapeutic effect of both drugs
2) Summary: Cabergoline is a long-acting dopamine receptor agonist with a high affinity for dopamine-2 receptors. It should not be administered concomitantly with dopamine-2 antagonists, such as phenothiazines, butyrophenones, thioxanthines, and metoclopramide (Prod Info Dostinex(R), 1996).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Cabergoline, a dopamine-2 receptor agonist, should not be used concurrently with a dopamine-2 antagonist, such as haloperidol.
7) Probable Mechanism: antagonistic pharmacologic effects

3.5.1.S Carbamazepine
1) Interaction Effect: decreased haloperidol effectiveness
2) Summary: In a case report, the addition of carbamazepine to patients stabilized with haloperidol resulted in mean reductions of haloperidol levels by 60%. Two other case reports and a clinical study supported this finding, while a third case report did not (Kahn et al, 1990a; Arana et al, 1986a; Fast et al, 1986; Klein et al, 1984; Hesslinger et al, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for the therapeutic efficacy of haloperidol following the addition of carbamazepine; higher haloperidol dosage may be required in some clinical situations.
7) Probable Mechanism: increased cytochrome P450 2D6 and 3A4-mediated haloperidol metabolism
8) Literature Reports
a) Serum haloperidol levels of 14 schizophrenic patients dropped an average of 50% when carbamazepine was added to their therapy. Haloperidol doses ranged from 2 mg to 20 mg daily and the carbamazepine dose was adjusted to yield levels of 8 to 12 mcg/mL. The drop in haloperidol lev resulted in the worsening of one patient's condition. Two patients had significant symptom reduction while on carbamazepine, despite the decrease in the haloperidol levels. Their improvement may hav been due to direct effects of the carbamazepine, or as a secondary effect due to the lowering of the haloperidol levels. The authors recommend monitoring serum medication levels when administering haloperidol in combination with carbamazepine (Kahn et al, 1990).
b) Serum haloperidol levels of seven patients treated for psychosis fell when carbamazepine was added to their therapy. Haloperidol doses ranged from 10 mg to 40 mg daily and carbamazepine do ranged from 400 mg to 1000 mg daily. After carbamazepine was added, haloperidol levels decrease by 19% to 100%. The two patients whose blood levels fell to undetectable levels had a marked worsening of symptoms. Careful monitoring should take place if carbamazepine is added to haloper therapy (Arana et al, 1986).
c) Concomitant administration of haloperidol and carbamazepine as reported to result in neurotoxic (drowsiness, slurred speech, concentration difficulties) in a 37-year-old woman with cerebral palsy a dipolar disorder (Brayley & Yellowlees, 1987). Withdrawal of carbamazepine resulted in subsidence symptoms on this second occasion. It is speculated that the interaction occurred at the level of the CNS, as opposed to toxic effects of either drug alone, as carbamazepine serum levels were subtherapeutic during the toxic episodes and due to the fact that carbamazepine is reported to enhance haloperidol metabolism. In addition, the patient received higher doses of carbamazepine following withdrawal of haloperidol without the occurrence of toxic effects. Cerebral palsy may have been a predisposing factor to the interaction.
d) Twenty-seven schizophrenic patients enrolled in a study to determine the effects of carbamazepi and valproic acid on the plasma levels of haloperidol and the psychopathologic outcome. Following four-day washout period, patients were assigned to receive treatment for four weeks with haloperidc monotherapy, haloperidol with carbamazepine, or haloperidol with valproic acid. Doses of haloperidc remained stable throughout the study, and the doses of carbamazepine and valproic acid were titrat to a plasma level of 6 to 12 mg/L and 50 to 100 mg/L, respectively. When administered with carbamazepine, haloperidol plasma levels decreased by 45% (from 7.6 ng/mL to 4.6 ng/mL) over th 28-day period. Decreases in the rating scores on the Positive subscale of the Positive and Negative Syndrome Scale (pPANSS) were significant during the carbamazepine phase of the study, indicatin that the coadministration of carbamazepine and haloperidol may worsen the clinical outcome compared to haloperidol monotherapy (Hesslinger et al, 1999).

3.5.1.T 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 therapeu 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 antipsychotics and chloral hydrate is recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999m), haloperidol (O'Brien et al, 1999h), quetiapine (Owens, 2001n), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001k), sultopride (Lande et al, 1992k), and zotepin (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloral hydrate and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the potential risk of developing torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998b). Periodic electrocardiographic monitoring is required in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high dos (Metzger & Friedman, 1993f; Wilt et al, 1993d). Three patients developed the dysrhythmia after administration of 211 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.

3.5.1.U 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), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999w), haloperidol (O'Brien et al, 1999p), quetiapine (Owens 2001x), risperidone (Duenas-Laita et al, 1999w), sertindole (Agelink et al, 2001u), sultopride (Lande et a 1992w), and zotepine (Sweetman, 2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as chloroquine is not recommended.
7) Probable Mechanism: additive effect on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999v; Ravin & Levenson, 1997e).

3.5.1.V 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 o the QT interval and is not recommended. Q and T wave distortions have been observed in patients takin phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999k), haloperidol (O'Brien et al, 1999g), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001m), risperidone (Duenas-Laita et al, 1999k), sertindole (Agelink e al, 2001j), sultopride (Lande et al, 1992i), ziprasidone (Prod Info GEODON(R) intramuscular injection, or 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.W Cisapride

1) Interaction Effect: worsening of psychotic symptoms and/or an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant therapy of cisapride with any drug that prolongs the QT interval, such as haloperidol, is contraindicated (Prod Info Propulsid(R), 2000a). Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 2003n; Prod Info Haldol(R), 2001h). No pharmacokinetic interaction was observed in a study of 15 schizophrenic patients taking cisapride with haloperidol, though psychiatric symptoms worsened (Mihara et al, 1999a).

3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: The concurrent administration of cisapride and agents that prolong the QT interval, such as haloperidol, is contraindicated.
7) Probable Mechanism: inhibition of haloperidol metabolism by cisapride; accelerated haloperidol absorption; additive effect on QT interval
8) Literature Reports
a) Psychiatric symptoms significantly increased with concomitant cisapride therapy in 15 schizophrenic patients receiving haloperidol, although no pharmacokinetic interaction was observed Patients received cisapride 5 milligrams (mg) twice daily along with haloperidol 12 mg to 36 mg daily for one week. No significant changes in the mean plasma concentrations of haloperidol or reduced haloperidol were observed during cisapride coadministration. Side effects, measured by the UKU rating scale, were not significantly affected. The authors noted that higher doses of cisapride may affect haloperidol concentrations (Mihara et al, 1999).
b) Prolonged QT interval, ventricular arrhythmias, and torsades de pointes have been reported in 2 cases from July 1993 through May 1999. Of these cases, 70 have resulted in death. A majority (85% of patients experiencing cardiotoxicity had risk factors that predisposed them to arrhythmias (Prod Ir Propulsid(R), 2000).
c) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc 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 dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre 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, 2003m).

3.5.1.X Clarithromycin
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 (Prod Info Solian(R), 1999d), haloperidol (O'Brien et al, 1999c), quetiapine (Owens, 2001e), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001d), sultopride (Lande et al, 1992c), and zotepi (Sweetman, 2004). Even though no formal drug interaction studies have been done, concomitant use of clarithromycin and antipsychotic agents may cause additive effects on the QT interval and is not recommended (Prod Info Biaxin(R), 2002).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of clarithromycin and agents that prolong the QT interval, such as antipsychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) A 32-year-old male with schizoaffective disorder and metabolic syndrome experienced a significa increase in plasma concentration following administration of quetiapine. The patient, hospitalized for acute psychotic symptoms was treated with 50 mg quetiapine daily, with a gradual increase in dosag to 700 mg over 10 days. Psychotic symptoms dissipated within 3 weeks. On day 28, the patient developed a lower airway infection, and was orally treated with 750 mg sultamicillin, 500 mg clarithromycin along with his evening dose of quetiapine 400 mg. The following morning, 750 mg sultamicillin, 500 mg clarithromycin, and the morning 300-mg quetiapine dose were given. Within ho the patient became somnolent, and plasma sample testing resulted in 826.8 microgram/L (normal range, 70 to 170 microgram/L). The patient developed severe impaired consciousness and respirato depression. Quetiapine overdose was suspected and treatment was discontinued. Plasma levels we continually measured over the course of a week until complete recovery was achieved (Schulz-Du E et al, 2008).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high dos (Metzger & Friedman, 1993a; Wilt et al, 1993). Three patients developed the dysrhythmia after administration of 211 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. Four patients developed the dysrhythmia after administration of 170 580 mg over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) respiratory insufficiency (1). All 4 patients recovered with no adverse sequelae.
c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info

Risperdal(R) risperidone, 2002).

3.5.1.Y 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) isoenzyme and haloperidol is a CYP3A4 substrate. Coadministration of these two agents may likely result in increas plasma concentrations of haloperidol, which may lead to QTc interval prolongation and risk of torsades d pointes (Prod Info SYNERCID(R) intravenous injection, 2003; Prod Info Haldol(R) Injection, 2001).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of quinupristin/dalfopristin and haloperidol shoul be avoided. Monitor ECG if used concomitantly.

7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated haloperidol metabolism

3.5.1.Z Dehydroepiandrosterone

1) Interaction Effect: reduced effectiveness of haloperidol

2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with psychosis (Howard, 1992a). In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated (Howard, 1992a). Patient being treated with haloperidol should avoid DHEA supplementation.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and haloperidol. If DHEA is elevated, treatment with dexamethasone 1 mg orally per day may be used to normalize DHEA levels.

7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to haloperidol

8) Literature Reports

a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 milligrams (mg), fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cushinoid with moon face, acne, facial hair, abdominal h and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured a part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. A two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded th elevated DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attent to personal hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited typ He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 10 mg. He was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 m thioridazine 1000 mg, perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppressi test with dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

3.5.1.AA Desipramine

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 (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsha & Forker, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include 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).

3.5.1.AB Dextromethorphan
1) Interaction Effect: exacerbation of dextromethorphan adverse effects (CNS excitement, mental confusion, respiratory depression, nervousness, tremors, insomnia, diarrhea)
2) Summary: Dextromethorphan is metabolized by the cytochrome P450IID6 isoenzyme in humans. Haloperidol is an inhibitor of CYP2D6 (Shen, 1995; Slaughter & Edwards, 1995). Coadministration of dextromethorphan and haloperidol may result in elevated concentrations of dextromethorphan and increased adverse effects.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patient for signs and symptoms of dextromethorphan toxicity (CNS excitement, mental confusion, respiratory depression, nervousness, tremors, insomnia, diarrhea). A reduction of dextromethorphan doses may reduce or resolve adverse effects.
7) Probable Mechanism: inhibition of dextromethorphan metabolism

3.5.1.AC Dibenzepin
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 (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratio a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsh & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include 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).

3.5.1.AD Dicumarol
1) Interaction Effect: decreased anticoagulant effectiveness
2) Summary: Haloperidol may increase the metabolism of dicumarol and reduce the hypoprothrombine effect of oral anticoagulants (Prod Info Dicumarol, 1995).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: In patients receiving oral anticoagulant therapy, the prothrombin time ratio or I (international normalized ratio) should be closely monitored with the addition and withdrawal of treatmen with haloperidol, and should be reassessed periodically during concurrent therapy. Adjustments of the dicumarol dose may be necessary in order to maintain the desired level of anticoagulation.
7) Probable Mechanism: increased dicumarol metabolism

3.5.1.AE 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), 1999z; O'Brien et al, 1999r; Pro Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001z; Duenas-Laita et al, 1999y; Agelin et al, 2001x; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increas 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 antipsychoti 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), 1997).

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 show an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and tir to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that tissue binding mechanism is more likely responsible for the plasma level changes than an eliminatio alteration (Young et al, 1993).

3.5.1.AF Dofetilide

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

2) Summary: Concurrent use of dofetilide and haloperidol is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin is advised. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003a).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of dofetilide and haloperidol is not recommende due to the potential for inducing life-threatening arrhythmias. 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.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have also demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant u of Class III antiarrhythmic agents such as dofetilide and haloperidol may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.AG Dolasetron

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 (Prod Info Solian(R), 1999i), haloperidol (O'Brien et al, 1999f), quetiapine (Owens, 2001k), risperidone (Duenas-Laita et al, 1999i), sertindole (Agelink et al, 2001h), sultopride (Lande et al, 1992g), and zotepir (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministration dolasetron and other drugs known to prolong the QTc interval, including antipsychotics, is not recommended (Prod Info Anzemet(R), 1997a).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In several studies, dolasetron resulted in significant, dose-related increases in mean PR, QRS, a

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 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).

b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high dos (Metzger & Friedman, 1993e; Wilt et al, 1993c). Three patients developed the dysrhythmia after administration of 211 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. Four patients developed the dysrhythmia after administration of 170 580 mg over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) respiratory insufficiency (1). All 4 patients recovered with no adverse sequelae.

c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info Risperdal(R) risperidone, 1999).

3.5.1.AH Doxepin

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 (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratio a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsh & Forker, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychoti not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include 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).

3.5.1.AI Droperidol

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 (Prod Info Solian(R), 1999t), haloperidol (O'Brien et al, 1999m), quetiapine (Owens, 2001u), risperidone (Duenas-Laita et al, 1999s), sertindole (Agelink et al, 2001p), sultopride (Lande et al, 1992t), and zotepir (Sweetman, 2003). 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 droperidol and other drugs known to prolong the QTc interval, including antipsychotics is not recommend (Prod Info Inapsine(R), 2002).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive cardiac effects

3.5.1.AJ Encainide

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

2) Summary: Coadministration of haloperidol with other drugs that potentially prolong the QTc interval, such as encainide, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001f; Prod Info Haldol(R), 1998b; Larochelle et al, 1984).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of encainide and haloperidol is not recommende due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AK Enflurane

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 (Agelink et al, 2001aa; Owe 2001ad; Prod Info Haldol(R), 1998j; Lande et al, 1992ac). Even though no formal drug interaction studie have been done, antipsychotic agents should not be coadministered with other drugs which are also kno to prolong the QTc interval, including enflurane (Owens, 2001ad).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999ab; Ravin & Levenson, 1997h).

3.5.1.AL 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 retrospect 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). Several antipsychot agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999x), haloperic (O'Brien et al, 1999q), risperidone (Duenas-Laita et al, 1999x), sertindole (Agelink et al, 2001v), sultopric (Lande et al, 1992x), and zotepine (Sweetman, 2003). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if erythromycin and antipsychotics are used concomitantly. Monitor QT interval at baseline and periodically during treatment.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study 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 develope increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 4 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarizati at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). 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 attribut to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongatior 15% or greater (Oberg & Bauman, 1995).

3.5.1.AM Flecainide

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

2) Summary: Coadministration of haloperidol with other drugs that potentially prolong the QTc interval, such as flecainide, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001f; Prod Info Haldol(R), 1998b; Prod Info Tambocor(R), 1998; Larochelle et al, 1984).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of flecainide and haloperidol is not recommende due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AN Fluconazole

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

2) Summary: Case reports have described QT prolongation and torsades de points associated with

fluconazole (Khazan & Mathis, 2002; Wassmann et al, 1999). Haloperidol (Prod Info Haldol(R), 1998e), risperidone (Prod Info Risperdal(R) risperidone, 2000), amisulpride (Prod Info Solian(R), 1999l), sertindo (Brown & Levin, 1998a); sultopride (Lande et al, 1992j), and zotepine (Sweetman, 2004) have been shov to prolong the QT interval at therapeutic doses. Even though no formal drug interaction studies have bee done, caution is advised if drugs known to prolong the QT interval are used concomitantly.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if fluconazole and antipsychotics are used concomitantly.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AO Fluoxetine
1) Interaction Effect: haloperidol toxicity (pseudoparkinsonism, akathisia, tongue stiffness) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003f; Prod Info Haldol(R), 2001d). Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Prozac(R), 2001). Caution is advised with coadministration of drugs that potentially prolong the QTc interval. In addition, several case reports describe development of extrapyramidal symptoms when fluoxetine and haloperidol were taken together, possibly due to inhibitior haloperidol metabolism (Benazzi, 1996a; Goff et al, 1991a; Stein, 1991a; Tate, 1989a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The concurrent administration of fluoxetine and haloperidol is not recommende
7) Probable Mechanism: inhibition of haloperidol metabolism by fluoxetine; theoretical additive effects or QT prolongation
8) Literature Reports
a) Fluoxetine increased plasma concentrations of haloperidol in 8 outpatients. Patients received fluoxetine 20 mg daily for 10 days with maintenance doses of haloperidol (average dose, 14 mg per day). After ten days, mean plasma concentrations of haloperidol had increased by 20%. Extrapyramidal symptom scores did not change appreciably after the addition of fluoxetine although one patient developed mild akathisia and another developed tremors. Extrapyramidal symptoms we expected to increase because of indirect inhibition of dopamine synthesis by fluoxetine (Goff et al, 1991).
b) A 39-year-old male experienced tardive dyskinesia with concomitant fluoxetine and haloperidol therapy. He was taking fluoxetine 20 mg daily for 2 months, then haloperidol 2 mg twice daily was started and later lowered to 1 mg per day. Five months later during a routine examination, tardive dyskinesia was diagnosed. The suggested mechanism was the down-regulation of dopamine activit (Stein, 1991).
c) A 39-year-old female developed tardive dyskinesia associated with concomitant fluoxetine and haloperidol therapy. She had been taking haloperidol 2 to 5 mg a day for two years (both with and without benztropine) with occasional mild, reversible extrapyramidal symptoms. Five days before stopping haloperidol, she started taking fluoxetine, which was increased over several days to 40 mg twice a day. After two weeks of fluoxetine she took haloperidol 5 mg each on two consecutive days (along with continuation of fluoxetine). She then experienced severe tongue stiffness, parkinsonism, and akathisia. Both fluoxetine and haloperidol were withdrawn. During the next seven days her extrapyramidal symptoms gradually disappeared (Tate, 1989).
d) A 40-year-old male developed urinary retention while taking fluoxetine and haloperidol. During a recurrence of depression, the patient was treated with fluoxetine 20 mg per day, alprazolam 1.5 mg day, and haloperidol 1 mg per day. The patient had previously taken fluoxetine and alprazolam with incident. Approximately one week after beginning therapy, the patient developed difficulty in voiding urine, dilated pupils, dry mouth, palpitations, restlessness, hand tremors, and insomnia. After discontinuation of haloperidol and alprazolam, side effects ceased within one week. The authors postulated that the interaction was due to fluoxetine inhibition of cytochrome CYP2D6, which metabolizes haloperidol (Benazzi, 1996).

3.5.1.AP Fluvoxamine
1) Interaction Effect: an increased risk of haloperidol toxicity
2) Summary: Haloperidol serum concentrations were increased by the coadministration of fluvoxamine i small double blind, randomized, placebo controlled, crossover study (Daniel et al, 1994a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution should be used when fluvoxamine is administered with haloperidol. Monitor serum concentrations of haloperidol and adjust the dose accordingly. Also monitor the patient fo signs and symptoms of worsening clinical and cognitive assessments.
7) Probable Mechanism: inhibition of cytochrome P450-mediated metabolism of haloperidol
8) Literature Reports

a) Four inpatient males with chronic schizophrenia were stabilized on haloperidol and benztropine orally. In randomized order, the patients were then placed on fluvoxamine for six weeks or identicall appearing placebo. Results showed that the addition of fluvoxamine to haloperidol therapy significar elevated serum concentrations of haloperidol. In addition, haloperidol concentrations did not plateau during the six-week period of fluvoxamine treatment, indicating that the haloperidol concentrations n have continued to increase at a constant dose of fluvoxamine. The coadministration of haloperidol a fluvoxamine also worsened all measures of clinical and cognitive function assessments, including delayed recall memory and attentional function. It is possible that haloperidol may require the cytochrome P450 1A2 system for metabolism, and fluvoxamine is known to be a potent inhibitor of t enzyme pathway (Daniel et al, 1994).

3.5.1.AQ Foscarnet

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999ab), haloperidol (O'Brien al, 1999s), quetiapine (Owens, 2001ac), risperidone (Duenas-Laita et al, 1999aa), sertindole (Agelink et 2001z), sultopride (Lande et al, 1992ab), and zotepine (Sweetman, 2003). Because antipsychotics may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of foscar and antipsychotics is not recommended (Prod Info Foscavir(R), 1998; Ravin & Levenson, 1997g).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of foscarnet and antipsychotics is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AR Gemifloxacin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although pharmacokinetic studies between gemifloxacin and drugs that prolong the QT interval, such as antipsychotics, have not been performed, gemifloxacin should be used cautiously in patients receiving antipsychotic medications (Prod Info Factive(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such a gemifloxacin and antipsychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AS 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. Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the interval (Agelink et al, 2001b; Owens, 2001c; Prod Info Solian(R), 1999c; Prod Info Haldol(R), 1998; Lan et al, 1992b). The concurrent administration of halofantrine with antipsychotics is not recommended (Pro Info Halfan(R), 1998).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halofantrine and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AT Halothane

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 (Agelink et al, 2001i; Owens 2001l; Prod Info Solian(R), 1999j; Prod Info Haldol(R), 1998d; Lande et al, 1992h). Even though no form drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs which may also prolong the QTc interval, including halothane (Owens, 2001l).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of halothane and agents that prolong the QT interval, such as antispychotics, is not recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999j; Ravin & Levenson, 1997b).

3.5.1.AU 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), 1999z; O'Brien et al, 1999r; Prc Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001z; Duenas-Laita et al, 1999y; Agelin et al, 2001x; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increas 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 antipsychoti 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), 1997).
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 show an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and tir to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that tissue binding mechanism is more likely responsible for the plasma level changes than an eliminatio alteration (Young et al, 1993).

3.5.1.AV Ibutilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of ibutilide and haloperidol is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ibutilide and haloperidol is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o Class III antiarrhythmic agents such as ibutilide and haloperidol may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.AW Imipramine
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 (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratior

a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsha & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include 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).

3.5.1.AX Isoflurane
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 (Agelink et al, 2001y; Owens 2001aa; Prod Info Solian(R), 1999aa; Prod Info Haldol(R), 1998i; Lande et al, 1992aa). Even though no formal drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs which are also known to prolong the QTc interval, including isoflurane (Owens, 2001aa).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isoflurane and agents that prolong the QT interval, such as antipsychotics, is not recommended.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999z; Ravin & Levenson, 1997f).

3.5.1.AY Isradipine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes, and its use with other drugs known to cause QT prolongation is not recommended (Prod Info DynaCirc(R), 2000). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999g), haloperidol (O'Brien e al, 1999d), quetiapine (Owens, 2001h), risperidone (Duenas-Laita et al, 1999f), sertindole (Agelink et al, 2001b), and zotepine (Sweetman, 2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.AZ 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 manifeste 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 th 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

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 a 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 1 international units/liter (IU/L) (normal: 35-135 IU/L) and serum gamma-glutamyltransferase of 426 IU (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 (Kavaspor Forte(R)) 150 mg twice daily for complaints of inner tension. Within 10 days, she noted a pronounce increase in her daily "off" periods both in terms of duration and number. Within 2 days of discontinui 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 m 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 (Schelos 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 painf 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 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.BA Levodopa

1) Interaction Effect: decreased levodopa effectiveness

2) Summary: The therapeutic effects of levodopa may be reduced when coadministered with haloperido (Prod Info Stalevo(TM), 2003).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Monitor for clinical response to levodopa. The therapeutic effects of levodopa may be reduced with concomitant administration of haloperidol.

7) Probable Mechanism: antagonistic pharmacologic effect

3.5.1.BB Levomethadyl

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

2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003a; Prod Info Haldol(R), 2001). Coadministration of levomethadyl with drugs that potentially prolong t QTc interval, such as haloperidol, is contraindicated (Prod Info Orlaam(R), 2001).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of levomethadyl with agents that prolong the QT interval, such as haloperidol, 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 (Tc 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 dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre 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).

3.5.1.BC 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 antipsychotics and other drugs known to prolong the QTc interval is not recommende Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Soliar (R), 1999), haloperidol (O'Brien et al, 1999), quetiapine (Owens, 2001), risperidone (Duenas-Laita et al, 1999), sertindole (Agelink et al, 2001), sultopride (Lande et al, 1992), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lidoflazine and antipsychotics is not recommended.
7) Probable Mechanism: additive cardiac effects

3.5.1.BD 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 fev 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 nc been established (Prod Info LITHOBID(R) slow-release oral tablets, 2005). Coadministration of lithium ar 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). Howeve 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 decreas neostriatal dopaminergic activity, probably through a direct action on the G protein and the capacity of th 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, 197 Loudon & Waring, 1976; Thomas, 1979). Irreversible neurological injuries have been reported (Sanc & Hurwitz, 1983; Keitner & Rahman, 1984).
b) Seizures, encephalopathy, delirium, and abnormal EEG occurred in four patients during combine lithium and thioridazine therapy (Spring, 1979). Serum lithium levels were below 1 mEq/L at the time the toxic reaction in all cases. All patients had previously tolerated lithium in combination with anothe phenothiazine. Three of these patients developed symptoms within eight days of initiating combinati 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 eit oral thiothixene, haloperidol, or fluphenazine in mean doses of 607.5 chlorpromazine equivalents pri to initiation of the lithium and were experiencing drug-induced extrapyramidal symptoms. Oral lithiun 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 patier four experienced significant neurologic effects, including jerking of limbs, facial spasms and tics, trer 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 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, abru withdrawal of the lithium may precipitate chlorpromazine cardiotoxicity. In this report, such toxicity w 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 t the interaction may only become significant with very high doses of one or both drugs or with failure 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-y history of bipolar disorder was started on risperidone 3 mg for the treatment of new-onset auditory a 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 dizzine worsening tremors, nausea and vomiting, polyuria, depression, and visual and auditory hallucinatior She was then admitted to the hospital for delirium. Her lithium serum level was 1.36 mEq/L at the tir 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 alm 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 regim 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 additi amantadine, which facilitates the release of presynaptic dopamine and has a mild anticholinergic effect, may have contributed (Chen & Cardasis, 1996).

3.5.1.BE 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 nc 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 possil 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. Whe administered diluent, prolactin levels decreased from 36 +/- 8 nanograms/milliliter (ng/mL) serum to +/- 4 ng/mL serum (p less than 0.005) when administered Lithospermum officinale FDE (40 milligrar (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 wit 6 to 9 hours after the injection (Sourgens et al, 1980).

3.5.1.BF Lorcainide

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

2) Summary: Coadministration of haloperidol with other drugs that potentially prolong the QTc interval, such as lorcainide, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001f; Prod Info Haldol(R), 1998b; Larochelle et al, 1984).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of lorcainide and haloperidol is not recommende due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BG 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, caution is advised if

mefloquine is used with other drugs which can prolong the QTc interval (Prod Info Lariam(R), 1999). Mefloquine was associated with significant QT prolongation in a study of 46 healthy subjects (Davis et al 1996). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998g), quetiapine (Owens, 2001s), risperidone (Prod Info Risperdal(R) risperidone, 2000b), amisulpride (Prod Info Solian(R), 1999r), sertinc (Agelink et al, 2001o); sultopride (Lande et al, 1992r), and zotepine (Sweetman, 2004) have been showr prolong the QT interval at therapeutic doses.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if mefloquine and antipsychotics are used concomitantly.
7) Probable Mechanism: additive effect on QT interval

3.5.1.BH 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 witl other drugs which prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999s), haloperidol (O'Brien et al, 1999l), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001t), risperidone (Duenas-Laita et al, 1999r), sertindole (Agelink et 2001n), sultopride (Lande et al, 1992s), 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.BI Methyldopa
1) Interaction Effect: CNS toxicity (dementia) or reversible parkinsonism
2) Summary: Cases of marked increases of psychotic behavior or newly developed bizarre behavior hav developed within one week after the addition of haloperidol to an established methyldopa regimen. The abnormal behavior dramatically improved within days upon discontinuation of either agent. The few case reported do not establish a cause-effect relationship, but the combination should be used with caution ar the patient observed closely for several days (Thornton, 1976a; Nadel & Wallach, 1979a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor psychiatric symptoms. Discontinue haloperidol if necessary.
7) Probable Mechanism: increased dopamine inhibition
8) Literature Reports
a) Two male patients experienced adverse mental effects resulting from combined methyldopa and haloperidol therapy (Thornton, 1976). The first case was a 48-year-old male with hypertension treate with 1 gram per day of methyldopa for three years. Following initiation of 8 milligrams per day of haloperidol for anxiety, the patient developed symptoms of psychomotor retardation, memory impairment, ideas of reference with accompanying inappropriate suspiciousness, and inability to do mathematical calculations. Discontinuing the haloperidol resulted in resolution of these symptoms within 48 hours. The second case was a 43-year-old male with hypertension treated with 1.5 grams day of methyldopa for 18 months who developed symptoms of disorientation, inability to recognize c handwriting, inability to concentrate and marked slowing of both motor and muscle performance with three days after starting 6 milligrams per day of haloperidol for anxiety. Following discontinuation of haloperidol, the symptoms disappeared completely within 72 hours.
b) A patient became irritable, aggressive, assaultive and unmanageable several days after receivin combination therapy with haloperidol and methyldopa (Nadel & Wallach, 1979). Improvement in symptoms occurred as soon as methyldopa was discontinued.
c) The potentiation of haloperidol by methyldopa was studied in schizophrenic patients (Chouinard al, 1973). Ten patients were maintained on haloperidol 10 milligrams and methyldopa 500 milligram daily from day 2 until the end of the 4-week trial. Among the ten patients, 20 incidences of extrapyramidal side effects were reported, which exceeds the expected incidence of extrapyramidal side effects of 25% following therapeutic doses of haloperidol (Anon, 1973). Antiparkinsonian medication was needed in eight out of 10 patients to control these drug-induced extrapyramidal effe Somnolence was noted in eight patients and considered severe in two.

3.5.1.BJ Nefazodone
1) Interaction Effect: an increased risk of extrapyramidal effects, hypotension, and sedation
2) Summary: A single dose of haloperidol administered with steady-state nefazodone decreased haloperidol clearance. Pharmacodynamic effects of haloperidol were not significantly altered (Prod Info

Serzone(R), 1998; DeVane, 1995).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving combined haloperidol with nefazodone should be monitored closely for signs of excessive haloperidol side effects. Reductions in haloperidol dosage may be necessa
7) Probable Mechanism: decreased haloperidol metabolism and clearance
8) Literature Reports
a) The effect of nefazodone on the pharmacokinetics and pharmacodynamics of haloperidol was studied in 12 healthy males. Nefazodone 200 mg every 12 hours had a slight effect on the pharmacokinetics of a single dose of haloperidol 5 mg. The average area under the plasma concentration curve (AUC), highest concentration, and 12-hour concentration of haloperidol were increased 36%, 13%, and 37%, respectively. Only the effect on the AUC reached statistical significance. The pharmacodynamics of haloperidol were not effected by nefazodone consistently (Barbhaiya et al, 1996).

3.5.1.BK Nortriptyline
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 (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratio a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsh & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychoti not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include 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).

3.5.1.BL 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 antipsychotics and other drugs known to prolong the QTc interval, including octreotide, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999u), haloperidol (O'Brien et al, 1999n), risperidone (Duen Laita et al, 1999t), sertindole (Agelink et al, 2001q), quetiapine (Owens, 2001v), sultopride (Lande et al, 1992u), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of octreotide and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BM Olanzapine
1) Interaction Effect: an increased risk of parkinsonism (cogwheeling rigidity, unstable gait)
2) Summary: A patient receiving haloperidol experienced extreme parkinsonism following the addition o olanzapine therapy. Possible explanations include a pharmacokinetic interaction between olanzapine, a weak cytochrome P450 2D6 (CYP2D6) inhibitor, and haloperidol, a CYP2D6 substrate. Pharmacodynamically, the small amount of dopamine (D2) blockade from olanzapine may have been enough to increase the patient's parkinsonism (Gomberg, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients should be closely monitored for signs and symptoms of increased parkinsonian adverse effects when olanzapine is added to haloperidol therapy. Doses of haloperidol ma

need to be decreased.
7) Probable Mechanism: competitive inhibition of cytochrome P450 2D6-mediated haloperidol metabolis increased dopamine D2 blockade
8) Literature Reports
a) A 67-year-old hospitalized male with bipolar disorder who had stopped taking his medications wa restarted on haloperidol 10 mg nightly, benztropine 1 mg nightly, and valproate 750 mg twice daily. I had been experiencing some mild parkinsonian symptoms at baseline, but these symptoms did not worsen when haloperidol was reinstituted. Following stabilization on this regimen, it was decided to change his antipsychotic medication to olanzapine to minimize any parkinsonism that was a result o his medications. While tapering the haloperidol and initiating olanzapine, the patient experienced extreme parkinsonism that resulted in an inability to walk. His mental status remained unchanged. Haloperidol was discontinued on day 7 of combination therapy, and two days later the patient's parkinsonism side effects had resolved back to baseline. Benztropine was then discontinued, and th parkinsonian symptoms did not reoccur while on olanzapine (Gomberg, 1999).

3.5.1.BN 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 antipsychotics and other drugs known to prolong the QTc interval, including pentamidine, is not recommended (Agelink et al, 2001e; Owens, 2001g; Prod Info Haldol(R), 2001b; Pro Info Solian(R), 1999f; Duenas-Laita et al, 1999e; Duenas-Laita et al, 1999e; Prod Info Nipolept(R), 1996 Metzger & Friedman, 1993c; Lande et al, 1992d).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pentamidine and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BO 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 amin 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 w catecholamine synthesis
8) Literature Reports
a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neurolept 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=1 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 Abnorma Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phenylalar level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p les than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading phenylalanine leve 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 plasn phenylalanine levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result o conversion of phenylalanine to tyrosine. Plasma levels of competing large neutral amino acids such tryptophan decreased slightly (Gardos et al, 1992).

3.5.1.BP Pimozide
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal

2003x; Prod Info Haldol(R), 2001m). According to the manufacturer, coadministration of pimozide with drugs that potentially prolong the QTc interval, such as haloperidol, is contraindicated (Prod Info Orap(R) 1999e).
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 (Tc 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 dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre 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, 2003w).
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 episode but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger & Friedman, 1993k; Wilt et al, 1993i). Torsades de pointes developed in 8 of 223 critically ill patients ir 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 possi mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. The manufacturer recommends that an electrocardiogram be performed before pimozid treatment is initiated and periodically thereafter, especially during the period of dose adjustment (Pro Info Orap(R) pimozide, 1999).

3.5.1.BQ 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), 1999z; O'Brien et al, 1999r; Pro Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001z; Duenas-Laita et al, 1999y; Agelin et al, 2001x; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increas 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 antipsychoti 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), 1997).
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 show an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and ti to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that tissue binding mechanism is more likely responsible for the plasma level changes than an eliminatio

alteration (Young et al, 1993).

3.5.1.BR 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), 1999z; O'Brien et al, 1999r; Prc Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001z; Duenas-Laita et al, 1999y; Agelin et al, 2001x; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increas 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 antipsychoti 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), 1997).

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 show an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and tir to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that tissue binding mechanism is more likely responsible for the plasma level changes than an eliminatio alteration (Young et al, 1993).

3.5.1.BS 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, the coadministration of drugs known to prolong the QTc interval is not recommended. Probucol has been shown to prolong the QTc interval (Gohn & Simmons, 1992; Prod Info Lorelco(R), 1991). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998f), quetiapine (Owens, 2001q), risperidone (Prod Info Risperdal(R) risperidone 2000a), amisulpride (Prod Info Solian(R), 1999p), sertindole (Brown & Levin, 1998c); sultopride (Lande e al, 1992p), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if probucol and antipsychotics are used concomitantly.

7) Probable Mechanism: additive effect on QT interval

3.5.1.BT 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), 1999z; O'Brien et al, 1999r; Prc Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001z; Duenas-Laita et al, 1999y; Agelin et al, 2001x; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increas 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 antipsychoti 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), 1997).
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 show an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and tir to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that tissue binding mechanism is more likely responsible for the plasma level changes than an eliminatio alteration (Young et al, 1993).

3.5.1.BU 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 o the QT interval and is not recommended. Q and T wave distortions have been observed in patients takin phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999k), haloperidol (O'Brien et al, 1999g), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001m), risperidone (Duenas-Laita et al, 1999k), sertindole (Agelink e al, 2001j), sultopride (Lande et al, 1992i), ziprasidone (Prod Info GEODON(R) intramuscular injection, or 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.BV Procyclidine
1) Interaction Effect: excessive anticholinergic effects (sedation, constipation, dry mouth)
2) Summary: Use of haloperidol in combination with anticholinergics may result in excessive anticholinergic effects (Prod Info Haldol(R), 2000). A significant reduction in haloperidol serum levels occurred following the addition of procyclidine in patients who were previously well stabilized. Following discontinuation of procyclidine haloperidol serum levels returned to baseline (Bamrah et al, 1986). In a number of case reports, the use of haloperidol with benztropine, trihexyphenidyl, or procyclidine has resulted in a worsening of schizophrenic symptoms. In addition, when anticholinergics are used with phenothiazines or haloperidol, there may be an increased incidence of tardive dyskinesia (Singh & Kay, 1979; Linnoila et al, 1980).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use this combination only when clearly indicated. Monitor for excessive anticholinergic effects. A dosage adjustment for haloperidol may be required in order to maintain or achie a therapeutic effect.
7) Probable Mechanism: additive anticholinergic effects

3.5.1.BW Propafenone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of haloperidol with other drugs that potentially prolong the QTc interval, such as propafenone, should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Owens, 2001f; Prod Info Haldol(R), 1998b; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of haloperidol and propafenone is not recommended due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BX Propranolol

1) Interaction Effect: an increased risk of hypotension and cardiac arrest

2) Summary: A case report described 3 hypotensive episodes and 2 cardiopulmonary arrests in a patier who received haloperidol and propranolol concomitantly on 3 separate occasions. Alpha-receptor bindin by haloperidol and an additive relaxant effect on peripheral blood vessels by haloperidol and propranolol possibly blunting sympathetic heart stimulation is a postulated mechanism for this interaction. The autho advise caution in coadministering haloperidol and propranolol or other beta blockers (Alexander et al, 1984). Monitoring the patient for signs of hypotension is warranted.

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concomitant use of haloperidol and propranolol may increase the risk of hypotension and cardiac arrest. Caution is advised when coadministering haloperidol and propranolol or other beta blockers (Prod Info INDERAL(R) LA oral capsules, 2007; Alexander et al, 1984). Monitor the patient for signs of hypotension.

7) Probable Mechanism: unknown

8) Literature Reports

a) A case report described 3 hypotensive episodes and 2 cardiopulmonary arrests with concomitan haloperidol and propranolol use in a 48-year-old woman with schizophrenia and hypertension. Two years after starting haloperidol 20 mg/day and trichlormethiazide 4 mg/day, the patient was admitte with psychosis due to discontinuing haloperidol. Her blood pressure (BP) was 205/100 mmHg. Propranolol 80 mg was initiated followed by haloperidol 10 mg nine hours later. Ninety minutes later she was unresponsive with shallow breathing and a BP of 80/0 mmHg. The patient recovered and w discharged with haloperidol 30 mg/day and trichlormethiazide 4 mg/day. Ten months later, the patie was admitted with agitation after stopping her medicine. Haloperidol 10 mg was administered. Ten hours later, she was given haloperidol 10 mg and propranolol 40 mg. Hypotension and cardiopulmonary arrest occurred 2.5 hours later. She was discharged the next day with loxapine 25 mg/day, trichlormethiazide 4 mg/day, and propranolol 80 mg twice per day. Five months later, the patient presented with acute psychosis and a BP of 210/110 mmHg. Because her chart could not be located to assess prior treatment, she was given propranolol 80 mg and 15 minutes later, haloperido 10 mg. Hypotension and cardiac arrest occurred 30 minutes later. After discharge, she continued to successfully maintained on trichlormethiazide 4 mg/day, propranolol 80 mg twice daily, and loxapine 30 mg/day. A postulated mechanism is alpha-receptor binding by haloperidol and an additive relaxa effect on peripheral blood vessels by haloperidol and propranolol that may blunt sympathetic heart stimulation (Alexander et al, 1984).

3.5.1.BY Protriptyline

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 (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratio a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsh & Forker, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychoti not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include 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).

3.5.1.BZ Quetiapine

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

2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003h; Prod Info Haldol(R), 2001e). Quetiapine may prolong the QT interval at therapeutic and toxic dos Coadministration of haloperidol 7.5 mg twice daily with quetiapine 300 mg twice daily did not alter the steady-state pharmacokinetics of quetiapine (Prod Info Seroquel(R), 2003). Caution is advised with

coadministration of drugs that potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is advised if haloperidol and quetiapine are used concomitantly. Scree patients for conditions that may predispose to QT prolongation and torsade de pointes (i.e. cardiomyopathy, alcohol abuse, hypothyroidism). Monitor the ECG and electrolytes at baseline and throughout therapy.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc 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, though TdP has been associated with a dose 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, 2003g).

3.5.1.CA 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) isoenzyme and haloperidol is a CYP3A4 substrate. Coadministration of these two agents may likely result in increas plasma concentrations of haloperidol, which may lead to QTc interval prolongation and risk of torsades d pointes (Prod Info SYNERCID(R) intravenous injection, 2003; Prod Info Haldol(R) Injection, 2001).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of quinupristin/dalfopristin and haloperidol shoul be avoided. Monitor ECG if used concomitantly.
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated haloperidol metabolism

3.5.1.CB Rifampin
1) Interaction Effect: decreased haloperidol effectiveness
2) Summary: Haloperidol blood levels and half-life were examined in 7 patients treated concurrently with haloperidol and rifampin(Takeda et al, 1986). Blood levels and half-lives of haloperidol were significantly decreased compared to controls.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the patient for a decreased clinical response to haloperidol when rifam is added to the drug therapy. The haloperidol dose may need to be increased while receiving rifampin ar decreased when rifampin is discontinued.
7) Probable Mechanism: increased hepatic metabolism

3.5.1.CC Rifapentine
1) Interaction Effect: decreased haloperidol effectiveness
2) Summary: Rifapentine is known to induce hepatic enzymes involved in the metabolism of haloperidol When haloperidol and rifapentine are administered together, it may be necessary to increase the dose o haloperidol used (Prod Info Priftin(R), 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the patient for a decreased clinical response to haloperidol when rifapentine is added to the drug therapy. The haloperidol dose may need to be increased while receiving rifapentine and decreased when rifapentine is discontinued.
7) Probable Mechanism: increased hepatic metabolism

3.5.1.CD Risperidone
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003j; Prod Info Haldol(R), 2001f). Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999o; Ravin & Levenson,

1997d; Gesell & Stephen, 1997a) and in overdose situations (Lo Vecchio et al, 1996a; Brown et al, 1993
Caution is advised with coadministration of drugs that potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if haloperidol and risperidone are used concomitantly. Scree
patients for conditions that may predispose to QT prolongation and torsade de pointes (i.e.
cardiomyopathy, alcohol abuse, hypothyroidism). Monitor the ECG and electrolytes at baseline and
throughout therapy.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking
risperidone therapeutically (Duenas-Laita et al, 1999n; Ravin & Levenson, 1997c; Gesell & Stephen
1997) and in overdose situations (Lo Vecchio et al, 1996; Brown et al, 1993).
b) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc
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 dos
as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre
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, 2003i).

3.5.1.CE Sematilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac
arrest)
2) Summary: Concurrent use of sematilide and haloperidol is not recommended due to the risk of additiv
effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin
is advised (Yamreudeewong et al, 2003a).
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of sematilide and haloperidol is not recommende
due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio
dosing and telemetric monitoring is advised.
7) Probable Mechanism: additive QT prolongation
8) Literature Reports
a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in
ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents
have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o
Class III antiarrhythmic agents such as sematilide and haloperidol may have additive effects on the
interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CF Sertindole
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal
2003r; Prod Info Haldol(R), 2001j). Sertindole has demonstrated QTc prolongation (Agelink et al, 2001t;
Brown & Levin, 1998e; Cardoni & Myer, 1997b). Caution is advised with coadministration of drugs that
potentially prolong the QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if haloperidol and sertindole are used concomitantly. Screer
patients for conditions that may predispose to QT prolongation and torsade de pointes (i.e.
cardiomyopathy, alcohol abuse, hypothyroidism). Monitor the ECG and electrolytes at baseline and
throughout therapy.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) 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 episode
but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger &
Friedman, 1993i; Wilt et al, 1993g). Torsades de pointes developed in 8 of 223 critically ill patients ir
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

b) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc 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 dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre 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, 2003q).

c) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the potential risk of developing torsade de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998d). Periodic electrocardiographic monitoring is required in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997a).

d) Thirty, otherwise healthy, schizophrenic patients participated in an open, dose titration (4 to 16 mg/day) study to determine the cardiovascular effects of sertindole. At the end of the 3-week study i was concluded that resting heart rate and frequency corrected QT intervals increased in a dose-rela 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 (Agelir et al, 2001s).

3.5.1.CG Sotalol

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

2) Summary: Concurrent use of sotalol and haloperidol is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin is advised (Yamreudeewong et al, 2003a).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of sotalol and haloperidol is not recommended d to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o Class III antiarrhythmic agents such as sotalol and haloperidol may have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CH Sparfloxacin

1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes

2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003v; Prod Info Haldol(R), 2001l). Coadministration of sparfloxacin with drugs that potentially prolong th QTc interval, such as haloperidol, is contraindicated (Prod Info Zagam(R), 1998a).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of sparfloxacin with agents that prolong the QT interval, such as haloperidol, is contraindicated.

7) Probable Mechanism: additive effects on QTc prolongation

8) Literature Reports

a) In clinical trials involving 1489 patients with a baseline QTc measurement, the mean prolongatior the QTc interval at sparfloxacin steady-state was 10 msec (2.5%). Of these subjects, 0.7% had a QT interval greater than 500 msec at steady-state. However, no arrhythmic effects were seen in any of t patients. The magnitude of the QTc effect does not increase with repeated administration of sparfloxacin, and the QTc interval returns to baseline within 48 hours after discontinuation of sparfloxacin (Prod Info Zagam(R), 1998).

b) A 47-year-old woman treated with sparfloxacin went into cardiac arrest as a result of torsade de pointes and required cardiopulmonary resuscitation. dizziness and lost consciousness. Her pre-treatment electrocardiogram showed QT and QTc intervals of 0.34 and 0.46 seconds, respectively. A electrocardiogram post-arrest revealed QT and QTc intervals of 0.35 and 0.60 seconds, respectively Continuous electrocardiography confirmed numerous episodes of torsade de pointes. Sparfloxacin v discontinued and the QTc returned to baseline within a week. Upon further testing, it was determine

that the patient suffered from a mild idiopathic long QT syndrome. Due to the onset of symptoms wit administration of sparfloxacin and the relief of symptoms following discontinuation of the drug, it is highly probable that sparfloxacin contributed to the torsades de pointes (Dupont et al, 1996).
c) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc 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 dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre 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, 2003u).

3.5.1.CI 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 antipsychotics and other drugs known to prolong the QTc interval, including spiramyc is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999v), haloperidol (O'Brien et al, 1999o), quetiapine (Owens, 2001w), risperidone (Duenas-Laita et al, 1999u), sertindole (Agelink et al, 2001r), sultopride (Lande et al, 1992v), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of spiramycin and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CJ 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 therapeu dose (Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including cotrimoxazole, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999h), haloperidol (O'Brien et al, 1999e), quetiapine (Owens 2001i), risperidone (Duenas-Laita et al, 1999g), sertindole (Agelink et al, 2001f), sultopride (Lande et al, 1992e), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CK Sultopride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003l; Prod Info Haldol(R), 2001g). Sultopride may induce prolongation of the QT interval and ventricula arrhythmias including torsades de pointes following therapeutic or toxic doses (Harry, 1997b; Lande et a 1992n; Montaz et al, 1992a). Caution is advised with coadministration of drugs that potentially prolong th QTc interval.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if haloperidol and sultopride are used concomitantly. Screer patients for conditions that may predispose to QT prolongation and torsade de pointes (i.e. cardiomyopathy, alcohol abuse, hypothyroidism). Monitor the ECG and electrolytes at baseline and throughout therapy.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) 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 episode but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger & Friedman, 1993h; Wilt et al, 1993f). Torsades de pointes developed in 8 of 223 critically ill patients i 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

b) Numerous case reports have described significant QTc prolongation and torsades de pointes (T 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 dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre 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, 2003k).

c) Sultopride may induce prolongation of the QT interval and ventricular arrhythmias including torsades de pointes following therapeutic or toxic doses (Harry, 1997a; Lande et al, 1992m; Montaz al, 1992).

3.5.1.CL Tacrine

1) Interaction Effect: Parkinsonian syndrome (akinesia, shuffling gait, masked facies, slurred speech, lea pipe rigidity, cogwheel signs)

2) Summary: Parkinsonian syndrome with concomitant use of tacrine and haloperidol has been reportec two separate case reports. Both patients were able to tolerate one of the drugs when the other was discontinued. Both of these drugs increase acetylcholine activity in the striatal region of the brain, which may have caused the effects observed (McSwain & Forman, 1995a; Maany, 1996a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Patients should be closely monitored for signs of a Parkinsonian syndrome wh being treated with haloperidol and tacrine. Discontinuation of one agent may be required.

7) Probable Mechanism: increased striatal acetylcholine activity

8) Literature Reports

a) The first case report of tacrine and haloperidol resulting in a parkinsonian syndrome was in an 87 year old male (McSwain & Forman, 1995). Haloperidol doses of 5 mg daily were being administered for agitation and paranoia. When tacrine 10 mg four times daily was added to his regimen, he developed severe parkinsonian symptoms within 72 hours, including akinesia, masked facies, shuffl gait, and lead-pipe rigidity. When both tacrine and haloperidol were discontinued, the symptoms resolved within approximately eight hours. Haloperidol was successfully reinitiated at a dose of 4 mg daily without recurrence of the parkinsonian syndrome.

b) A 72-year old female with agitated paranoid psychosis became controlled on haloperidol 10 mg daily without undue side effects, including extrapyramidal syndrome. When tacrine 10 mg four times daily was added to her regimen for dementia, she developed a disabling parkinsonian syndrome wit a week. Symptoms included severe akinesia, shuffling gait, masked facies, slurred speech, and pronounced rigidity and cogwheel signs. The haloperidol regimen was tapered off and replaced with risperidone 1 mg twice daily, with resolution of the parkinsonian syndrome within a few days. She di not experience further extrapyramidal signs, even after the tacrine dose was increased to 20 mg fou times daily (Maany, 1996).

3.5.1.CM Tedisamil

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

2) Summary: Concurrent use of tedisamil and haloperidol is not recommended due to the risk of additive effects on the QT interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitorin is advised (Yamreudeewong et al, 2003a).

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of haloperidol and tedisamil is not recommende due to the potential for inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautio dosing and telemetric monitoring is advised.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Class III antiarrhythmics have been shown to prolong the QT interval, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including haloperidol (O'Brien et al, 1999a). Concomitant use o

Class III antiarrhythmic agents such as tedisamil and haloperidol may have additive effects on the C interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CN Telithromycin

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 (Agelink et al, 2001g; Owens 2001j; Prod Info Haldol(R), 1998c; Lande et al, 1992f). Even though no formal drug interaction studies ha been done, antipsychotic agents should not be coadministered with other drugs which are also known to prolong the QTc interval, including telithromycin (Owens, 2001j).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive effects on the QT interval, the concurrent administration of telithromycin and an antipsychotic is not recommended.

7) Probable Mechanism: additive effect on QT interval

8) Literature Reports

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

3.5.1.CO 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), 2002a; Owens, 2001ab; Prod Info Orap(R), 1999d). Even thou 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 Q 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 include 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), 1999c).

3.5.1.CP Tetrabenazine

1) Interaction Effect: increased risk of QT interval prolongation, neuroleptic malignant syndrome, extrapyramidal disorders

2) Summary: Tetrabenazine causes a small increase in the correct QT interval. As the degree of prolongation increases, QT prolongation can develop into torsade de pointes-type VT. The concomitant u of tetrabenazine with other drugs known for QT prolongation (eg, haloperidol) should be avoided. In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 2 mg or 50 mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive contro The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008). In addition to QT prolongation, tetrabenazine may also cause adverse reactions such as neuroleptic malignant syndrome and extrapyramidal disorders, which may be exaggerated when coadministered with neuroleptic drugs (eg, haloperidol) (Prod Info XENAZINE(R) oral tablets, 2008)

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of tetrabenazine with haloperidol or other neuroleptic drugs m increase tetrabenazine adverse reactions, such as QT interval prolongation and increased risk of torsade de pointes. Other adverse reactions, such as neuroleptic malignant syndrome and extrapyramidal disord may be enhanced when given with a dopamine agonist such as haloperidol (Prod Info XENAZINE(R) ora tablets, 2008).

7) Probable Mechanism: increased dopamine levels; additive effects on QT interval prolongation

3.5.1.CQ 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), 1999q), haloperidol (O'Brien et al, 1999k), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001 paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et 1999q), sertindole (Agelink et al, 2001n), sultopride (Lande et al, 1992q), ziprasidone (Prod Info GEODC (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.CR Tramadol
1) Interaction Effect: an increased risk of seizures
2) Summary: Seizures have been reported in patients using tramadol. The manufacturer of tramadol sta that combining neuroleptic medications with tramadol may enhance the risk of seizures (Prod Info Ultran (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 t might predispose to seizures.
7) Probable Mechanism: unknown

3.5.1.CS 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 o the QT interval and is not recommended. Q and T wave distortions have been observed in patients takin phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999k), haloperidol (O'Brien et al, 1999g), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001m), risperidone (Duenas-Laita et al, 1999k), sertindole (Agelink e al, 2001j), sultopride (Lande et al, 1992i), ziprasidone (Prod Info GEODON(R) intramuscular injection, or 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 Trihexyphenidyl
1) Interaction Effect: excessive anticholinergic effects (sedation, constipation, dry mouth)
2) Summary: Use of haloperidol in combination with anticholinergics may result in additive anticholinergi effects (Prod Info Haldol(R), 2000b). In a number of case reports, the use of haloperidol with benztropine trihexyphenidyl, or procyclidine has resulted in a worsening of schizophrenic symptoms. In addition, whe anticholinergics are used with phenothiazines or haloperidol, there may be increased incidence of tardive dyskinesia (Singh & Kay, 1979b; Linnoila et al, 1980b).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use this combination only when clearly indicated. Monitor for excessive anticholinergic effects. Dosage adjustments may be required.
7) Probable Mechanism: additive anticholinergic effects

3.5.1.CU 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 therapeu dose (Lopez et al, 1987). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and other drugs known to prolong the QTc interval, including cotrimoxazole, is not recommended. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999h), haloperidol (O'Brien et al, 1999e), quetiapine (Owens

2001i), risperidone (Duenas-Laita et al, 1999g), sertindole (Agelink et al, 2001f), sultopride (Lande et al, 1992e), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CV Trimipramine
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 (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), quetiapine (Owens, 2001b), sultopride (Lande et al, 1992a), and zotepi (Sweetman, 2003). Even though no formal drug interaction studies have been done, the coadministratio a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R), 2001; Marsh & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychoti not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have include 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).

3.5.1.CW Vasopressin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Antipsychotics and vasopressin have been shown to prolong the QTc interval at the recommended therapeutic dose (Owens, 2001a; Prod Info Solian(R), 1999a; Duenas-Laita et al, 1999a; Brown & Levin, 1998; Harry, 1997; Prod Info Nipolept(R), 1996; Metzger & Friedman, 1993; Mauro et al, 1988). Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QTc interval is not recommended.
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of drugs that prolong the QT interval, such as antipsychotics and vasopressin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CX Venlafaxine
1) Interaction Effect: increased haloperidol serum concentrations and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Venlafaxine may inhibit haloperidol metabolism (Prod Info Effexor(R) XR, 2003a). Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 2003p; Proc Info Haldol(R), 2001i). Venlafaxine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Effexor(R) XR, 2003a). Concomitant use is not recommended.
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concurrent administration of haloperidol and venlafaxine is not recommended.
7) Probable Mechanism: decreased haloperidol metabolism; theoretical additive effect on QT prolongati
8) Literature Reports
a) Under steady-state conditions, venlafaxine 150 mg daily decreased the total oral clearance of a single 2 mg dose of haloperidol by 42% in 24 healthy subjects. This resulted in a 70% increase in th haloperidol area under the concentration-time curve (AUC). The haloperidol maximum concentratio (Cmax) was increased by 88% when venlafaxine was coadministered, but the elimination half-life of haloperidol was not affected. The mechanism behind this interaction is not known (Prod Info Effexor XR, 2003).
b) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc

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 dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre 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, 2003o).

3.5.1.CY 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 du to hyperprolactinemia and in relieving symptoms related to premenstrual tension syndrome (Milewicz et a 1993a; Lauritzen et al, 1997a). Vitex reduced prolactin secretion in humans (Milewicz et al, 1993a). In vit 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 2 to 22.5 nanogram (ng)/mL; p equal to 0.23), normalized shortened luteal phases (from 5.5 days to 1 days; p less than 0.005), and eliminated deficits in luteal progesterone synthesis (from 2.46 ng/mL t 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 cast (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 a 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 sk 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. Ba prolactin release was significantly inhibited by 0.5 milligram (mg) and 1 mg of vitex extract/mL cultur 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 tha 0.05). Dopaminergic action was demonstrated in the rat corpus striatum membrane dopamine recep 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 pituitar hormone secretion. The effect was not due to a cytotoxic effect as demonstrated by the lack of effec 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.CZ Ziprasidone

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003e; Prod Info Haldol(R), 2001c). Coadministration of ziprasidone with drugs that potentially prolong th QTc interval, such as haloperidol, is contraindicated (Prod Info Geodon(R), 2002a).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone with agents that prolong the QT interval, such as haloperidol, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) 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 episode but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger &

Friedman, 1993d; Wilt et al, 1993b). Torsades de pointes developed in 8 of 223 critically ill patients i 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

b) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc 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 dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre 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, 2003d).

c) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 millisecond (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more wit ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002).

3.5.1.DA Zolmitriptan

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

2) Summary: Zolmitriptan has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Zomig(R), 2001). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998h), quetiapine (Owens, 2001y), risperidone (Prod Info Risperdal(R) risperidone, 2000c), amisulpride (Prod In Solian(R), 1999y), sertindole (Agelink et al, 2001w); sultopride (Lande et al, 1992y), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses. Even though no formal drug interaction studies have been done, the coadministration of drugs known to prolong the QT interval is not recommended.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive effect on QT interval

3.5.1.DB Zotepine

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

2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Bal 2003t; Prod Info Haldol(R), 2001k). Zotepine may cause QT prolongation (Sweetman, 2003). Caution is advised with coadministration of drugs that potentially prolong the QTc interval.

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if haloperidol and zotepine are used concomitantly. Screen patients for conditions that may predispose to QT prolongation and torsade de pointes (i.e. cardiomyopathy, alcohol abuse, hypothyroidism). Monitor the ECG and electrolytes at baseline and throughout therapy.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Numerous case reports have described significant QTc prolongation and torsades de pointes (Tc 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 dos as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, scre 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, 2003s).

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 episode but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger & Friedman, 1993j; Wilt et al, 1993h). 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)** Since zotepine can prolong the QT interval it is recommended that an ECG is performed before starting treatment. Patients with pre-existing prolongation of the QT interval should not be given zotepine (Sweetman, 2003).

3.5.5 Intravenous Admixtures

Drugs

Solutions

3.5.5.1 Drugs

Haloperidol

Haloperidol Lactate

3.5.5.1.A Haloperidol

Amitriptyline

Amsacrine

Benztropine

Biperiden

Buprenorphine

Chlorpromazine

Cimetidine

Diacetylmorphine

Diazepam

Dobutamine

Dopamine

Famotidine

Filgrastim

Fluconazole

Fludarabine

Fluphenazine

Foscarnet

Heparin Sodium

Imipramine

Lidocaine

Lorazepam

Mesoridazine

Nitroglycerin

Nitroprusside

Norepinephrine

Ondansetron

Paclitaxel

Phenylephrine

Prochlorperazine

Sargramostim

Tacrolimus

Theophylline

Trifluoperazine

3.5.5.1.A.1 Amitriptyline

a) Compatible

1) Amitriptyline in a 1:1 or 3:1 mixture with haloperidol, visually compatible with no decreas in haloperidol concentration in 4 hours at room temperature; drug concentrations not specif (Pers Comm, 1990)

3.5.5.1.A.2 Amsacrine

a) Compatible

1) Amsacrine 1 mg/mL with haloperidol 0.2 mg/mL visually compatible in Dextrose 5% in water for a 4-hour study period at room temperature under fluorescent lighting (Trissel et a 1990)

3.5.5.1.A.3 Benztropine

a) Incompatible

1) Benztropine in a 1:1 or 2:1 mixture with haloperidol, precipitate formation reported in 1 hour at room temperature and 53% haloperidol decomposition reported in 4 hours; drug concentrations not specified (Pers Comm, 1990)

3.5.5.1.A.4 Biperiden

a) Compatible

1) Biperiden in a 1:1 mixture with haloperidol, visually compatible with no decrease in haloperidol concentration in 4 hours at room temperature; drug concentrations not specifie (Pers Comm, 1990)

3.5.5.1.A.5 Buprenorphine

a) Compatible

1) Buprenorphine in a 1:1 volume ratio with haloperidol, physically and chemically compati for up to 7 hours at room temperature (Pers Comm, 1990)

3.5.5.1.A.6 Chlorpromazine

a) Conflicting Data

1) Incompatible

a) Chlorpromazine in a 2:1 mixture with haloperidol, visually compatible for 4 hours at room temperature, but 44% decrease in haloperidol concentration reported (Pers Com 1990); however, chlorpromazine in a 1:1 mixture with haloperidol, visually compatible with no decrease in haloperidol concentration in 4 hours at room temperature; drug concentrations not specified (Pers Comm, 1990)

2) Compatible

a) Chlorpromazine in a 1:1 mixture with haloperidol, visually compatible with no decrease in haloperidol concentration in 4 hours at room temperature; drug concentrations not specified (Pers Comm, 1990)

b) Chlorpromazine in a 2:1 mixture with haloperidol, visually compatible for 4 hours at room temperature, but 44% decrease in haloperidol concentration reported (Pers Com 1990)

3.5.5.1.A.7 Cimetidine

a) Compatible

1) Cimetidine 6 mg/mL with haloperidol 5 or 0.5 mg/mL visually compatible in Dextrose 5% water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991b)

3.5.5.1.A.8 Diacetylmorphine

a) Conflicting Data

1) Incompatible

a) Diacetylmorphine in high concentration incompatible with haloperidol; drug concentrations and conditions not specified (Allwood, 1991)

2) Compatible

a) Diacetylmorphine (up to 1 g with haloperidol 7.5 mg compatible in a 10-mL syringe; conditions not specified) (Allwood, 1991a)

3.5.5.1.A.9 Diazepam

a) Incompatible

1) Diazepam in a 1:1 or 2:1 mixture with haloperidol, precipitate formation reported within 2 hours at room temperature; drug concentrations not specified (Pers Comm, 1990)

3.5.5.1.A.10 Dobutamine

a) Compatible

1) Dobutamine 4 mg/mL with haloperidol 5 or 0.5 mg/mL visually compatible in Dextrose 5 in water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991e)

3.5.5.1.A.11 Dopamine

a) Compatible

1) Dopamine 1.6 mg/mL with haloperidol 5 or 0.5 mg/mL visually compatible in Dextrose 5 in water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991a)

3.5.5.1.A.12 Famotidine

a) Compatible

1) Famotidine 0.267 mg/mL with haloperidol 5 or 0.5 mg/mL visually compatible in Dextros 5% in water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991g)

3.5.5.1.A.13 Filgrastim

a) Compatible

1) Filgrastim 30 mcg/mL in Dextrose 5% in water with haloperidol 0.2 mg/mL in Dextrose 5 in water, compatible for up to 4 hours at 22 degrees C (Trissel & Martinez, 1994)

3.5.5.1.A.14 Fluconazole

a) Incompatible

1) Fluconazole 2 milligrams/milliliter (mg/mL) with haloperidol 5 mg/mL, visually incompatil delayed precipitation reported (Lor et al, 1991)

3.5.5.1.A.15 Fludarabine

a) Compatible

1) Fludarabine 1 mg/mL with haloperidol 0.2 mg/mL, both in Dextrose 5% in water, visually compatible for a 4-hour study period at room temperature under fluorescent light (Trissel et 1991a)

3.5.5.1.A.16 Fluphenazine

a) Incompatible

1) Fluphenazine in a 1:1 mixture with haloperidol, immediate precipitate formation reported with 65% haloperidol decomposition in 4 hours at room temperature; drug concentrations n specified (Pers Comm, 1990)

3.5.5.1.A.17 Foscarnet

a) Incompatible

1) Foscarnet 24 mg/mL with haloperidol 5 mg/mL, delayed formation of a fine white precipitated reported (Lor & Takagi, 1990)

3.5.5.1.A.18 Heparin Sodium

a) Incompatible

1) Heparin sodium 100 or 200 U/mL in a Dextrose 5% in water or Sodium chloride 0.9% infusion running at 1000 U/hr, with haloperidol 5 mg/1 mL injected over 1 minute, formation a white precipitate reported immediately; the authors recommend that heparin infusions be stopped and the line flushed with Dextrose 5% in water or Sodium chloride 0.9% before an after the injection of haloperidol and that a similar flushing procedure be followed for administration of haloperidol through a heparin lock (Solomon & Nasinnyk, 1982)

2) Heparin sodium 50 U/mL in a Sodium chloride 0.9% infusion running at 1 mL/min with haloperidol 5 mg/1 mL given over 3 minutes, formation of white turbidity reported (Trissel, 1990)

3) Heparin sodium 2500 U/1 mL with haloperidol 5 mg/1 mL, turbidity or precipitate formati reported within 5 minutes in syringe (Trissel, 1990)

3.5.5.1.A.19 Imipramine

a) Conflicting Data

1) Incompatible

a) Haloperidol in a 1:1 or 1:2 mixture with imipramine, compatibility is questionable because the mixture exhibited no visual changes in 1 hour, was slightly cloudy and viscous in 2 hours, was clear and very viscous in 4 hours at room temperature, but no haloperidol decomposition was observed in a 4 hour study period; drug concentrations not specified (Pers Comm, 1990)

2) Compatible

a) Haloperidol in a 1:1 or 1:2 mixture with imipramine, compatibility is questionable because the mixture exhibited no visual changes in 1 hour, was slightly cloudy and viscous in 2 hours, was clear and very viscous in 4 hours at room temperature, but no haloperidol decomposition was observed in a 4 hour study period; drug concentrations not specified (Pers Comm, 1990)

3.5.5.1.A.20 Lidocaine

a) Compatible

1) Haloperidol 5 or 0.5 mg/mL with lidocaine 4 mg/mL visually compatible in Dextrose 5% water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991f)

3.5.5.1.A.21 Lorazepam

a) Compatible

1) Haloperidol 5 mg/1 mL with lorazepam 2 or 4 mg/1 mL, physically compatible for 4 hour in syringe; temperature not specified (Prod Info Ativan(R) Injection compatibility charts, 198

2) Haloperidol in a 1:1 mixture with lorazepam, physically compatible for 16 hours at room temperature; drug concentrations not specified (Pers Comm, 1990)

3.5.5.1.A.22 Mesoridazine

a) Incompatible

1) Haloperidol in a 1:1 mixture with mesoridazine, immediate precipitate formation reported drug concentrations not specified (Pers Comm, 1990)

3.5.5.1.A.23 Nitroglycerin

a) Compatible

1) Haloperidol 5 or 0.5 mg/mL with nitroglycerin 0.4 mg/mL visually compatible in Dextrose 5% in water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991h)

3.5.5.1.A.24 Nitroprusside

a) Conflicting Data

1) Incompatible

a) Haloperidol 5 mg/mL with nitroprusside 0.2 mg/mL, immediate formation of cloudy solution reported in Dextrose 5% in water; however, nitroprusside 0.2 mg/mL has beer

reported to be compatible with haloperidol 0.5 mg/mL in Dextrose 5% (Outman & Monolakis, 1991i)

2) Compatible

a) Haloperidol 0.5 mg/mL with nitroprusside 0.2 mg/mL visually compatible in Dextros 5% in water for 24 hours at 21 degrees C under fluorescent light; however, nitroprussi 0.2 mg/mL has been reported to be incompatible with haloperidol 5 mg/mL in Dextrose 5% (Outman & Monolakis, 1991)

3.5.5.1.A.25 Norepinephrine

a) Compatible

1) Haloperidol 5 or 0.5 mg/mL with norepinephrine 0.032 mg/mL visually compatible in Dextrose 5% in water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991j)

3.5.5.1.A.26 Ondansetron

a) Compatible

1) Haloperidol 0.2 mg/mL in Dextrose 5% in water with ondansetron 1 mg/mL in Sodium chloride 0.9% was physically compatible for 4 hours at 22 degrees C under ambient lightin (Trissel et al, 1991b; Prod Info Zofran(R), 1999)

3.5.5.1.A.27 Paclitaxel

a) Compatible

1) Haloperidol 0.2 mg/mL in Dextrose 5% injection with paclitaxel 1.2 mg/mL in Dextrose 5 injection in glass container, no visual or turbidimetric evidence of incompatibility in simulate Y-site injection for a 4-hour study period, admixture stored at room temperature under fluorescent light (Trissel & Bready, 1992). However, this admixture was not tested for chemical stability.

3.5.5.1.A.28 Phenylephrine

a) Compatible

1) Haloperidol 5 or 0.5 mg/mL with phenylephrine 0.02 mg/mL visually compatible in Dextrose 5% in water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991d)

3.5.5.1.A.29 Prochlorperazine

a) Incompatible

1) Haloperidol in a 1:1 or 1:2 mixture with prochlorperazine, immediate formation of cloudy solution reported with precipitate formation reported in 1 to 2 hours at room temperature; d concentrations not specified (Pers Comm, 1990)

3.5.5.1.A.30 Sargramostim

a) Incompatible

1) Haloperidol lactate 0.2 mg/mL with sargramostim 10 mcg/mL, both in sodium chloride 0.9%, formation of small particles reported in 1 of 2 samples within 4 hours at 22 degrees C under fluorescent light (Trissel et al, 1992)

3.5.5.1.A.31 Tacrolimus

a) Compatible

1) Haloperidol 2.5 mg/mL in 5% Dextrose injection with tacrolimus 1 mg/mL in 0.9% Sodiu chloride injection, visually compatible for 24 hours at room temperature under fluorescent li (Min et al, 1992)

3.5.5.1.A.32 Theophylline

a) Compatible

1) Haloperidol 5 or 0.5 mg/mL with theophylline, premixed 1.6 mg/mL visually compatible i Dextrose 5% in water for 24 hours at 21 degrees C under fluorescent light (Outman & Monolakis, 1991c)

3.5.5.1.A.33 Trifluoperazine

a) Incompatible

1) Haloperidol in a 1:1 mixture with trifluoperazine, immediate formation of a cloudy solutio reported; drug concentrations not specified (Pers Comm, 1990)

3.5.5.1.B Haloperidol Lactate

Allopurinol Sodium

Amifostine

Aztreonam

Cyclizine Lactate

Fenoldopam Mesylate

Gallium Nitrate

Granisetron Hydrochloride

Piperacillin Sodium/Tazobactam

Propofol

Vinorelbine

3.5.5.1.B.1 Allopurinol Sodium

a) Incompatible

1) Haloperidol lactate is physically incompatible in solution with allopurinol sodium for injection; conditions not specified; do not mix with or administer through the same intravenc port (Prod Info Aloprim(TM), 1999).

2) Allopurinol sodium 3 mg/mL in Sodium chloride 0.9% injection with haloperidol lactate 0 mg/mL in Sodium chloride 0.9% injection, heavy turbidity formed immediately and develope into crystalline particles within 1 hour (Trissel & Martinez, 1994a)

3.5.5.1.B.2 Amifostine

a) Compatible

1) Amifostine 10 mg/mL in Dextrose 5% in water with haloperidol lactate 0.2 mg/mL in 5% Dextrose injection, compatible during simulated Y-site administration (Trissel & Martinez, 1995a)

3.5.5.1.B.3 Aztreonam

a) Compatible

1) Aztreonam 40 mg/mL in 5% Dextrose in water with haloperidol lactate 0.2 mg/mL in Dextrose 5% in water, compatible for up to 4 hours at 23 degrees C (Trissel & Martinez, 1995)

3.5.5.1.B.4 Cyclizine Lactate

a) Incompatible

1) Cyclizine lactate 50 mg/mL (3 mL) with haloperidol lactate 5 mg/mL (0.3 mL) in 0.9% Sodium chloride injection (17 mL), crystals were seen within 24 hours when mixed in syring driver; however, no crystals were noted when water for injection or Dextrose 5% injection were used and stored at 25 degrees C for 24 hours (Fawcett et al, 1994).

3.5.5.1.B.5 Fenoldopam Mesylate

a) Compatible

1) Fenoldopam mesylate 80 mcg/mL in Sodium chloride 0.9% injection with haloperidol lactate 0.2 mg/mL in Sodium chloride 0.9% injection, visually and physically compatible for to 4 hours at 23 degrees C in a clear glass tube under constant fluorescent light during simulated Y- site administration (Trissel et al, 2003).

3.5.5.1.B.6 Gallium Nitrate

a) Incompatible

1) Gallium nitrate (Ganite(R)) 1 mg/mL in Sodium chloride 0.9% admixed from a plastic syringe in a 1:1 ratio simulating Y-site administration with haloperidol lactate (undiluted) 5 mg/mL, immediate white haze that adhered to test tube after centrifugation, leaving a clear liquid at 15 minutes which remained clear for 24-hour study period, stored at room temperature under fluorescent light in a glass container; chemical stability not tested (Lobe Dollard, 1993)

3.5.5.1.B.7 Granisetron Hydrochloride

a) Compatible

1) Granisetron hydrochloride diluted with 5% dextrose injection to a concentration of 50 mcg/mL is compatible with haloperidol lactate at a concentration of 0.2 mg/mL (D5W) durin simulated Y-site injection. Compatibility was measured using visual examinations in fluorescent light and in high-intensity monodirectional light. Turbidity, particle size and parti counts were completed for certain solutions. The mixtures were assessed at 1 and 4 hours (Trissel, 1997).

3.5.5.1.B.8 Piperacillin Sodium/Tazobactam

a) Incompatible

1) Piperacillin sodium 40 mg/mL plus tazobactam 5 mg/mL in Dextrose 5% in water with haloperidol lactate 0.2 mg/mL in Dextrose 5% in water, white turbidity and numerous white particles formed immediately (Trissel & Martinez, 1994b)

3.5.5.1.B.9 Propofol

a) Compatible

1) Propofol 1% injectable emulsion and haloperidol lactate 0.2 milligrams/milliliter in a 1:1 volume mixture (simulated Y-site administration) are visually compatible in polycarbonate t tubes at 15 minutes and 1 hour at approximately 23 degrees Celsius as determined by visualization with fluorescent light and a high-intensity, mono-directional light source (Tynd beam) (Trissel et al, 1997).

3.5.5.1.B.10 Vinorelbine

a) Compatible

1) Haloperidol lactate 0.2 mg/mL in Sodium chloride 0.9% with vinorelbine 1 mg/mL in Sodium chloride 0.9%, compatible for up to 4 hours at 22 degrees C (Trissel & Martinez, 1994c)

3.5.5.2 Solutions

Haloperidol

Haloperidol Lactate

3.5.5.2.A Haloperidol

Dextrose 5% in water

Total Parenteral Nutrition

3.5.5.2.A.1 Dextrose 5% in water

a) Compatible

1) Dextrose 5% in water with haloperidol 100 mg/L stable for 38 days at 24 degrees C in a amber glass bottle or a plastic container (Das Gupta & Stewart, 1982)

3.5.5.2.A.2 Total Parenteral Nutrition

a) Compatible

1) Haloperidol 0.2 mg/mL in Dextrose 5% in water added to total parenteral nutrition soluti compatible in simulated Y-site administration for 4 hours at 23 degrees C; specific composition of total parenteral nutrition solution listed below (Trissel et al, 1997a):

Amino acids 10% (Aminosyn(R) II)	3.5%
Dextrose	5%
Sterile water for injection	516.8 mL
Potassium phosphates	3.5 mM
Sodium chloride	25 mEq
Potassium chloride	35 mEq
Magnesium sulfate	8 mEq
Multivitamins	10 mL
Trace elements	1 mL
Calcium gluconate	9.3 mEq

2) Haloperidol 0.2 mg/mL in Dextrose 5% in water added to total parenteral nutrition soluti compatible in simulated Y-site administration for 4 hours at 23 degrees C; specific composition of total parenteral nutrition solution listed below (Trissel et al, 1997a):

Amino acids 10% (FreAmine(R) III)	3.5%
Dextrose	5%
Sterile water for injection	516.75 mL
Sodium chloride	37.5 mEq
Potassium chloride	40 mEq
Magnesium sulfate	8 mEq
Multivitamins	10 mL
Trace elements	1 mL
Calcium gluconate	5 mEq

3) Haloperidol 0.2 mg/mL in Dextrose 5% in water added to total parenteral nutrition soluti compatible in simulated Y-site administration for 4 hours at 23 degrees C; specific composition of total parenteral nutrition solution listed below (Trissel et al, 1997a):

Amino acids 10% (Aminosyn(R) II)	4.25%
Dextrose	25%
Sterile water for injection	161 mL
Potassium phosphates	15 mM
Sodium chloride	25 mEq
Potassium chloride	18 mEq
Magnesium sulfate	8 mEq
Multivitamins	10 mL
Trace elements	1 mL
Calcium gluconate	9.15 mEq

4) Haloperidol 0.2 mg/mL in Dextrose 5% in water added to total parenteral nutrition soluti compatible in simulated Y-site administration for 4 hours at 23 degrees C; specific composition of total parenteral nutrition solution listed below (Trissel et al, 1997a):

Amino acids 10% (FreAmine(R) III)	4.25%
Dextrose	25%
Sterile water for injection	158.6 mL
Potassium phosphates	5.75 mM
Sodium chloride	40 mEq
Potassium chloride	25 mEq
Magnesium sulfate	8 mEq
Multivitamins	10 mL
Trace elements	1 mL
Calcium gluconate	7.5 mEq

3.5.5.2.B Haloperidol Lactate

Dextrose 5% and Sodium chloride 0.225%

Dextrose 5% in water

lactated Ringer's injection

Lactated Ringer's injection

Sodium chloride 0.45%

Sodium chloride 0.9%

3.5.5.2.B.1 Dextrose 5% and Sodium chloride 0.225%

a) Conflicting Data

1) Incompatible

a) Haloperidol 3 mg/mL (as the lactate salt) in 10 mL of Dextrose 5% and Sodium chloride 0.225%, precipitated by 0.5 hour (Fraser & Riker, 1994a)
b) Haloperidol 2 mg/mL (as the lactate salt) in 10 mL of Dextrose 5% and Sodium chloride 0.225%, precipitated by 1 hour (Fraser & Riker, 1994a)

2) Compatible
a) Haloperidol 0.1, 0.5, 0.75, 1 mg/mL (as the lactate salt) in 10 mL of Dextrose 5% a Sodium chloride 0.225%, visually compatible for up to 7 days at 21 degrees C (Fraser Riker, 1994)

3.5.5.2.B.2 Dextrose 5% in water

a) Compatible
1) Haloperidol 0.1, 0.5, 0.75, 1, 2, 3 mg/mL (as the lactate salt) in 10 mL of Dextrose 5% i water, visually compatible for up to 7 days at 21 degrees C (Fraser & Riker, 1994)

3.5.5.2.B.3 lactated Ringer's injection

a) Incompatible
1) Haloperidol 3 mg/mL (as the lactate salt) in 10 mL of lactated Ringer's injection, precipitated immediately (Fraser & Riker, 1994c)
2) Haloperidol 2 mg/mL (as the lactate salt) in 10 mL of lactated Ringer's injection, precipitated by 0.25 hour (Fraser & Riker, 1994c)

3.5.5.2.B.4 Lactated Ringer's injection

a) Compatible
1) Haloperidol 0.1, 0.5, 0.75, 1 mg/mL (as the lactate salt) of 10 mL of lactated Ringer's injection, visually compatible for up to 7 days at 21 degrees C (Fraser & Riker, 1994b).

3.5.5.2.B.5 Sodium chloride 0.45%

a) Conflicting Data
1) Incompatible
a) Haloperidol 3 mg/mL (as the lactate salt) in 10 mL Sodium chloride 0.45%, precipitated immediately, and haloperidol 2 mg/mL, precipitated by 0.25 hour (Fraser & Riker, 1994e)
2) Compatible
a) Haloperidol 0.1, 0.5, 0.75, 1 mg/mL (as the lactate salt) in 10 mL of Sodium chlorid 0.45%, visually compatible for up to 7 days at 21 degrees C (Fraser & Riker, 1994d)

3.5.5.2.B.6 Sodium chloride 0.9%

a) Conflicting Data
1) Incompatible
a) Haloperidol 1,2,3 mg/mL (as the lactate salt) in 10mL of Sodium chloride 0.9% precipitated immediately, and the precipitate became more dense over time (Fraser & Riker, 1994e)
b) Haloperidol 10,20, or 30 mg/mL with sodium chloride 0.9%, slight precipitate formation reported with the precipitate increasing with time in the larger concentrations however, sodium chloride 0.9% has been reported to be compatible with haloperidol 1 5 mg/mL (Outman & Monolakis, 1991l).
2) Compatible
a) Haloperidol 0.1, 0.5, 0.75 mg/mL (as the lactate salt) in 10 mL of Sodium chloride 0.9%, visually compatible for up to 7 days at 21 degrees C (Fraser & Riker, 1994d)
b) Haloperidol 1 or 5 mg/10mL with sodium chloride 0.9%, visually compatible for an hour study period at 21 degrees C under fluorescent light; however, sodium chloride 0.9% has been reported to be incompatible with haloperidol 10, 20 or 30 mg/10 mL (Outman & Monolakis, 1991k)

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) Haloperidol

1) Therapeutic

a) Physical Findings

1) Decrease in severity or elimination of target psychotic symptoms:

a) Positive psychotic symptoms (delusions, auditory hallucinations, racing thoughts)

b) Negative psychotic symptoms (anhedonia, apathy, amotivation, ambivalence).

2) Improvement in socialization, grooming, and attention to activities of daily living.

2) Toxic

a) Laboratory Parameters

1) Complete blood counts (every 6 months)

2) Electrocardiogram at baseline and periodically while on therapy, especially if administered intravenously (US Food and Drug Administration, 2007; Pacher & Kecskemeti, 2004).

a) Torsades de Pointes and QT prolongation, including sudden death, have been reported especially when haloperidol is administered intravenously or at doses higher than recommende (US Food and Drug Administration, 2007; Pacher & Kecskemeti, 2004)

3) Hepatic function tests (every 6 months)

b) Physical Findings

1) Abnormal involuntary movement scale (AIMS) examination or similar test for tardive dyskinesia every 6 months.

2) Assessment for extrapyramidal symptoms (EPS) during dose adjustment and every 3 months.

B) Haloperidol Lactate

1) Therapeutic

a) Physical Findings

1) Control of agitation is indicative of clinical response.

2) Toxic

a) Physical Findings

1) Allergic reactions should be monitored, especially in patients with known allergies, or a history of drug-induced allergic reactions.

2) Bronchopneumonia with symptoms including lethargy, decreased thirst, and reduced pulmonary ventilation should be monitored, especially in the elderly.

3) Electrocardiogram at baseline and periodically while on therapy to monitor for arrhythmias (including Torsades de Pointes) and QT prolongation, especially when haloperidol is administered intravenously (route not approved) or at doses higher than recommended (Prod Info HALDOL(R) immediate release IM injection, 2008; US Food and Drug Administration, 2007; Pacher & Kecskeme 2004).

4) Hypotension and/or anginal pain should be monitored in patients with comorbid cardiovascular disorders.

5) Involuntary dyskinetic movements (including tardive dyskinesia), which are potentially irreversible should be monitored, especially in elderly women or patients receiving longer durations of treatment

6) Neuroleptic malignant syndrome (NMS) should be monitored and includes symptoms of hyperpyrexia, muscle rigidity, altered mental status, irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias. If confirmed, haloperidol therapy may need to be discontinue and medical management instituted. Following recovery from NMS, if therapy is to be reinstituted, careful monitoring is recommended to prevent recurrences (Prod Info HALDOL(R) immediate releas IM injection, 2008).

7) Seizure monitoring is recommended especially in patients with a history of seizures or EEG abnormalities.

4.2 Patient Instructions

A) Haloperidol (By mouth)

Haloperidol

Treats symptoms of mental and emotional disorders. Helps patients with Tourette's syndrome and children w severe behavior problems, including hyperactivity.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to haloperidol, or if you have Parkinson disease. This medicine should not be given to patients with severe brain disease.

How to Use This Medicine:
Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it

more often than your doctor tells you to.

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

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

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamii and herbal products.
You must be careful if you are also using other medicine that might cause similar side effects as haloperidol. This includes medicine that might cause low blood pressure, overheating, or liver problems.
Make sure your doctor knows about all other medicines you are using.
Tell you doctor if you are also using lithium, phenindione, medicine for seizures, or medicine to treat Parkinson's disease.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold a allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have liver disease, kidney disease, heart or blood vessel disease, blood pressure problems, overactive thyroid, or history of seizure or breast cancer.
Tell your doctor about any other medicine you have used to treat a mental disorder, especially if the medicine caused problems.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.
You might get overheated more easily while using this medicine. Be aware of this if you are exercising o the weather is hot. Drinking water might help. If you get too hot and feel dizzy, weak, tired, confused, or sick to your stomach, you need to cool down.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or thro chest tightness, trouble breathing.
Change in how much or how often you urinate.
Changes in vision.
Fast or pounding heartbeat.
Fever or chills.
Jerky muscle movement you cannot control (often in your face, tongue, or jaw).
Headache, confusion, lightheadedness, or fainting.
Painful, prolonged erection of your penis.
Problems with balance or walking.
Seeing or hearing things which are not there.
Seizures or tremors.
Severe muscle stiffness.
Troubled breathing.
Unusual bleeding, bruising, or weakness.
Yellowing of skin and eyes.

If you notice these less serious side effects, talk with your doctor:
Breast pain or swelling.
Change in menstrual periods.
Decreased thirst or dry mouth.
Loss of appetite.
Nausea, vomiting, diarrhea, or constipation.
Skin rash.

Trouble sleeping, restlessness.

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

B) Haloperidol (Injection)

Haloperidol

Treats mental illness (such as schizophrenia), behavior problems, agitation, and symptoms of Tourette's syndrome.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to haloperidol, or if you have Parkinson disease. This medicine should not be given to patients with severe brain disease.

How to Use This Medicine:
Injectable

Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is giv as a shot into one of your muscles.
A nurse or other trained health professional will give you this medicine.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitami and herbal products.

Make sure your doctor knows if you are also using lithium (Eskalith®, Lithane®, Lithobid®), rifampin (Rimactane®, Rifadin®), a blood thinner (such as phenindione), or medicine for Parkinson's disease (su as carbidopa, levodopa, Sinemet®).
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold a allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have liver disease, kidney disease, lung disease, glaucoma, an overactive thyroid, or a history of seizures or neuroleptic malignant syndrome (NMS). Your doctor needs to know if you have any kind of heart or blood vessel problems, including blood pressure problems, heart rhythm problems, or mineral imbalance.
Older adults may be more sensitive to the side effects of this medicine, including heart failure or pneumonia. This medicine is not used to treat behavioral problems in older adults with dementia.
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine. Check with your doctor right away if you or your child have any of the following symptoms whil taking this medicine: lip smacking or puckering, puffing of the cheeks, rapid or worm-like movements of t tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.
This medicine may make you more sensitive to sunlight and heat. Avoid sunlamps, hot tubs, tanning bec and saunas. Take care not to get overheated during exercise or outdoor activity. Use a sunscreen when outdoors.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else tha could be dangerous if you are not alert. You may also feel lightheaded when getting up suddenly from a lying or sitting position, so stand up slowly.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or thro chest tightness, trouble breathing.
Change in how much or how often you urinate.
Chills, cough, sore throat, and body aches.
Fast, slow, or irregular heartbeat.
Feeling very thirsty or hungry.
Fever, sweating, confusion, uneven heartbeat, or muscle stiffness.
Jerky muscle movement you cannot control (often in your face, tongue, or jaw).
Lightheadedness or fainting.
Painful, prolonged erection of your penis.
Problems with vision, speech, or walking.
Seeing or hearing things which are not there.
Seizures or tremors.
Trouble breathing or swallowing.
Twitching or muscle movements you cannot control.

Unexplained fever or muscle stiffness.
Unusual facial expressions.
Unusual bleeding, bruising, or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Breast pain or swelling.
Drowsiness, depression, or headache.
Dry mouth.
Hair loss.
Irregular menstrual periods.
Loss of appetite.
Nausea, vomiting, constipation, or stomach upset.
Skin rash.
Trouble having sex.
Trouble sleeping, restlessness.

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

C) Haloperidol Decanoate (Injection)

Haloperidol Decanoate

Treats mental disorders such as schizophrenia.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to haloperidol decanoate, or if you have Parkinson's disease. This medicine should not be given to patients with severe brain disease.

How to Use This Medicine:
Injectable
Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is giv as a shot into one of your muscles.
A nurse or other trained health professional will give you this medicine.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamii and herbal products.
Make sure your doctor knows if you are also using lithium (Eskalith®, Lithane®, Lithobid®), rifampin (Rimactane®, Rifadin®), a blood thinner (such as phenindione), or medicine for Parkinson's disease (suc as carbidopa, levodopa, Sinemet®).
Do not drink alcohol while you are using this medicine.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold a allergy medicine, narcotic pain relievers, and sedatives.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have liver disease, kidney disease, lung disease, glaucoma, an overactive thyroid, or a history of seizures or neuroleptic malignant syndrome (NMS). Your doctor needs to know if you have any kind of heart or blood vessel problems, including blood pressure problems, heart rhythm problems, or mineral imbalance.
Older adults may be more sensitive to the side effects of this medicine, including heart failure or pneumonia. This medicine is not used to treat behavioral problems in older adults with dementia.
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine. Check with your doctor right away if you or your child have any of the following symptoms whil taking this medicine: lip smacking or puckering, puffing of the cheeks, rapid or worm-like movements of t tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and legs.
This medicine may make you more sensitive to sunlight and heat. Avoid sunlamps, hot tubs, tanning bec and saunas. Take care not to get overheated during exercise or outdoor activity. Use a sunscreen when outdoors.
This medicine may make you drowsy or dizzy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert. You may also feel lightheaded when getting up suddenly from a lying or sitting position, so stand up slowly.
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your dose before stopping it completely.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or thro

chest tightness, trouble breathing.
Blood in your urine.
Chills, sore throat, and body aches.
Decreased thirst.
Fast or uneven heartbeat.
Feeling very thirsty or hungry.
Fever, sweating, confusion, or muscle stiffness.
Lightheadedness or fainting.
Problems with vision, speech, balance, or walking.
Seeing or hearing things which are not there.
Seizures (convulsions).
Tremors or movements that you cannot control in the tongue, face, neck, jaw, or eyes
Trouble breathing or swallowing.
Unusual bleeding, bruising, or weakness.
Unusual facial expressions.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Anxiety, drowsiness, or depression.
Decrease in how much or how often you urinate.
Dry mouth, cough, or headache.
Hair loss.
Loss of appetite.
Nausea, vomiting, diarrhea, or stomach upset.
Pain in the breast, irregular menstrual periods.
Skin rash, sunburn, or pain at the injection site.
Trouble having sex, or increased development of breasts (in men).
Trouble sleeping, restlessness.

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

4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs and typical antipsychotic drugs (including haloperidol) had a simi dose-dependent risk of sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The study included patients age 30 to 74 years (mean 45.7 +/ 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had 1 outpatier visit in each of the 2 preceding years. Sudden cardiac death was defined as occurring in the community and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or cause not related to ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescripti was filled and the end of the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine, and doses comparable to chlorpromazine 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic drugs in 79,5 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The risk of sudden cardiac death in current haloperidol users in 21,728 person-years was 1.61 (95% CI, 1.16 to 2.24, p=0.005). The risk of sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug groups. In typical antipsychotic use, the incidence rate ratio increased from 1.31 (95% 0.97 to 1.77) in low-dose use to 2.42 (95% CI, 1.91 to 3.06) in high-dose use. To limit the effects of confounding c the study results, there was a secondary analysis performed in a cohort of patients matched by propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In an editorial in The New England Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence of benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients) there should be an age-dependent justification required prior to administration. It has also been suggested (althou not formally tested) that ECGs be performed before and shortly after initiation of antipsychotic therapy to screen fo existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).

B) Haloperidol is a butyrophenone-derivative antipsychotic agent with a very low incidence of sedative, anticholinergic, and cardiovascular adverse effects; however, it may produce a very high incidence of extrapyrami symptoms. The drug is useful in treating a variety of psychiatric disorders including schizophrenia and Tourette's syndrome. Haloperidol decanoate is a long-acting depot dosage form, which may be administered in up to 4-week intervals, which is a potential advantage in noncompliant patients.

C) Clinical evidence demonstrates that all the commonly marketed neuroleptic agents have therapeutic equivaler when adequate doses are utilized (Appleton et al, 1980). When a flexible dosage regimen is used to titrate the chosen agent to maximum effect, all neuroleptics will demonstrate statistical equivalence in a study population. However, one agent may be effective while another will not in any given individual patient. Pharmacokinetic and pharmacodynamic differences as well as possible multiple etiologies of the patient's schizophrenia may be reasor for the individual inequivalence (Young & Koda-Kimble, 1988). The patient's past medication history of neuroleptic agents should play an important role in drug selection. The patient's subjective response to neuroleptics should al be used in deciding on a specific agent. A reduction in symptoms or a pleasurable response following the first

neuroleptic dose will improve patient compliance better than if the patient has a bad experience after the first dose (May, 1978). The last factor in deciding which neuroleptic agent to use is its adverse effect profile. Almost all neuroleptic agents possess similar adverse effects; however, the overall incidence of a particular category of adverse effects varies between the agents.

D) The US Food and Drug Administration (FDA) issued an alert concerning reports of Torsades de Pointes and C prolongation, some with fatal outcomes associated with the use of haloperidol, haloperidol decanoate, and haloperidol lactate, especially when administered intravenously (not an approved route of administration) or in higher doses than recommended. At least 28 published case reports exist, and case-control studies have demonstrated a dose-response relationship between intravenous haloperidol use and the development of Torsad de Pointes. Two post-marketing analyses of the association of QT prolongation or Torsades de Pointes with oral c injectable haloperidol revealed 242 cases, with at least 8 fatalities involving intravenous administration. Risk facto for the development of QT prolongation or Torsades de Pointes include concomitant QT-prolonging conditions, su as electrolyte imbalance; underlying cardiac abnormalities; hypothyroidism; familial long QT syndromes; or concomitant use of drugs known to prolong the QT interval. However, some cases have occurred in patients with predisposing factors. The true incidence of QT prolongation or Torsades de Pointes cannot be determined at this time (US Food and Drug Administration, 2007).

E) Based upon a critical review of the literature, it is suggested that haloperidol decanoate provides no advantage and safety and is more expensive (Hemstrom et al, 1988). It is recommended that haloperidol decanoate be reserved for schizophrenic patients who have responded to oral haloperidol and who may significantly benefit fror long-acting preparation. Haloperidol and haloperidol decanoate are effective agents in the treatment of certain psychiatric disorders and should be included on hospital formularies where these types of patients are routinely treated.

See Drug Consult reference: CHEMOTHERAPY AND RADIOTHERAPY TREATMENT GUIDELINES FOR NAUS AND VOMITING

See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHRENIA

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Haloperidol is pharmacologically related to the piperazine phenothiazines (Ayd, 1978). Similar to other neuroleptics, haloperidol centrally blocks the action of dopamine by binding previously to DA-2 receptors, anc a lesser extent, DA-1 receptors. The potency of all antipsychotic drugs correlates well with their affinity for DA receptors (AMA Department of Drugs, 1983; Snyder, 1981).

2) Haloperidol is relatively non-sedating but is more likely to produce extrapyramidal symptoms as compared other antipsychotic agents; autonomic side effects are less than with other agents (AMA Department of Drugs 1983).

3) Haloperidol 2 mg is approximately equivalent to 100 mg chlorpromazine, 2 mg fluphenazine, 10 mg loxapi and 4 mg thiothixine in antipsychotic potency (AMA Department of Drugs, 1983). The drug is used primarily i schizophrenia and acute psychosis. Other indications are schizoaffective disorders, paranoid syndrome, and Tourette's syndrome (AMA Department of Drugs, 1983).

B) REVIEW ARTICLES

1) A pharmacokinetics update of haloperidol has been reviewed (Kudo & Ishizaki, 1999).

2) The pharmacokinetics and therapeutic use of IM haloperidol decanoate in the treatment of psychosis have been reviewed (Beresford & Ward, 1987a).

3) A comprehensive review of haloperidol pharmacokinetics has been published and included all factors whi have the potential of influencing the serum levels of haloperidol (Froemming et al, 1989a).

4) The use of haloperidol in the treatment of psychotic symptoms in the elderly has been reviewed, including pharmacokinetics, indications and principles for use, side effects, and advantages of haloperidol (Steinhart, 1983).

5) Practice guidelines for the treatment of schizophrenia have been developed by the American Psychiatric Association (Anon, 1997).

4.5 Therapeutic Uses

Haloperidol

Haloperidol Decanoate

Haloperidol Lactate

4.5.A Haloperidol

Agitation

Alcohol withdrawal syndrome

Anorexia nervosa

Behavioral syndrome - Dementia

Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

Delirium

Dementia

Flashbacks, LSD

Gilles de la Tourette's syndrome

Hiccoughs

Hiccoughs, Intractable

Hyperactive behavior, (Short-term treatment) after failure to respond to non-antipsychotic medication and psychotherapy

Migraine

Nausea and vomiting; Treatment and Prophylaxis

Obsessive-compulsive disorder; Adjunct

Ocular hypertension

Opioid withdrawal

Pain

Postoperative nausea and vomiting; Prophylaxis

Problematic behavior in children (Severe), With failure to respond non-antipsychotic medication or psychotherapy

Psychotic disorder

Rheumatoid arthritis

Schizophrenia

Severe major depression with psychotic features

Sneezing

4.5.A.1 Agitation

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effective treatment for agitated, critical care patients (Ziehm, 1991)
Controlled studies are needed to identify the most effective and safe method of haloperidol administration

c) Adult:

1) HALOPERIDOL given intramuscularly (IM), intravenously (IV), or orally has been reported effecti in the management of disruptive patients in the emergency room setting (Clinton et al, 1987). The average total doses of HALOPERIDOL administered were 8 mg, 6 mg, and 9 mg for the IM, IV, and oral routes, respectively.

d) Pediatric:

1) Haloperidol provided effective sedation for a 9-month-old girl during mechanical ventilation after bone marrow transplant. Sedation with fentanyl 18 micrograms/kilogram (mcg/kg) per hour and midazolam 1 milligram (mg) per hour was not adequate. By day 33 of mechanical ventilation, she wa receiving fentanyl 30 mcg/kg/hour, methadone 1.4 mg/kg intravenously (IV) every 6 hours, and lorazepam 1.1 mg/kg IV every 4 hours. Eleven doses of pancuronium over 24 hours were needed to minimize movement. Intravenous haloperidol 0.06 mg/kg was administered, followed 6 hours later b maintenance regimen of 0.015 mg/kg IV every 6 hours. Twelve hours after the loading dose, the patient was reported to be calm, with no thrashing. She required 2 additional doses of haloperidol during the next 8 hours in response to intermittent agitation, and, during the 24 hours after the loadi dose, a dose of pancuronium and 2 extra doses of fentanyl were administered. Two days after initiat of haloperidol, she needed no extra doses of fentanyl, lorazepam, or pancuronium. She was successfully extubated 3 days after starting haloperidol, after which haloperidol was discontinued ar the other sedatives tapered. Similar, successful treatments with haloperidol were reported for 4 othe pediatric cases (ages 11 months, 12 years, 14 years, and 16 years) (Harrison et al, 2002).

4.5.A.2 Alcohol withdrawal syndrome

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

b) Summary:
bolus doses of haloperidol and clonidine provided better patient outcome than continuous infusion doses

c) Adult:

1) Severity and duration of alcohol withdrawal syndrome (AWS) was significantly lower in patients receiving bolus rather than infusions of haloperidol and clonidine. In a prospective, randomized, stuc adult patients with AWS who had trauma or gastrointestinal surgery, a history of alcohol abuse (grea than 60 grams per day), and a clinical withdrawal assessment for alcohol score (CIWA-Ar) greater th 20 were randomized to the infusion-titrated group (ITG) or the bolus-titrated group (BTG). All patient received bolus doses of flunitrazepam (for agitation), haloperidol (for hallucinations), and clonidine (autonomic signs) to achieve a CIMA- Ar score less than 20. An infusion of flunitrazepam infusion (25 100 micrograms/kilogram/hour (mg/kg/hr)) was started to prevent convulsions. Patients were then randomized to the ITG (n=21) or the BTG (n=23), in which, haloperidol plus clonidine was administe as infusion or bolus doses to achieve a CIWA-Ar score of less than 10 and Ramsey Sedation Score (RSS) of 2 to 4. Doses were dependent on the initial need for the drug and ranged from 50 to 200 mcg/kg/hr or bolus doses less than 20 milligrams (mg), 20 to 40 mg, or greater than 40 mg for haloperidol and 150 to 300 mcg/kg/hr or bolus doses less than 150 mcg, 150 to 300 mcg, or greater than 300 mcg for clonidine. Propofol 50 to 400 mg was given as a rescue medication. The primary outcome, severity and duration of AWS, favored the BTG. CIWA-Ar scores increased following ITG from approximately 21 to 29, p less than or equal to 0.01, but not in the BTG where scores remained approximately 23 (p less than or equal to 0.01 compared to ITG). The duration of AWS was significantly longer for patients in the ITG (median interquartile range: 4 to 10 days) than patients in BTG (median interquartile range: 2 to 4 days), p less than or equal to 0.01. In addition, the days spe in the intensive care unit (ICU) were significantly longer for ITG patients (median interquartile range: to 25 days) than BTG patients (median interquartile range: 5 to 10 days), p less than or equal to 0.0 Pneumonia developed in 9 of 23 (39%) of BTG patients and 15 of 21 (71%) of ITG patients, p less th or equal to 0.01 (Spies et al, 2003).

4.5.A.3 Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

4.5.A.4 Behavioral syndrome - Dementia

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb

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

b) Summary:
May be efficacious for treating behavioral problems associated with Alzheimer's disease
Use may expose the patient to unnecessary adverse reactions

c) Adult:

1) HALOPERIDOL 1 to 5 milligrams orally each day was effective in improving psychotic and behavioral symptoms in patients with probable ALZHEIMER'S DISEASE during a single-blind pilot study (Devanand et al, 1989). However, severe adverse effects were observed during therapy, primarily extrapyramidal symptoms, and no patient could be maintained on the maximum dose of 5 milligrams daily. The average daily dose at the end of the 8-week haloperidol phase (preceded and followed by 4-week placebo phases) was 2.44 milligrams daily. Cognitive function deteriorated durin HALOPERIDOL therapy, with only partial recovery by the end of the subsequent 4-week placebo phase. This small study suggests that HALOPERIDOL is effective in treating psychosis and other behavioral disturbances in Alzheimer's patients, but that severe extrapyramidal adverse effects and adverse effects on cognitive function can compromise efficacy. However, in most cases, benefits of therapy appear to outweigh adverse effects (based upon opinions of physician and family members) Larger controlled studies are required to further evaluate neuroleptic therapy in Alzheimer's disease

4.5.A.5 Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

See Drug Consult reference: CHEMOTHERAPY AND RADIOTHERAPY TREATMENT GUIDELINES FC NAUSEA AND VOMITING

4.5.A.6 Delirium

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

b) Summary:
Effective in controlling patients with delirium and agitation

c) Adult:

1) Haloperidol, administered via continuous infusion, was effective in controlling delirium and agitati in a series of three critically ill intensive care unit patients. In all of the three patients, symptoms wer previously not adequately controlled with high doses of benzodiazepines and narcotics and bolus injections of intravenous haloperidol. Control of delirium was rapidly attained following initiation of continuous intravenous haloperidol (4 to 24 mg/hour) which allowed other sedatives to be discontinu and facilitated weaning from the ventilator. Two of the patients had underlying psychiatric illness (Seneff & Mathews, 1995).

2) Eight critically ill, mechanically ventilated patients with severe agitation unresponsive to benzodiazepines, narcotics, and intermittent bolus haloperidol were eventually controlled with haloperidol by continuous intravenous infusion. Initial infusion rates ranged from 3 to 25 milligrams (mg)/hour (mean 9 mg/hour), with titration as high as 40 mg/hour for control (mean maintenance infusion 18 mg/hour). Control of agitation was demonstrated by a decline in the number of daily supplemental sedative doses (from 23 to 7) and by declines in the Sedation-Agitation Scale. Nursing time per patient decreased from 320 to 96 minutes, although one patient still required 2 nurses and adjunctive sedative doses daily (Riker et al, 1994a).

3) AIDS patients with organic mental disorders were treated for their delirium with high-dose intravenous haloperidol in combination with lorazepam (Fernandez et al, 1989). Although effective ir treating symptoms of delirium, half of the 38 patients treated developed extrapyramidal symptoms. A subsequent study randomized hospitalized AIDS patients with delirium to either haloperidol, chlorpromazine, or lorazepam (Breitbart et al, 1996b). Both neuroleptic agents significantly improvec symptoms of delirium with a low incidence of side effects. Lorazepam, however, was not effective, a the majority of patients treated with this agent developed treatment-limiting adverse effects. The me dose of haloperidol used was 2.8 mg during the first 24 hours of treatment and 1.4 mg for the remainder of the protocol.

4) In a prospective study of 14 delirious, medically ill patients with severe agitation, it was shown th those patients receiving intravenous (IV) HALOPERIDOL 4 milligrams/day plus at least 1 mg of benzodiazepine had fewer extrapyramidal symptoms than those patients receiving intravenous HALOPERIDOL 4 mg/day alone (Menza et al, 1988). DIAZEPAM, LORAZEPAM, OXAZEPAM, and ALPRAZOLAM were used with the dosage reported in milligram equivalents of DIAZEPAM. Doses were oral except four cases of IV LORAZEPAM. The approximate ratio of milligram of HALOPERIDC to milligram equivalents of DIAZEPAM was 4:1. In the HALOPERIDOL plus benzodiazepine treated patients, only one patient suffered very mild parkinsonian-like extrapyramidal symptoms, and there were no cases of akathisia or dystonia. The authors concluded that IV HALOPERIDOL combined wi benzodiazepines may be safely and effectively used to control severe agitation in delirious, medicall patients in critical care areas.

5) Intravenous HALOPERIDOL (100 to 480 milligrams/day) with LORAZEPAM (36 to 480 mg/day) successfully treated delirium in critically ill cancer patients. Mild to moderate levels of sedation were achieved in 24 of 25 patients within 90 minutes; most within 20 minutes. Seven patients died from underlying disease within 1 month of institution of therapy, and 18 patients recovered after correctio of the underlying problem. The longest duration of therapy was 3 months. Only 1 of the 25 patients experienced side effects (a dystonic reaction) serious enough to discontinue therapy (Adams et al, 1986).

4.5.A.7 Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.A.8 Flashbacks, LSD

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Useful in decreasing flashbacks associated with LSD

c) Adult:

1) Oral doses of 1 to 2 milligrams 3 times daily were effective in decreasing the frequency, intensity and duration of flashbacks associated with LSD ingestion. In a series of 8 patients, 3 patients were noted to have an increase in the number of flashbacks when HALOPERIDOL was discontinued (Moskowitz, 1971).

4.5.A.9 Gilles de la Tourette's syndrome

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (3 yr and older)
Efficacy: Adult, Evidence favors efficacy; 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 RATINGS

b) Summary:

Indicated for the control of tics and vocal utterances of Tourette's disorder in adults and childrer age 3 years and older (Prod Info haloperidol oral tablets, 2008; Prod Info haloperidol oral soluti 2008).

In pediatric patients (n=22) haloperidol was not significantly more effective on the Tourette Syndrome Global Scale compared with placebo, and was associated with a significantly greate incidence of extrapyramidal symptoms, while pimozide demonstrated effectiveness over placeb according to a 24-week, randomized, crossover study (Sallee et al, 1997a).

More effective than pimozide on the Gilles de la Tourette's syndrome severity scale and more effective than placebo on 4 of 6 measurement scales, according to a randomized, placebo-controlled, double-blind parallel and crossover study (n=57) in adults and children (Shapiro et a 1989a).

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c) Adult:

1) Haloperidol was more effective than pimozide on the Gilles de la Tourette's syndrome (TS) seve scale and was more effective than placebo on 4 of 6 measurement scales according to a randomize placebo-controlled, double-blind, parallel-group and crossover study (n=57). Patients with DSM-III criteria for TS, aged 8 to 46 years (mean 21.1 +/- 11 years) were randomized to receive haloperidol (n=20), pimozide (n=18), or placebo (n=19) during the 6-week, parallel-phase study (period 1), followed by a 3-week single-blind placebo or drug-free period. The study included previously untreat patients, and patients with inadequate prior response or history of adverse effects from haloperidol, clonidine, or other drugs. In the crossover phase (period 2), patients who received 6 weeks of active treatment (haloperidol or pimozide) were crossed over to the alternate study drug while patients initi assigned to placebo during the parallel phase were randomized to either haloperidol or pimozide an then crossed-over to the alternate drug for an additional 6 weeks. Patients received once daily dosir titrated to clinical effect up to a maximum dose of pimozide 0.3 milligram/kilogram (mg/kg) or 20 mg, whichever was smaller, or haloperidol 10 mg. Haloperidol was more effective than pimozide on the physician-rated TS severity scale (p=0.011). Haloperidol was also more effective than placebo on 1) the physician-rated TS severity scale (p=0.01), 2) total vocal tics (p=0.019), 3) Clinical Global Impression Scale (CGI scale) of therapeutic effects (rated by physician p=0.009, rated by patient p=0.01), and 4) the CGI scale of adverse effects (rated by physician p=0.01, rated by patient p=0.01 There was not a significant difference in the incidence of QTc interval greater than 0.44 sec (pimozi n=9 vs haloperidol n=1). The results of the study may have been limited by the short duration of treatment (Shapiro et al, 1989a).

2) Although haloperidol is the drug of choice in the treatment of Tourette's syndrome, more than on drug has been effective (Shapiro & Shapiro, 1981a). In some cases, combination therapy with haloperidol and nicotine or nifedipine has been effective (McConville et al, 1991); (Sandberg et al, 1989)(Alessi et al, 1989). The goal of treatment is to determine the lowest dosage that results in 70% improvement and the fewest side effects (Erenberg, 1992).

3) Nine out of 10 patients with Tourette's syndrome, not adequately controlled with haloperidol, wer successfully treated with adjunct nicotine gum (McConville et al, 1991). The patients began a therap of a 2 mg nicotine gum in conjunction with a mean dose of 2.8 mg per day of haloperidol. The numb of vocal and motor tics were recorded after chewing the gum 30 and 60 minutes. Nine out of the ten patients experienced reduced tic frequency. The mechanism of action is still under investigation.

d) Pediatric:

1) Haloperidol was not significantly more effective on the Tourette Syndrome (TS) Global Scale compared with placebo, and was associated with a significantly greater incidence of extrapyramidal symptoms, while pimozide demonstrated effectiveness over placebo, according to a 24-week, randomized, crossover study in pediatric patients (n=22). Patients with DSM-III-R criteria for TS, age 7 to 16 years (mean 10.2 +/- 2.5 years) were included in the study. Following an initial 2-week place baseline period, patients were randomized to receive 6 weeks of treatment with either haloperidol 1 milligram (mg), pimozide 1 mg, or placebo with dose titration of 2 mg/week to produce a 70% reduct in tic symptoms. Each 6-week treatment period was followed by a 2-week placebo washout period prior to crossing over to alternate therapy. A 70% tic reduction on the total TS global scale was achieved in 64% (14/22) with equivalent mean effective doses of pimozide 3.4 +/- 1.6 mg or haloperidol 3.5 +/- 2.2 mg/day compared with 23% (5/22) who received placebo (p=0.02 for treatme group effect). In a post hoc analysis, pimozide was significantly more effective than placebo on the total TS global scale , TS global tic subscale, the TS symptom list tic subscale score, Clinical Global Impression (CGI) tic severity scale, and on the clinician-rated Children's Global Assessment Scale (less than 0.05 on all scores). Haloperidol was significantly more effective than placebo on the CGI ti severity scale and on the clinician-rated Children's Global Assessment Scale (p less than 0.05 for bo scores). The number of extrapyramidal symptoms was higher during the haloperidol-treatment perio (mean 4.1 +/- 6.9) compared with the pimozide-treatment period (mean 2 +/- 3) (p less than 0.05), o placebo (mean 1.4 +/- 3) (p less than 0.01). Moderate to severe adverse events including depressio anxiety, or severe dyskinesias occurred in 9 of 22 patients during the haloperidol-treatment phase compared with 3 of 22 patients during the pimozide-treatment phase. There were no significant electrocardiovascular effects on heart rate, rhythm, or waveform in either the pimozide or haloperidc treatment phases compared with placebo (Sallee et al, 1997a).

2) Nicotine potentiated the effects of haloperidol in the treatment of Tourette's syndrome (Sandberg al, 1989). Ten children between the ages of 7 and 17 years (mean 12 years) who were taking haloperidol in doses ranging from 1 to 3 mg/day (mean 1 mg/day) were given nicotine gum 2 mg thr times daily. Eighty percent of the children showed both decreases of tics and improvement of concentration and attention span. This positive effect lasted from 45 to 60 minutes. However, 70% o the children discontinued the gum due to side effects. The side effects included stomach pain, naus decreased appetite, complaints of bitter taste and burning sensation in the mouth, and weight loss. T mechanism of action by which nicotine potentiates haloperidol is not known and more studies are needed. Two cases were reported of children in which NICOTINE gum 2 mg helped control Tourette syndrome that could not be adequately controlled with haloperidol alone (Sandberg et al, 1988).

3) The combination of haloperidol (1 milligram orally twice daily) plus nifedipine (10 milligrams orally times daily) was effective in the treatment of Gilles de la Tourette's syndrome in a 9-year-old boy wh was refractory to both nifedipine and haloperidol when administered as single agent therapy (Alessi al, 1989). The mechanism of apparent synergism in this patient is unclear, however, the authors postulate that the combination results in a relative reduction in D2 receptor-binding sites, causing a relative increase in the site specific potency of haloperidol. More studies are required to investigate t combination in Tourette's patients.

4.5.A.10 Hiccoughs

See Drug Consult reference: HICCUPS - ETIOLOGY AND TREATMENT

4.5.A.11 Hiccoughs, Intractable

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Intramuscular HALOPERIDOL 2 mg successfully treated intractable hiccups in 2 patients (Ives et al, 1985)

4.5.A.12 Hyperactive behavior, (Short-term treatment) after failure to respond to non-antipsychotic medication and psychotherapy

FDA Labeled Indication
a) Overview
FDA Approval: Adult, no; Pediatric, yes (3 yr and older)
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
b) Summary:
Indicated for short-term treatment of hyperactive children with excessive motor activity and concomitant conduct disorders such as impulsivity, difficulty sustaining attention, aggressivity, mood lability and poor frustration tolerance (Prod Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

4.5.A.13 Migraine
a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class III; Pediatric, Class III
Strength of Evidence: Adult, Category C; Pediatric, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
b) Summary:
In case reports, intravenous haloperidol has been effective in relieving symptoms of migraine headache
c) Adult:
1) Intravenous haloperidol was effective in relieving symptoms of migraine headache in a series of s cases. Haloperidol was primarily administered for the relief of nausea and vomiting, but was also fou to alleviate headache pain. Following an intravenous bolus of 500 to 1000 milliliters of normal saline haloperidol was given as a dose of 5 mg over 2 to 3 minutes. Headache pain was better after 25 to (minutes, and none of the six patients returned for additional treatment within the next two days (Fish 1995). Randomized prospective trials are needed to validate these findings.
d) Pediatric:
1) HALOPERIDOL 0.05 to 0.1 milligrams/kilogram/day orally has been effective in relieving hemiple episodes of MIGRAINE HEADACHE in children (Salmon & Wilson, 1984).

4.5.A.14 Nausea and vomiting; Treatment and Prophylaxis
a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
b) Summary:
Prevents nausea and vomiting due to numerous causes
c) Adult:
1) Numerous studies have indicated that HALOPERIDOL in 1 to 4 milligram doses, intramuscular o oral, is an effective ANTIEMETIC in the prevention or treatment of nausea and vomiting due to varic causes including POSTOPERATIVE NAUSEA and vomiting, CANCER CHEMOTHERAPY, IRRADIATION, and GASTROINTESTINAL DISORDERS (Barton et al, 1975; Robbins & Nagel, 197 Cole & Duffy, 1974; Christman et al, 1974; Plotkin et al, 1973; Tornetta, 1972); (Shields et al, 1971). postoperative nausea, HALOPERIDOL by the intravenous route was more rapid in onset than either DROPERIDOL or PROCHLORPERAZINE (Loeser et al, 1979).
2) Two cases were reported of HALOPERIDOL combined with LORAZEPAM to successfully treat nausea and vomiting associated with the intravenous use of DIHYDROERGOTAMINE for treatment intractable migraine headaches (Backonja et al, 1989). The authors found that the intravenous administration of 0.5 to 1 mg each of HALOPERIDOL and LORAZEPAM 15 minutes prior to the intravenous administration of DIHYDROERGOTAMINE prevents nausea and vomiting. HALOPERIDOL and LORAZEPAM cause marked sedation and the authors therefore recommend th 0.25 mg of each drug be given initially and an additional 0.25 to 0.5 mg be added as needed.
3) HALOPERIDOL gave better results in emesis induced by platinol and NITROGEN MUSTARD; BENZQUINAMIDE gave better results with DOXORUBICIN. This was in a study where BENZQUINAMIDE was compared with HALOPERIDOL for relief of emesis due to specific antineoplastic agents in 64 patients. In patients not being relieved by the first agent, crossover usua resulted in some relief. More PROCHLORPERAZINE resistant patients obtained relief with HALOPERIDOL than with BENZQUINAMIDE (Neidhart et al, 1981b).

4.5.A.15 Obsessive-compulsive disorder; Adjunct
a) Overview
FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Useful as adjunct therapy in treating refractory obsessive compulsive disorder

c) Adult:
1) The addition of haloperidol was useful in treating refractory obsessive compulsive disorder. In a double-blind, randomized, placebo-controlled trial lasting four weeks, 34 patients receiving, but refractory to, fluvoxamine (maximum 300 mg/day) for obsessive compulsive disorder had either haloperidol (maximum 10 mg/day) or placebo added to their regimen (McDougle et al, 1994). Severa scales used to assess obsessive compulsive symptoms, tics, depression, and related symptoms showed that the addition of haloperidol was significantly better than the addition of placebo in reduci the severity of obsessive compulsive symptoms with chronic tic disorders. The only significant adver effect occurring with haloperidol was akathisia in 9 of 31 patients. Haloperidol addition was of limitec benefit in treating obsessive compulsive disorder patients without tics.

4.5.A.16 Ocular hypertension

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

b) Summary:
Not effective

c) Adult:
1) Topical administration of the HALOPERIDOL ophthalmic solution (0.125% and 1%) produced modest reductions in intraocular pressure in healthy volunteers; however, reductions were not considered statistically significant (Lavin & Andrews, 1986).
2) HALOPERIDOL 3 milligrams orally was reported to produce significant decreases in intraocular pressure in non-glaucomatous volunteers at 3 to 4 hours post-administration (Sheppard & Schaid, 1986). However, significant reductions in intraocular pressure were not observed in glaucomatous patients receiving topical antiglaucoma medications, and more studies are required to determine benefits in glaucomatous patients; the authors suggest that lack of response in this group was relate to use of the concurrent topical medications.

4.5.A.17 Opioid withdrawal

See Drug Consult reference: DRUG THERAPY OF OPIOID WITHDRAWAL

4.5.A.18 Pain

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

b) Summary:
Questionable effects on pain control

c) Adult:
1) No shift to the left in dosage histograms was found in 424 cancer patients treated with MORPHIN vs MORPHINE plus HALOPERIDOL. The authors concluded that HALOPERIDOL did not potentiate MORPHINE analgesia (Hanks et al, 1983).
2) In a single case report (Daw & Cohen-Cale, 1981), HALOPERIDOL was shown to have an independent analgesic effect as well as a narcotic-potentiating effect in the treatment of severe pelv pain.
3) In intractable pain, HALOPERIDOL has successfully been used as an analgesic. A review of the cases reveals that it has been used for terminal cancer pain, intractable arthritic pain, and severe denervation dysesthesia. Some of these patients have been able to greatly decrease their consumption of narcotics; others have managed on HALOPERIDOL alone. The rationale for use of HALOPERIDOL for this purpose rests with its structural similarity to MEPERIDINE, its effectiveness preventing withdrawal symptoms upon removal of narcotics in addicts, a recognition of an analgesic dose-response seen at doses which, until recently, were rarely used (ie, 20 to 40 mg/day), and the demonstration that HALOPERIDOL binds to the opiate receptor. Further study of the analgesic effec of HALOPERIDOL is warranted (Maltbie et al, 1979a).
4) In chronic facial pain, nonmigranous and nonneuralgiform in nature, HALOPERIDOL along with relaxation therapy was successful in relieving pain in 12 of 12 patients. Although this type of pain ha very high psychogenic component and improvement in the psychiatric well-being of the patient coul

be the rationale of successful therapy, HALOPERIDOL has also been shown to have analgesic properties. The author suggests that further study might elucidate more clearly the use of HALOPERIDOL in these patients (Raft et al, 1979).

4.5.A.19 Postoperative nausea and vomiting; Prophylaxis

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

The administration of haloperidol after spinal anesthesia reduced the incidence of postoperative nausea and vomiting

c) Adult:

1) Prophylactic administration of haloperidol after spinal anesthesia reduced the incidence of postoperative nausea and vomiting during the first 24 hours after surgery. In a randomized, double-blind, placebo- controlled study (n=108), patients undergoing lower limb orthopedic or endoscopic urologic surgery under spinal anesthesia received a single intramuscular dose of haloperidol 1 milligram (mg), haloperidol 2 mg, or placebo after spinal anesthesia with local anesthetic and morph 0.3 mg for the prophylaxis of postoperative nausea and vomiting. Treatment failure was defined as a nausea score of 1 (mild) or higher, any episode of vomiting, or a request for rescue antiemetic. Over 60% of patients met criteria for treatment failure within the first 12 hours following surgery, with both haloperidol doses demonstrating a significant dose-related reduction in incidence of postoperative nausea, vomiting, or antiemetic use (treatment failure, placebo 76%, haloperidol 1 mg 56%, haloperidol 2 mg 50%; p=0.012). The total treatment failure rate at 24 hours was 65% (placebo 76% haloperidol 1 mg 64%, haloperidol 2 mg 55%; p=0.03). No difference was found between the two haloperidol doses. No extrapyramidal effects were observed with the use of haloperidol during the study (Parlow et al, 2004).

4.5.A.20 Problematic behavior in children (Severe), With failure to respond non-antipsychotic medication or psychotherapy

FDA Labeled Indication

a) Overview

FDA Approval: Adult, no; Pediatric, yes (3 yr and older)
Efficacy: Pediatric, Effective
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated in the treatment of severe behavior problems in children with combative, explosive hyperexcitability which is not accounted for by immediate provocation
Also effective in the short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders (i.e. impulsivity, difficulty sustaining attention, aggressivity, mood lability and poor frustration tolerance)
Recommended for children unresponsive to psychotherapy or medications other than antipsychotics

c) Pediatric:

1) Symptomatic improvement was seen with HALOPERIDOL in 12 hospitalized patients 7 to 11 yea old who suffered from childhood-onset PERVASIVE DEVELOPMENTAL DISORDER. The average dose of HALOPERIDOL was 0.04 milligrams/kilogram per day. There was remarkable improvement peer interaction, reduction in autistic-like behavior, improved reality testing, and decreased impulsivi and hyperactivity. This low-dose treatment with HALOPERIDOL produced minimal side effects. Thre children exhibited transient drowsiness in the initial phase of treatment, but this decreased over time and did not interfere with their cognitive performance. Two children suffered mild extrapyramidal symptoms with rigidity and cogwheeling. These symptoms were treated with oral DIPHENHYDRAMINE and did not recur when the drug was withdrawn (Joshi et al, 1988).

2) HALOPERIDOL (0.5 to 4 milligrams/kilogram) was more effective than placebo in a double-blind crossover study of 41 patients aged 2.3 to 6.9 years with INFANTILE AUTISM. HALOPERIDOL resulted in a significant decrease in behavioral symptoms and significant increases in facilitation and retention of discrimination (Anderson et al, 1984).

3) HALOPERIDOL 0.5 to 4 milligrams was compared with placebo in a double-blind, crossover stud in nine autistic children, ages 2 to 7 years, confirming the efficacy of HALOPERIDOL in autism (Coh et al, 1980). It was found effective in reducing rates of stereotypy and facilitating low rates of orientir to the rater, while not affecting other behaviors, including motor activity, speech, affect, or irritability. The results of this ongoing study, involving 33 patients, have been updated (Campbell et al, 1982a).

4.5.A.21 Psychotic disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (3 yr and older (oral formulations only))
Efficacy: Adult, Evidence favors efficacy; 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 RATINGS

b) Summary:

Indicated for management of manifestations of psychotic disorders (Prod Info haloperidol oral tablets, 2006; Prod Info haloperidol oral solution, 2001)

4.5.A.22 Rheumatoid arthritis

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Improves clinical features and laboratory parameters of RHEUMATOID ARTHRITIS

c) Adult:

1) Patients with rheumatoid arthritis previously treated only with nonsteroidal antiinflammatory drugs were found to have no significant difference in responses to either 150 milligrams (mg)/day indomethacin or 1.5 mg/day HALOPERIDOL. A proposed mechanism for this effect of HALOPERID is membrane-stabilization on platelets (Grimaldi & Bergonzi, 1980). A follow-up study (Grimaldi, 198 suggested a specific antirheumatic activity of HALOPERIDOL, based on increased serum sulfphydry levels and decreased PIP joints technetium index, ESR, and joint count.

4.5.A.23 Schizophrenia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (3 yr and older (oral formulations only))
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

b) Summary:

Indicated in the management of schizophrenia

c) Adult:

1) Haloperidol is effective in the treatment of SCHIZOPHRENIA and ACUTE PSYCHOSIS, as well schizoaffective disorders and paranoid syndrome. Usual oral haloperidol doses range from 5 to 20 milligrams/day, but doses of 100 mg/day or more may be indicated (Carter, 1986).

2) Intravenous HALOPERIDOL was used successfully in five severely regressed, nonviolent, psychiatric inpatients with psychotic disorders (Plotnick & Brown, 1991). Five psychiatric patients unable to thrive without intravenous fluids and nutrition and incapable of ingesting oral medications were given intravenous HALOPERIDOL in therapeutic doses to alleviate psychotic symptoms and were studied in retrospect. All five cases showed significant improvement in symptoms shortly following use of intravenous HALOPERIDOL. Four of the five patients were discharged in complete remission of symptoms after brief hospital stays. The authors suggested that HALOPERIDOL given a slow intravenous push was a safe and rapidly effective treatment for severely regressed, nonviole psychotic inpatients.

3) A double-blind study with 20 patients suffering manic or schizomanic psychoses determined that CARBAMAZEPINE and HALOPERIDOL in combination were as effective as HALOPERIDOL alone. The doses were haloperidol 24 mg/day and CARBAMAZEPINE 600 mg/day. No evidence was foun to show that the combination was more effective than HALOPERIDOL alone (Moller et al, 1989). Similarly, the combination of CARBAMAZEPINE plus HALOPERIDOL was compared with HALOPERIDOL plus placebo in a controlled study involving 43 patients with excited psychoses. Combination therapy was reported superior to HALOPERIDOL alone with clinical benefits being as apparent in excited schizophrenia as in mania (Klein et al, 1984a).

4) The positive correlation between early response and clinical outcome in schizophrenic patients treated with HALOPERIDOL was reported. Doses were not reported, but averaged 26 and 32 mg at hours in dysphoric and nondysphoric patients, respectively. Eighty-two percent of patients classified nondysphoric after 24 hours had good clinical results after 3 weeks, while 23% of dysphoric patients after 24 hours had poor clinical results after 3 weeks. The authors concluded that early subjective ar symptom improvement is an indicator of therapeutic outcome (Awad & Hogan, 1985).

5) Amphetamine was beneficial when added to chronic haloperidol therapy in 21 patients with undifferentiated or paranoid schizophrenia (Goldberg et al, 1991). Thirty-two percent reflected negat symptoms, 46% displayed positive symptoms, and 11% had paranoid symptoms. The study assess

changes in neuropsychological function such as positive effects on affect and cognition. A single dos of 0.25 milligrams/kilogram of dextroamphetamine was administered and the patients were evaluate for cognitive function, performance and comprehension. Six patients showed improvement after administration of the amphetamine. Increases in spontaneous eye-blink rate and enlarged cerebral ventricles were associated with improvement. The authors concluded that amphetamine paired with haloperidol had a positive effect on symptoms of schizophrenia; however, no definite conclusions co be drawn because no long term study was done.

4.5.A.24 Severe major depression with psychotic features

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Successfully used in combination with tricyclic antidepressants to treat psychotic depression

c) Adult:

1) Two cases were reported of patients suffering from PSYCHOTIC DEPRESSION successfully be treated with a combination of low dose HALOPERIDOL (1 to 3 mg/day) and DESIPRAMINE (100 mg/day). The HALOPERIDOL serum levels of the patients were 1.5 to 2.4 ng/mL. The authors concluded that the higher doses of neuroleptics commonly used to treat this condition may not be necessary (Lin et al, 1989).

4.5.A.25 Sneezing

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in 1 case report

c) Adult:

1) A single case of intractable sneezing of 139 days (every 4 to 5 seconds except when sleeping or talking) was slowed to every 30 seconds with a dose of haloperidol 1.5 milligrams (mg) twice daily. T rate continued to slow as the dose was increased and stopped altogether at a dose of 5 mg 3 times daily. The dose was then gradually reduced over 6 months without recurrence (Davison, 1982).

4.5.B Haloperidol Decanoate

Chronic schizophrenia

Gilles de la Tourette's syndrome

4.5.B.1 Chronic schizophrenia

FDA Labeled Indication

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the treatment of schizophrenic patients who require prolonged parenteral antipsychotic therapy (Prod Info haloperidol decanoate injection, 2005)

c) Adult:

1) Monthly intramuscular injections of HALOPERIDOL DECANOATE 50 milligrams for 5 months wa reported effective in the treatment of chronic schizophrenic patients, many of whom showed poor compliance to oral medication (Bucci & Marini, 1985).

4.5.B.2 Gilles de la Tourette's syndrome

a) Overview

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

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

b) Summary:
Effective in treatment of severe, intractable Tourette's syndrome unresponsive to oral haloperid in 1 case report (Clarke & Ford, 1988)

c) Adult:
1) HALOPERIDOL DECANOATE intramuscularly was reported effective in the treatment of severe, intractable Tourette's syndrome unresponsive to oral HALOPERIDOL in a 23-year-old male (Clarke Ford, 1988). The patient had been unresponsive to oral HALOPERIDOL (doses of up to 10 milligran orally four times daily) for several years. Oral HALOPERIDOL was discontinued and a test dose of HALOPERIDOL DECANOATE 100 milligrams intramuscularly was administered, resulting in a reduction in tics, coprolalia, and copropraxic gestures over the ensuing two weeks. HALOPERIDOL DECANOATE was continued in doses of up to 400 milligrams intramuscularly monthly, then was subsequently reduced to 200 milligram maintenance doses. Tourette's symptoms disappeared completely after 4 months of treatment.

4.5.C Haloperidol Lactate

Gilles de la Tourette's syndrome

Schizophrenia

4.5.C.1 Gilles de la Tourette's syndrome

FDA Labeled Indication

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

b) Summary:
Indicated for the control of tics and vocal utterances of Tourette's disorder (Prod Info HALDOL(I immediate release IM injection, 2008)

c) Adult:
1) Indicated for the control of tics and vocal utterances of Tourette's disorder (Prod Info HALDOL(R immediate release IM injection, 2008).
2) In some cases, combination therapy with haloperidol and nicotine or nifedipine has been effectiv the treatment of Tourette's syndrome (McConville et al, 1991); (Sandberg et al, 1989)(Alessi et al, 1989). The goal of treatment is to determine the lowest dosage that results in 70% improvement and the fewest side effects (Erenberg, 1992).
3) Nine out of 10 patients with Tourette's syndrome, not adequately controlled with haloperidol, wer successfully treated with adjunct nicotine gum (McConville et al, 1991). The patients began a therap of a 2 mg nicotine gum in conjunction with a mean dose of 2.8 mg per day of haloperidol. The numb of vocal and motor tics were recorded after chewing the gum 30 and 60 minutes. Nine out of the ten patients experienced reduced tic frequency. The mechanism of action is still under investigation.

4.5.C.2 Schizophrenia

FDA Labeled Indication

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

b) Summary:
Indicated for the treatment of schizophrenia in adult patients (Prod Info HALDOL(R) immediate release IM injection, 2008).

c) Adult:
1) Haloperidol is effective in the treatment of schizophrenia and acute psychosis, as well as schizoaffective disorders and paranoid syndrome (Carter, 1986).
2) A double-blind study with 20 patients suffering manic or schizomanic psychoses determined that carbamazepine and haloperidol in combination were as effective as haloperidol alone. The doses w haloperidol 24 mg/day and carbamazepine 600 mg/day. No evidence was found to show that the combination was more effective than haloperidol alone (Moller et al, 1989). Similarly, the combinatio

of carbamazepine plus haloperidol was compared with haloperidol plus placebo in a controlled study involving 43 patients with excited psychoses. Combination therapy was reported superior to haloperidol alone with clinical benefits being as apparent in excited schizophrenia as in mania (Kleir al, 1984a).
3) The positive correlation between early response and clinical outcome in schizophrenic patients treated with haloperidol was reported. Doses were not reported, but averaged 26 and 32 mg at 24 hours in dysphoric and nondysphoric patients, respectively. Eighty-two percent of patients classified nondysphoric after 24 hours had good clinical results after 3 weeks, while 23% of dysphoric patients after 24 hours had poor clinical results after 3 weeks. The authors concluded that early subjective ar symptom improvement is an indicator of therapeutic outcome (Awad & Hogan, 1985).
4) Amphetamine was beneficial when added to chronic haloperidol therapy in 21 patients with undifferentiated or paranoid schizophrenia (Goldberg et al, 1991). Thirty-two percent reflected negat symptoms, 46% displayed positive symptoms, and 11% had paranoid symptoms. The study assesse changes in neuropsychological function such as positive effects on affect and cognition. A single dos of 0.25 milligrams/kilogram of dextroamphetamine was administered and the patients were evaluate for cognitive function, performance and comprehension. Six patients showed improvement after administration of the amphetamine. Increases in spontaneous eye-blink rate and enlarged cerebral ventricles were associated with improvement. The authors concluded that amphetamine paired with haloperidol had a positive effect on symptoms of schizophrenia; however, no definite conclusions co be drawn because no long term study was done.

4.6 Comparative Efficacy / Evaluation With Other Therapies

Alizapride

Alprazolam

Amisulpride

Amitriptyline

Amobarbital

Aripiprazole

Ascorbic Acid

Benzquinamide

Bromperidol

Carbamazepine

Chlorpromazine

Chlorprothixene

Clocapramine

Clomipramine

Clonazepam

Clonidine

Clozapine

Diazepam

Diphenhydramine

Droperidol

Flunitrazepam

Flupenthixol

Fluphenazine

Imipramine

Lithium

Lorazepam

Loxapine

Melperone

Mesoridazine

Metoclopramide

Midazolam

Molindone

Olanzapine

Oxazepam

Oxcarbazepine

Penfluridol

Perazine

Periciazine

Perphenazine

Phenelzine

Physostigmine

Pimozide

Pramipexole

Prochlorperazine

Quetiapine

Remoxipride

Risperidone

Sertindole

Sulpiride

Sultopride

Tetrabenazine

Tetrahydrocannabinol

Thioridazine

Thiothixene

Timiperone

Trifluoperazine

Trimethobenzamide

Valproic Acid

Ziprasidone

Zotepine

Zuclopenthixol

4.6.A Alizapride

4.6.A.1 Nausea

a) The combination of tropisetron and haloperidol was compared with alizapride to treat nausea and vomiting in high-dose alkylating agent cancer chemotherapy. Twenty-six patients received only alizapride therapy. In the initial 24-hour period, six patients on tropisetron and haloperidol experienced no nausea o vomiting, opposed to one patient taking alizapride. At the end of the study period (72 hours), six patients taking tropisetron plus haloperidol showed no signs of nausea and vomiting compared with zero patients receiving alizapride (Bregni et al, 1991).

4.6.B Alprazolam

4.6.B.1 Dementia - Problem behavior

a) Alprazolam was as effective as low-dose haloperidol in a double-blind, cross-over trial in elderly, nurs home patients with disruptive behaviors associated with delirium, dementia, amnestic disorders, and oth cognitive disorders (Christensen & Benfield, 1998). Patients (n=48) currently receiving haloperidol 1 milligram (mg) or less on a scheduled basis had behavioral episodes measured at baseline. Thereafter patients either continued haloperidol for 6 weeks or entered a 2-week washout period followed by alprazolam 0.5 mg daily for 4 weeks. Both groups were reassessed and then crossed-over into the other group. There was no significant difference in the number of behavioral episodes for patients taking alprazolam compared to patients receiving haloperidol. There was also no difference in either group as compared to baseline. Since no placebo was used in this study, it is difficult to determine whether the patients actually benefited from either therapy.

4.6.C Amisulpride

4.6.C.1 Schizophrenia

a) Amisulpride was superior to haloperidol for the treatment of acute exacerbations of schizophrenia, in regard to both efficacy and safety. In a randomized, double-blind study, patients aged 18 to 45 years witl paranoid schizophrenia or schizophreniform disorder (by DSM-IV criteria) were treated for 4 months with oral haloperidol 10 to 30 milligrams (mg) per day (n=105) or amisulpride 400 to 1200 mg/day (n=94). Starting doses were 20 mg/day for haloperidol and 800 mg/day for amisulpride. Doses were then adjuste according to the patient's condition. Significantly more patients in the haloperidol group than in the

amisulpride group withdrew from the study, due mainly to adverse effects (21% vs 4%) and lack of effica (9% vs 6%). At the end of the study, scores on the Positive and Negative Syndrome Scale (PANSS) had improved more in the amisulpride group than in the haloperidol group, with the difference reaching significance on the negative PANSS score (p=0.01). The percentage of responders ("much" or "very muc improved on the Clinical Global Impressions (CGI) global improvement scale) was 71% in the amisulprid group and 47% in the haloperidol group (p=0.0006). Five percent of the patients in the amisulpride group were considered "worse" after treatment, compared to 15% of those in the haloperidol group. At the end the study, 40% of the amisulpride group were considered "normal," "borderline," or "mildly ill," vs 25% of the haloperidol group. Half of the patients who received haloperidol reported at least one extrapyramidal adverse event, compared to 33% of those who received amisulpride. At least one serious adverse event (mainly psychotic disorders and extrapyramidal effects) occurred in 16% of patients receiving haloperido and 4% of those receiving amisulpride. Weight gain (increase of 5% or more from baseline) was more frequent in the amisulpride group (33% vs 17%, p=0.051) (Carriere et al, 2000).

b) SUMMARY: AMISULPRIDE has been shown to be as effective as HALOPERIDOL in short-term and long-term treatment of schizophrenia. In some studies, AMISULPRIDE demonstrated greater efficacy related to negative symptomatology and improved tolerability (eg, fewer extrapyramidal effects).

c) In an open-label, randomized, multi-center trial (n=488), a 12-month course of AMISULPRIDE produc a similar incidence of drug-related adverse effects (69%) compared to HALOPERIDOL (70%), with amisulpride inducing lower rates of extrapyramidal side effects than haloperidol (13% vs 28%), in patient with subchronic or chronic schizophrenia with acute exacerbation (DSM-III-R). Amisulpride showed simil efficacy to haloperidol on positive symptoms of schizophrenia and significantly greater effectiveness thar haloperidol on negative symptoms (p=0.0001). Enrollees included patients with at least moderate scores 2 or more of the 4 positive items of the Brief Psychiatric Rating Scale (BPRS). Randomization was in a 3 1 ratio, amisulpride (n=370) to haloperidol (n=118). Scores on the Simpson-Angus extrapyramidal scale, Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS) favored amisulpride ove haloperidol (p=0.0001; p less than 0.0001; and p=0.014, respectively). Serious adverse events (primarily psychiatric, including psychosis, agitation, aggression, and suicide attempts) occurred in 10% and 7%, respectively, of amisulpride- and haloperidol-treated patients. Rates of weight gain and amenorrhea were 11% and 6% for amisulpride compared with 3% and 0, respectively, for haloperidol. Discontinuations due adverse effects were 8% and 10%, respectively (amisulpride vs haloperidol). Withdrawals due to lack of efficacy were significantly less in the amisulpride group (12% vs 22%; p=0.009). At the end of 12 months the rate of change in BPRS scores was 44.8% and 33.7% from baseline in the amisulpride and haloperic groups, respectively. Mean decreases in the Positive and Negative Syndrome Scale (PANSS) positive scores were similar across groups (amisulpride, 48.4%; haloperidol 44.2%), whereas changes in PANSS negative scores were significantly greater for amisulpride (35.1% decrease vs 12% decrease; p=0.0001) Dosing was flexible, based on efficacy and tolerability. Maximum doses permitted during acute episodes were 1200 milligrams/day (mg/d) for amisulpride and 30 mg/d for haloperidol; during stable periods, dose were to fall between 200 and 800 mg for amisulpride and between 5 and 20 mg for haloperidol (mean da doses by study end were amisulpride 605 mg and haloperidol 14.6 mg) (Colonna et al, 2000).

d) In a double-blind, randomized study, AMISULPRIDE 800 milligrams (mg)/day over 6 weeks was shov to be as effective as HALOPERIDOL 20 mg/day for the treatment of subchronic schizophrenia or chronic schizophrenia with an acute exacerbation (DSM-III-R criteria), with AMISULPRIDE showing possibly greater efficacy in improving negative symptoms, as well as greater tolerability (n=191). On the Positive and Negative Symptom Scales (PANSS), negative symptoms were significantly improved in amisulpride-treated patients compared with the haloperidol group (mean change, 7.5 vs 5.1; p=0.038). Results on so parts of the Clinical Global Impression (CGI) rating also favored amisulpride (p=0.01 and p less than 0.0 respectively). Overall, 54 of 95 patients (56.8%) in the amisulpride group had at least one adverse event (mostly extrapyramidal symptoms) compared with 72 of 96 patients (75%) in the haloperidol group; 25 a 39 patients, respectively, dropped out of the study (p=0.04) (Moller et al, 1997).

e) Amisulpride was as effective for relapse prevention as haloperidol over a 1-year period in long-term i patients with predominantly negative symptoms of schizophrenia (Speller et al, 1997). Patients were randomly allocated to receive either amisulpride (n=29) or haloperidol (n=31) at a dose calculated to be equivalent to their previous antipsychotic medication. Amisulpride doses were 800 milligrams (mg), 600 450 mg, 300 mg, 150 mg, and 100 mg daily. For haloperidol doses were 20 mg, 16 mg, 11.5 mg, 8 mg, mg, and 3 mg daily. Dose reductions were undertaken every 3 months with the trial medication reduced the next lowest level, unless the lowest dose had been achieved or there was evidence of psychotic exacerbation. During the year, 18% of the amisulpride group and 35% of the haloperidol group experienc psychotic exacerbations (not statistically significant). At the end of the year, 76% of the amisulpride grou had achieved the lowest dose while 58% of the haloperidol group were on the lowest dose (either 3 mg c 4.5 mg). Amisulpride patients did show a greater reduction of the affective flattening and the avolition-apathy global items on the Scale for the Assessment of Negative Symptoms but it was again not significa

f) In a double-blind study, 41 schizophrenic patients were treated, with flexible doses, of haloperidol (n= and amisulpride (n=21) over a period of 42 days (Delcker et al, 1990). On the basis of the Brief Psychiat Rating Scale subscore for anxiety-depression syndrome, and the Arbeitsgemeinschaft fuer Methodik unc Dokumentation in der Psychiatrie (AMDP) system subscore for the somatic depressive syndrome and th hypochondriac syndrome, the amisulpride group showed better results than the haloperidol group. No difference between the two drugs was found in improvement of psychotic symptoms. Amisulpride showe tendency to cause fewer extrapyramidal adverse effects.

g) In a double-blind study, amisulpride (10 milligrams/kilogram (mg/kg) daily) was compared to haloperic (0.5 mg/kg daily) in treatment over one month of patients with acute schizophrenia. The 9 patients in the amisulpride group completed the study, whereas 5 of 10 patients of haloperidol group dropped out of the trial, 3 because of adverse effects. Both drugs significantly improved the acute psychotic symptomatolog and were tolerated in a comparable manner. Extrapyramidal effects were much more pronounced in the haloperidol group (Ruther et al, 1989).

h) In a comparative, double-blind study, 40 patients hospitalized for acute psychosis were treated with amisulpride (800 to 1200 milligrams (mg)/day, 20 patients) or haloperidol (20 to 30 mg/day, 20 patients) 21 days (Costa & Silva, 1989). No significant difference in efficacy was reported between the two drugs according to the Brief Psychiatric Rating Scale. Amisulpride showed less frequent and less intense extrapyramidal adverse effects. Larger, long-term comparative studies are needed to more clearly asses the efficacy, safety and therapeutic role of amisulpride in schizophrenia.

i) A double-blind trial evaluated the therapeutic effects and tolerance of high doses of amisulpride (800 t 1200 milligrams (mg) daily) (20 patients) versus haloperidol (20 to 30 mg daily) (19 patients) in acute psychotic disorders (acute delusional attacks and positive symptoms of schizophrenia). Both drugs exhibited good antipsychotic activity, but amisulpride had a prompt effect, provided more improvement o symptoms (particularly on the anergy, thought disorder, and activation items of the Brief Psychiatric Rati Scale), and exhibited a better tolerance (Pichot & Boyer, 1988).

4.6.C.2 Adverse Effects

a) AMISULPRIDE appears to have better tolerability compared with HALOPERIDOL in both short-term a long-term regimens.

b) In an open-label, randomized, multi-center trial (n=488), a 12-month course of AMISULPRIDE produc a similar incidence of drug-related adverse effects (69%) compared to HALOPERIDOL (70%), with amisulpride inducing lower rates of extrapyramidal side effects than haloperidol (13% vs 28%), in patient with subchronic or chronic schizophrenia with acute exacerbation (DSM-III-R). Amisulpride showed simil efficacy to haloperidol on positive symptoms of schizophrenia and significantly greater effectiveness thar haloperidol on negative symptoms (p=0.0001). Enrollees included patients with at least moderate scores 2 or more of the 4 positive items of the Brief Psychiatric Rating Scale (BPRS). Randomization was in a 3 1 ratio, amisulpride (n=370) to haloperidol (n=118). Scores on the Simpson-Angus extrapyramidal scale, Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS) favored amisulpride ove haloperidol (p=0.0001; p less than 0.0001; and p=0.014, respectively). Serious adverse events (primarily psychiatric, including psychosis, agitation, aggression, and suicide attempts) occurred in 10% and 7%, respectively, of amisulpride- and haloperidol-treated patients. Rates of weight gain and amenorrhea were 11% and 6% for amisulpride compared with 3% and 0, respectively, for haloperidol. Discontinuations due adverse effects were 8% and 10%, respectively (amisulpride vs haloperidol). Withdrawals due to lack of efficacy were significantly less in the amisulpride group (12% vs 22%; p=0.009). At the end of 12 months the rate of change in BPRS scores was 44.8% and 33.7% from baseline in the amisulpride and haloperic groups, respectively. Mean decreases in the Positive and Negative Syndrome Scale (PANSS) positive scores were similar across groups (amisulpride, 48.4%; haloperidol 44.2%), whereas changes in PANSS negative scores were significantly greater for amisulpride (35.1% decrease vs 12% decrease; p=0.0001) Dosing was flexible, based on efficacy and tolerability. Maximum doses permitted during acute episodes were 1200 milligrams/day (mg/d) for amisulpride and 30 mg/d for haloperidol; during stable periods, dose were to fall between 200 and 800 mg for amisulpride and between 5 and 20 mg for haloperidol (mean da doses by study end were amisulpride 605 mg and haloperidol 14.6 mg) (Colonna et al, 2000).

c) AMISULPRIDE produces fewer disturbances of psychomotor, cognitive, extrapyramidal, and affective functions compared with HALOPERIDOL, according to a double-blind, randomized, cross-over study in healthy volunteers (n=21). Enrollees received 4 different 5-day regimens, with at least 10 days of washo between treatments. On days 1 and 5, subjects ingested 2 capsules in the morning: (1)placebo plus placebo; (2)amisulpride 50 milligrams (mg) plus placebo; (3)amisulpride 200 mg plus amisulpride 200 mg (400 mg/day); or (4)haloperidol 2 mg plus haloperidol 2 mg (4 mg/day). On days 2, 3, and 4, the same dosages were given but divided between morning and evening. Amisulpride 50 mg/day had no effect comparing baseline with post-treatment measurements. Amisulpride 400 mg was associated with a few adverse effects on psychomotor and cognitive performance (on day 5 only). Haloperidol was problematic from day 1; it induced several affective disturbances, including higher ratings for depression on the Hamilton Scale, lower feelings of well-being on the Subjective Well-Being under Neuroleptics Scale, and more negative symptoms on the Positive and Negative Symptoms Scale. With respect to affective measures, only drowsiness was significantly greater after amisulpride 400 mg than after placebo (p=0.01 Mean ratings of extrapyramidal symptoms and akathisia were always significantly higher after haloperidc than amisulpride 400 mg (Simpson-Angus Extrapyramidal Side Effect Scale, p equal or less than 0.01; Barnes Akathisia Scale, p equal or less than 0.02). Five times more patients requested anti-cholinergic agents while receiving haloperidol than during amisulpride 400-mg treatment. Two patients dropped out due to side effects of haloperidol vs no drop-outs for amisulpride (Ramaekers et al, 1999).

4.6.D Amitriptyline

4.6.D.1 Schizoaffective disorder

a) Amitriptyline (mean 148 mg/day, maximum 150 mg/day), haloperidol (mean 7.2 mg/day, maximum 12 mg/day), and placebo were compared in 64 patients with unstable and schizotypal borderline disorders.

a wide variety of psychological tests, haloperidol was shown to be significantly more effective than amitriptyline in these disorders, including disorders with a depressive component (Soloff et al, 1986).

4.6.E Amobarbital

4.6.E.1 Psychotic disorder

a) A single-blind study of 15 healthy male schizophrenic patients showed that intramuscular administrati of sodium amytal 250 mg or midazolam 5 milligrams was significantly more effective than haloperidol 10 mg in controlling motor agitation. They were also more effective than haloperidol in controlling hostility, though this did not reach statistic significance (Wyant et al, 1990).

4.6.F Aripiprazole

4.6.F.1 Schizophrenia

a) SUMMARY: Aripiprazole (up to 30 mg daily) and haloperidol (up to 20 mg daily) appear similarly effective in patients with acutely relapsed schizophrenia or schizoaffective disorder; adverse effects may less with aripiprazole.

b) Haloperidol 5 to 20 mg daily, but not aripiprazole (5 to 30 mg daily), was superior to placebo with respect to improvement in BPRS scores in a 4-week study involving acutely relapsed inpatients with DSI III/IV schizophrenia (n=103). Both haloperidol and aripiprazole were more effective than placebo in responder analysis based on CGI-severity scores (Prod Info Abilify(TM), 2002).

c) In a placebo-controlled, phase III study involving relapsed schizophrenic or schizoaffective patients (n=414), aripiprazole 15 or 30 mg daily and haloperidol 10 mg daily (fixed doses) were each statistically superior to placebo with regard to changes in PANSS-total and BPRS-total scores; based on responder analysis (a 30% reduction in PANSS-total scores from baseline at last visit), each dose of aripiprazole w significantly more effective than placebo, whereas haloperidol was not. There was evidence of better tolerability with aripiprazole compared to haloperidol (eg, benztropine requirements for extrapyramidal effects, prolactin increases, weight increase). Extrapyramidal symptoms were reportedly similar with aripiprazole and placebo, and fewer patients receiving aripiprazole discontinued treatment due to advers events compared to haloperidol and placebo (Kane et al, 2000). However, this study did not report statistical comparisons of aripiprazole and haloperidol for any parameter (efficacy versus baseline or adverse effects); responder-analysis data revealed only a small difference between the two drugs. Overa this study does not provide evidence that aripiprazole is significantly more efficacious than haloperidol.

d) Results of phase II studies also suggested fewer adverse effects with aripiprazole compared to haloperidol (Saha et al, 1999; Anon, 2000). In these studies, lower changes from baseline in Simpson-Angus Scale scores (parkinsonian symptoms) and less requirement for benztropine were observed with doses of aripiprazole (2, 10, or 30 mg daily) than with haloperidol 10 mg daily; prolactin levels were not increased by aripiprazole, compared to significant increases with haloperidol, and significantly less weigl gain was evident in the aripiprazole groups (all doses). Comparative efficacy data were not presented.

4.6.G Ascorbic Acid

4.6.G.1 PCP intoxication

a) Four treatment regimens for phencyclidine intoxication were compared: 10 patients received placebo 10 received 1 gram intramuscular ascorbic acid, 10 received 5 mg intramuscular haloperidol, and 10 received both the haloperidol and ascorbic acid. Treatments were administered at 0 and 30 minutes and assessments were made at 0, 30, and 60 minutes by blinded evaluators. The order of responses, each being significantly better than the previous by statistical analysis, was ascorbic acid, placebo, haloperido and the combination therapy. The authors concluded that ascorbic acid potentiated the action of haloperidol, either by inhibiting the binding of phencyclidine to the dopamine receptor or by interfering wi the metabolism of haloperidol (Giannini et al, 1987).

4.6.H Benzquinamide

4.6.H.1 Vomiting

a) Although benzquinamide may be a useful antiemetic for some conditions, haloperidol appears to be superior. Effectiveness of antiemetic agents may vary in the treatment of nausea and vomiting due to different chemotherapeutic agents. The efficacy of haloperidol was compared with that of benzquinamide 64 patients receiving cancer chemotherapy. In a randomized, cross-over, double-blind study, 36 patients received haloperidol 2 milligrams (mg) or benzquinamide 50 mg intramuscularly, 10 minutes before chemotherapy administration. Patients preferred haloperidol over benzquinamide for control of emesis induced by cisplatin (78% versus 22%) or nitrogen mustard (67% versus 16%). However, patients receiv doxorubicin preferred benzquinamide (46% versus 38%). In patients previously unrelieved by prochlorperazine, haloperidol was more effective than benzquinamide (54% versus 29%). Complete relie of vomiting was achieved in 14 of 45 and 5 of 41 patients receiving haloperidol and benzquinamide, respectively (Neidhart et al, 1981a).

4.6.I Bromperidol

4.6.I.1 Psychotic disorder

a) In a double-blind 4-week study, bromperidol was compared with haloperidol in the initial treatment of psychotic patients (Denijs, 1980). The median daily oral dose was 9 to 12 mg for bromperidol and 12 mg haloperidol. Brief Psychiatric Rating Scale scores showed marked intragroup improvements for both bromperidol and haloperidol. Differences between the drugs were slight at all times. Nurses' Observation Scale for Inpatient Evaluation-30 scores also showed intragroup improvement without significant intergrc differences. Bromperidol had more of an activating effect, while haloperidol was more antimanic. Most frequent side effects were tremor, parkinsonism, akathisia and increased salivation. For the bromperidol group, paroxysmal dyskinesia, sedation and orthostatic hypotension were also noted. Overall results showed that all bromperidol patients were either improved or unchanged (similar for haloperidol) and 19 20 patients tolerated bromperidol well. Bromperidol is equally effective as haloperidol in treating psychos

b) Bromperidol was compared with haloperidol in a double-blind study with 40 psychotic (mostly schizophrenic) patients (Poeldinger et al, 1977). Initial doses were 5 mg/day orally of either bromperidol haloperidol, with subsequent dosage adjustments At study end, the mean daily dose of each drug was 6 mg/day, with a range of 5 to 12 mg/day for bromperidol and 5 to 9 mg/day for haloperidol. Sixty-five perc of patients showed improvement with bromperidol and 50% with haloperidol, with negligible differences between the two drugs when directly compared. Global evaluation revealed that a majority of patients (1 out of 20 for each drug) had either very good, good, or moderate improvement, with only one bromperidc patient showing no improvement and one haloperidol patient having deteriorated. Parkinsonian side effe were observed in four bromperidol and three haloperidol patients. There were no autonomic or psychic s effects. Bromperidol is at least as effective a treatment for psychic disorders as haloperidol, on the basis its quicker onset of action.

c) The efficacy of bromperidol was compared with that of haloperidol in a 12-week double-blind controlle study involving 164 schizophrenic patients. Dosages were started at 3 to 6 mg daily and individually adjusted for best therapeutic response. Fifty-five percent of the bromperidol patients showed improveme compared to 38% for haloperidol. Bromperidol was judged to be a better form of treatment than the previous neuroleptic in 42.9% of the cases versus 23.8% for haloperidol. General improvement scores showed that bromperidol was more effective and had a quicker onset of action. Specific symptoms on th Brief Psychiatric Rating Scale were improved significantly more with bromperidol. Side effects reported (dystonia, akathisia, parkinsonism) were either less with bromperidol, or equal to haloperidol (Itoh, 1985)

4.6.J Carbamazepine

4.6.J.1 Drug-induced psychosis, Inhalant

a) Carbamazepine demonstrated comparable efficacy to haloperidol in the treatment of inhalant-induced psychotic disorder (Hernandez- Avila et al, 1998). Patients received either 1 capsule of carbamazepine 2 milligrams (mg) 3 times daily (n=20) or 1 capsule of haloperidol 5 mg 3 times daily (n=20) for 5 weeks. Doses were increased at weekly intervals by 1 capsule if the patient failed to show a 25% decrease in th Brief Psychiatric Rating Scale (BPRS). At the end of the study, mean daily doses were carbamazepine 9 mg (serum level of 10.8 micrograms/liter) and haloperidol 21.7 mg. Similar improvements were found in both groups with 48.3% improvement in the carbamazepine group and 52.7% improvement in the haloperidol group.

4.6.K Chlorpromazine

Delirium

Drug-induced psychosis - Phencyclidine-related disorder

Schizophrenia

4.6.K.1 Delirium

a) Chlorpromazine (n=13) and haloperidol (n=11) were effective and had few side effects in the treatmer of delirium in AIDS patients in a double-blind study; lorazepam (n=6) was not effective and was associat with adverse effects (Breitbart et al, 1996a). Average doses for the first 24 hours of treatment were lorazepam 3 mg, chlorpromazine 50 milligrams, and haloperidol 1.4 milligram. There was significant improvement in the 2 neuroleptic-treated groups in the first 24 hours as measured by the Delirium Rating Scale scores (p less than 0.001 for both groups). Very little further improvement was seen after day 2. Delirium symptoms did not improve in the lorazepam-treated group. Cognitive status as measured by the Mini-Mental State scale improved in the chlorpromazine group (p less than 0.001) and haloperidol group (NS), but did not improve in the lorazepam group. Few extrapyramidal side effects were associated with either neuroleptic drug, but all lorazepam-treated patients developed adverse effects that led to the remc of this drug from the protocol. The authors recommend further study to confirm their finding that early intervention with low-dose neuroleptics is effective in managing delirium in AIDS patients (Breitbart et al,

1996a).

4.6.K.2 Drug-induced psychosis - Phencyclidine-related disorder

a) Haloperidol was reported more effective than chlorpromazine in treating signs of psychosis secondary phencyclidine in one uncontrolled report (Giannini & Eighan, 1984). Haloperidol 5 milligrams intramuscularly (IM) was given in 2 separate doses 20 minutes apart or chlorpromazine 50 milligrams IM was administered in 2 separate doses according to the same schedule. The authors suspect that the greater benefits of haloperidol were attributable to specificity for DA-2 presynaptic sites.

4.6.K.3 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo- controlled , fixed-dose and fixed-dose-ranging drug development trials, the minimum effective dose of haloperidol was 4 milligrams/day (equivalent to chlorpromazine 200 milligrams/day) (Woods SW, 2003).

b) Haloperidol was compared with placebo, chlorpromazine, diazepam, and imipramine as prophylactic agents to prevent relapse of schizophrenic patients. At the end of the three year trial, haloperidol and chlorpromazine significantly prolonged remission as compared to the other three treatments. Daily doses haloperidol were 3 milligrams; chlorpromazine doses were 75 milligrams (Nishikawa et al, 1982b).

4.6.K.4 Adverse Effects

a) Haloperidol, chlorpromazine, and sulpiride were compared in normal volunteers to test mood state (McClelland et al, 1990a). The twelve volunteers were assessed using sixteen visual analogue scales su as elapsed time estimation, tapping rate, body sway and tremor. The volunteers were divided into four groups: haloperidol (3 milligrams per day), chlorpromazine (50 milligrams per day), sulpiride (400 milligrams per day) and a placebo group. The results showed chlorpromazine and haloperidol users experienced reduced alertness and contentedness. Haloperidol reduced feelings of "calmness" in the volunteers. Sulpiride did not significantly alter vision in the volunteers. Haloperidol affected the informatic processing function, but did not affect motor ability and speed in the group taking this drug.

4.6.L Chlorprothixene

Schizophrenia

Tardive dyskinesia

4.6.L.1 Schizophrenia

a) Chlorprothixene was compared with (mean dose 251 milligrams/day; dose range 100 to 400 mg/day) haloperidol (mean dose 9 milligrams/day; dose range 5 to 16 mg/day) and placebo in a 3-week randomized, double-blind, crossover study of 34 patients with acute schizophrenia. There were no statistically significant differences in relation to efficacy (Marjerrison et al, 1971).

4.6.L.2 Tardive dyskinesia

a) The Nordic Dyskinesia Study Group (Anon, 1986) compared the effects of several neuroleptic drugs c tardive dyskinesia and parkinsonian symptoms in 33 chronic psychiatric patients in a crossover, randomized, open study. Treatment consisted of 6 months of therapy in each of 4 groups, preceded by a week, placebo-washout period. Treatment groups were chlorprothixene 132 to 142 milligrams/day, haloperidol 5.5 to 5.6 milligrams/day, perphenazine 16.8 to 24.2 mg/day, and haloperidol 11 milligrams/d in combination with biperiden 7 mg/day. Doses were chosen to be relatively equipotent according to established tables. Perphenazine, haloperidol, and haloperidol/biperiden all caused a reduction in tardive dyskinesia and an increase in parkinsonian symptoms. Chlorprothixene reduced tardive dyskinesia sligh and had no effect on parkinsonian symptoms. All drugs were equally effective at controlling psychotic symptoms. The authors concluded that long-term therapy with low-potency drugs presented a minimal ris of potentially irreversible tardive dyskinesia and a lower likelihood of inducing acute parkinsonian symptoms.

4.6.L.3 Adverse Effects

a) The Nordic Dyskinesia Study Group (Anon, 1986) compared the effects of several neuroleptic drugs c tardive dyskinesia and parkinsonian symptoms in 33 chronic psychiatric patients in a crossover, randomized, open study. Treatment consisted of 6 months of therapy in each of 4 groups, preceded by a week, placebo-washout period. Treatment groups were chlorprothixene 132 to 142 milligrams/day, haloperidol 5.5 to 5.6 milligrams/day, perphenazine 16.8 to 24.2 mg/day, and haloperidol 11 milligrams/d in combination with biperiden 7 mg/day. Doses were chosen to be relatively equipotent according to established tables. Perphenazine, haloperidol, and haloperidol/biperiden all caused a reduction in tardive dyskinesia and an increase in parkinsonian symptoms. Chlorprothixene reduced tardive dyskinesia sligh and had no effect on parkinsonian symptoms. All drugs were equally effective at controlling psychotic symptoms. The authors concluded that long-term therapy with low-potency drugs presented a minimal ris of potentially irreversible tardive dyskinesia and a lower likelihood of inducing acute parkinsonian symptoms.

4.6.M Clocapramine

4.6.M.1 Schizophrenia

a) In 26 chronic schizophrenia patients, clocapramine (75 mg/day initially, to a maximum of 700 mg/day) was compared with haloperidol (3 mg/day, to a maximum of 30 mg/day) in a double-blind, crossover stud lasting 28 weeks. There was no significant difference between the 2 drugs. Although no side effects were significant enough to terminate therapy, clocapramine produced fewer and milder side effects. The author concluded that clocapramine was equivalent to haloperidol in antipsychotic efficacy but superior in terms safety (Yamagami, 1985).

4.6.N Clomipramine

4.6.N.1 Autistic disorder

a) Among subjects who completed full therapeutic trials of haloperidol and clomipramine for treatment of autistic disorder, the two drugs were comparable; however, haloperidol was superior to clomipramine on intent-to-treat basis, because of the large proportion of patients who were unable to complete clomipram treatment due to side effects and behavior problems. In a double- blind, placebo-controlled crossover study, 36 subjects with a DSM- IV diagnosis of autism were given placebo, haloperidol, and clomipramin for periods of 7 weeks each. Clomipramine was begun at 25 milligrams (mg) at bedtime for 2 days and increased to 25 mg twice a day for 2 days, 25 mg 3 times a day for 2 days, and finally 50 mg twice a day Haloperidol was begun at 0.25 mg at bedtime for 2 days and increased to 0.25 mg twice a day for 2 days 0.25 mg 3 times a day for 2 days, and finally 0.5 mg twice a day. For both drugs, adjustments of the final dose could be made as clinically indicated. During week 7 of each period, drug dosages were tapered in preparation for the next treatment. Percentages of subjects completing each trial were 70% for haloperid 38% for clomipramine, and 66% for placebo. In the haloperidol trials, 7 of 10 discontinuations were for si effects (fatigue or lethargy, dystonia, depression) and the remainder for behavior problems. With clomipramine, 12 of 20 discontinuations were for side effects (fatigue or lethargy, tremors, tachycardia, insomnia, diaphoresis, nausea or vomiting, and decreased appetite) and the remainder for behavior problems. In the placebo trials, 10 of 11 discontinuations were for behavior problems. On an intent-to-tre basis, significant improvement in irritability (p less than 0.05) and hyperactivity (p less than 0.05) was see with haloperidol only (versus baseline). No differences among treatments were observed for stereotypic behavior, lethargy, or inappropriate speech. When data only from patients completing full therapeutic tria were assessed, both haloperidol and clomipramine were superior to baseline with regard to irritability and stereotypy (Remington et al, 2001).

4.6.O Clonazepam

Gilles de la Tourette's syndrome

Psychotic disorder

4.6.O.1 Gilles de la Tourette's syndrome

a) In a retrospective study, haloperidol, clonazepam, and clonidine were compared in the treatment of 8 patients suffering multifocal tic disorders, either Tourette's syndrome or chronic motor tics. The most effective drug for treating Tourette's syndrome was haloperidol, mean dose of 5.8 milligrams/day. The m effective drug for treating chronic motor tics was clonazepam, mean dose of 4.8 milligrams/day. Clonidin was effective in six patients, but only in combination with either haloperidol or clonazepam. The authors recommend treatment with clonazepam first, due to the risk of tardive dyskinesia associated with haloperidol. Then clonazepam in combination with clonidine, if clonazepam alone is not effective. Then in nonresponsive patients haloperidol should be used (Troung et al, 1988a).

4.6.O.2 Psychotic disorder

a) Clonazepam and haloperidol (both given by the intramuscular route) were compared for tranquilizatio of agitated psychotic patients with manic symptoms. Fifteen patients received three doses of either clonazepam 1 to 2 milligrams or haloperidol 5 to 10 milligrams at 30 minute intervals. Both drugs successfully controlled the agitation, but haloperidol gave a more rapid response (Chouinard et al, 1993a Better results may have been obtained by administering single higher doses of intramuscular (IM) clonazepam: 4 to 5 milligrams of IM clonazepam every 30 to 60 minutes seems to be effective, safe and rapid for the control of acute psychotic agitation and onset of action may be similar to IM haloperidol (Benazzi & Mazzoli, 1994).

4.6.P Clonidine

4.6.P.1 Gilles de la Tourette's syndrome

a) In a retrospective study, haloperidol, clonazepam, and clonidine were compared in the treatment of 8 patients suffering multifocal tic disorders, either Tourette's syndrome or chronic motor tics. The most effective drug for treating Tourette's syndrome was haloperidol, mean dose of 5.8 mg/day. The most effective drug for treating chronic motor tics was clonazepam, mean dose of 4.8 mg/day. Clonidine was effective in six patients, but only in combination with either haloperidol or clonazepam. The authors recommend treatment with clonazepam first, due to the risk of tardive dyskinesia associated with haloperidol. Then clonazepam in combination with clonidine, if clonazepam alone is not effective. Then i nonresponsive patients haloperidol should be used (Troung et al, 1988).

4.6.Q Clozapine

Hostile behavior

Schizophrenia, Refractory

4.6.Q.1 Hostile behavior

a) Clozapine reduced hostility in patients with schizophrenia and was superior to haloperidol and risperidone in that regard. One hundred fifty seven patients with a diagnosis of schizophrenia or schizoaffective disorder and a history of poor response to drug treatment were randomly assigned to receive clozapine, olanzapine, risperidone, or haloperidol in cross-titration with the antipsychotic drug us prior to the start of the study. Concomitant mood stabilizers and antidepressants had been phased out earlier. Daily doses of olanzapine, risperidone, and haloperidol were escalated within the first week to th target doses of 20, 8, and 20 milligrams (mg), respectively. Patients receiving clozapine were scheduled achieve the target daily dose of 500 mg on day 24. Doses remained fixed for the remainder of the initial 8 week period. In a second (6-week) period, doses were allowed to vary: 200 to 800 mg for clozapine, 10 t 40 mg for olanzapine, 4 to 16 mg for risperidone, and 10 to 30 mg for haloperidol. Hostility, measured by the hostility item of the Positive and Negative Syndrome Scale (PANSS), improved significantly (in comparison to baseline) in the clozapine group only (p=0.019). This effect was independent of effects on psychotic symptoms (delusional thinking, hallucinations) or on sedation. The effect of clozapine on hostil was superior to that of haloperidol (p=0.021) or risperidone (p=0.012) but not to that of olanzapine (Citro et al, 2001).

4.6.Q.2 Schizophrenia, Refractory

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine i patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvemer over time in global neurocognitive score was seen for olanzapine and risperidone. In general executive a perceptual organization and in processing speed and attention, improvement was seen with olanzapine. simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modes Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocationa functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002b).

b) Schizophrenic patients treated with clozapine were more likely to be rated as improved and less likel discontinue treatment due to lack of efficacy than a matched group treated with haloperidol. Seventy-one patients between the ages of 20 to 55 years with a diagnosis of schizophrenic or schizoaffective disorde were enrolled in this 6-month, double-blind, prospective, randomized trial. These outpatients, were documented as poor or partial responders to antipsychotic therapy and had a rating of at least moderate 1 of 4 Brief Psychiatric Rating Scale (BSRS) items (conceptual disorganization, suspiciousness, hallucinatory behavior, or unusual thought content). The two major outcome measures for this study wer time to discontinuation of study medication due to lack of clinical response and 20% improvement in the item BPRS cluster during two consecutive rating periods. The haloperidol group (n=34) was targeted to receive 10 milligrams (mg)/day, along with 2 mg/day of benztropine, while the clozapine group was to receive 500 mg/day (n=37). Doses could be adjusted in either group to a range of 4 to 16 mg/day for the haloperidol group and 200 to 800 mg/day for the clozapine group depending upon the patient's clinical course. At the end of 29 weeks, 50.5% of the haloperidol-treated group (mean dose 18.9 mg/day) and 11.6% of the clozapine group (mean dose 523 mg/day) had discontinued treatment due to lack of efficac (p=0.02). The mean BPRS ratings at the end of the study were 3.2 and 4.2 for the clozapine and haloperidol groups respectively (p less than 0.001). There was no difference found between the groups a

measured by the Schedule for Assessment of Negative Symptoms (SANS) score using the sum of the 4 global ratings. Haloperidol-treated patients experienced more dry mouth and decreased appetite, while t clozapine-treated group reported more salivation, sweating, and dizziness. Three haloperidol and 2 clozapine-treated patients dropped-out of the study due to adverse drug effects (Kane et al, 2001).

c) Clozapine exhibited improved efficacy with fewer adverse effects as compared to haloperidol in a randomized, double-blind, 12-month study conducted at Veterans Affairs medical centers (n=423 with refractory schizophrenia). Using intention-to-treat analysis, schizophrenia symptom scores were significantly improved with clozapine over haloperidol at 6 weeks (p equals 0.008) and 6 months (p equa 0.001), with no statistical difference in quality of life measures. When crossover cases were excluded, quality of life measures were significantly better in the clozapine group at 3 months and 1 year (p equals 0.02). Clozapine also reduced scores for tardive dyskinesia, akathisia and extrapyramidal syndrome. Clozapine's higher costs for drug acquisition and laboratory monitoring were offset by decreased inpatie hospital stays (Rosenheck et al, 1997).

d) These investigators later evaluated compliance with clozapine versus haloperidol. The results confirm that clozapine established better medication continuation and regimen compliance. Patients taking clozapine continued taking the study drug for a mean of 35.5 weeks as compared with on 27.2 weeks among haloperidol patients (p=0.0001). No differences were found between the groups in the proportion prescribed pills that were returned at any time point. Continuation with medication is greater with clozapi than haloperidol and is partly explained by greater symptom improvement and reduced side effects. No differences were discovered in regimen compliance (Rosenheck et al, 2000).

4.6.Q.3 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher inciden of PANCREATITIS than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean do 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003b

b) No significant difference was found in sexual disturbances occurring in clozapine-treated versus haloperidol-treated patients (Hummer et al, 1999). Inpatients receiving either clozapine (n=100) or haloperidol (n=53) were screened. The most common adverse event in both groups was diminished sexu desire occurring in 4 (33.3%) of the haloperidol-treated women, 26 (63.4%) of the haloperidol-treated me 7 (28%) of the clozapine-treated women, and 43 (57.3%) of the clozapine-treated men. Among women treated, amenorrhea occurred in 4 (33.3%) of the haloperidol patients and in 3 (12%) of the clozapine patients. Larger studies may be needed to show differences.

c) In a prospective study, the incidence of alanine aminotransferase (ALT) elevation to more than twice upper normal limit was statistically greater with clozapine (37%, n=167) than with haloperidol (17%, n=7 Among those receiving clozapine, the rates of elevations in aspartate aminotransferase (AST) and gamm glutamyl transpeptidase (GGT) to more than twice the upper normal limit were 12% and 15%, respective No such increases in bilirubin or alkaline phosphatase occurred in clozapine-treated patients. These effe were transient in the majority of patients (disappearing by week 13) with no clinical manifestations report (Hummer et al, 1997).

4.6.R Diazepam

4.6.R.1 Schizophrenia

a) Haloperidol was compared with placebo, chlorpromazine, diazepam, and imipramine as prophylactic agents to prevent relapse of schizophrenic patients. At the end of the three year trial, haloperidol and chlorpromazine significantly prolonged remission as compared to the other three treatments. Daily doses haloperidol were 3 mg; chlorpromazine doses were 75 mg (Nishikawa et al, 1982a).

4.6.S Diphenhydramine

4.6.S.1 Dementia - Restlessness and agitation

a) Oxazepam, haloperidol, and diphenhydramine were equally efficacious in the treatment of agitated behavior in 59 elderly demented inpatients in an 8-week, double-blind study (Coccaro et al, 1990a). The mean daily doses were oxazepam 30 +/- 19.4 mg, haloperidol 1.5 +/- 0.9 mg, and diphenhydramine 81.3 +/- 48.5 mg. Chloral hydrate was given if the study medication did not adequately control agitation. Ratin scale scores indicated that diphenhydramine and haloperidol were more effective than oxazepam, but nc of the differences in scores among the groups was significant. Only modest improvement was seen in terms of agitated behavior and activities of daily living. There was only a slight decrease in the use of chloral hydrate in all 3 groups during the study and no difference among the groups.

4.6.T Droperidol

Agitation

Postoperative nausea and vomiting

4.6.T.1 Agitation

a) In equal doses, intramuscular (IM) droperidol controlled agitation more rapidly than haloperidol withou difference in side effect occurrence. A randomized, double-blind, prospective study (Thomas et al, 1992) compared haloperidol versus droperidol for chemical restraint in agitated or violent patients. Sixty-eight patients randomly received 5 mg of haloperidol or droperidol by the intravenous (IV) or IM routes and we monitored for behavior control on a combativeness scale ranging 1 to 5. Patients were also monitored fo side effects and vital sign changes. Patients were compared at 5, 10, 15, 30 and 60 minutes after injectic of drug. Intramuscular droperidol controlled combativeness significantly more than IM haloperidol at ten, and 30 minutes while no significant difference was noted at 60 minutes in equal doses. No significant difference in behavior control was seen when the drugs were given IV.

b) In a double-blind study (Resnick & Burton, 1984), intramuscular droperidol and haloperidol were compared in the treatment of 27 acutely agitated patients. Patients received either droperidol 5 milligram or haloperidol 5 milligrams intramuscularly, and were psychologically evaluated at 15 minutes following initial injection and at 30-minute intervals for 3 hours thereafter. At 30 minutes following the initial treatme 36% of the droperidol-treated and 81% of the haloperidol-treated patients required a second injection. Bo agents were well tolerated. The investigators recognize the greater sedative effect associated with droperidol, and admit that this property may explain the more rapid control of patients in the droperidol-treated group.

4.6.T.2 Postoperative nausea and vomiting

a) Intramuscular (IM) droperidol 5 mg was compared with a single IM dose of haloperidol 2 mg and prochlorperazine 10 mg as a premedicant in a group of 65 patients. The incidence of vomiting with droperidol at 0.5 to 1 hour postoperatively was 50% compared to 7% with haloperidol. However, droperic exerted its antiemetic effect up to 24 hours as compared with haloperidol and prochlorperazine, which ha a duration of only 4 hours. Ideally a combination of droperidol and haloperidol should be used to provide rapid onset with a long duration of effect (Loeser et al, 1979).

4.6.U Flunitrazepam

4.6.U.1 Aggressive behavior - Psychotic disorder

a) Intramuscularly administered flunitrazepam and haloperidol were similarly effective in controlling agitated or aggressive behavior in emergency psychiatric situations (Dorevitch et al, 1999). In the study group of 28 patients, 19 with schizophrenia, 7 with schizoaffective disorder, and 2 with bipolar disorder), intramuscular injection of either flunitrazepam 1 milligram (mg) or haloperidol 5 mg during an acute aggressive outburst significantly reduced Overt Aggression Scale scores (p less than 0.001, time effect). 90 minutes post-administration, the rate of response reduction in total Overt Aggression Scale score was 80% (12/15) in the flunitrazepam group and 92% (12/13) in the haloperidol group (p=0.34). Flunitrazepar reached its maximal antiaggressive effect 30 minutes after administration, while haloperidol increased its activity more gradually, and the difference in antiaggressive effect over time was significant (p less than 0.01, time-by-group interaction). In both groups, the reduction in aggression level lasted for at least 120 minutes after drug administration. Each drug induced marked sedation in 3 patients.

4.6.V Flupenthixol

Psychotic disorder

Schizophrenia

4.6.V.1 Psychotic disorder

a) An open trial of flupenthixol versus haloperidol was conducted in 40 acutely psychotic patients in an open, 28-day controlled study. Patients received oral flupenthixol 32 to 192 milligrams/day (mean dose 1 mg/day) or oral haloperidol 2 to 50 milligrams/day (mean dose 18 mg/day) as required for control of psychotic symptoms. While global assessment revealed a significant reduction in severity of symptoms i both groups, 5 patients receiving flupenthixol had complete or almost complete remission of symptoms a the 28-day assessment, whereas none of those taking haloperidol had achieved this degree of remissior In addition, anxiety/depression scores improved considerably with flupenthixol, whereas haloperidol had little effect. Flupenthixol also had an activating effect, but haloperidol did not. The authors felt that while both drug were effective, flupenthixol had a faster onset of symptom control than haloperidol. However, a these doses it caused more extrapyramidal symptoms than haloperidol (Parent & Toussaint, 1983).

4.6.V.2 Schizophrenia

a) Haloperidol decanoate (mean dose 131 to 151 milligrams/4 weeks) was compared with flupenthixol

decanoate (mean dose 56 to 66 milligrams/4 weeks) in 32 schizophrenic patients in a 48 week, double-blind, crossover study. Side effects of the two drugs were comparable, but therapeutic efficacy near the e of each dosing period was significantly better for haloperidol than flupenthixol. The investigators recommended a shorter dosing interval for flupenthixol (Eberhard & Hellbom, 1986).
b) Haloperidol was reported superior to flupenthixol in producing lower levels of psychopathology in chronic schizophrenic inpatients in a double-blind, crossover study (Ehmann et al, 1987). Average doses haloperidol and flupenthixol at the time of final assessments were 33 milligrams daily (range, 10 to 84 milligrams) and 27 mg daily (range, 8 to 84 mg daily), respectively. Significantly less psychiatric disturba was observed during haloperidol therapy as determined by the Rating Scale of the Mental State (RSMS) and the BPRS Agitation-Excitement Scale: Less psychopathology was also observed with haloperidol or total scores for BPRS but this was not significant. Side effects were similar with both agents, primarily extrapyramidal symptoms. In addition, no evidence was observed to suggest that flupenthixol is useful in "activating" chronic schizophrenic patients, or in alleviating affective symptoms.

4.6.W Fluphenazine

Gilles de la Tourette's syndrome

Schizophrenia

4.6.W.1 Gilles de la Tourette's syndrome

a) In 23 patients with Tourette's syndrome who had previously been treated with haloperidol, fluphenazi treatment was equally efficacious but fluphenazine produced fewer side effects. The previous treatment consisted of haloperidol 1.5 to 9 milligrams/day for 2 months to 9 years and was replaced with fluphenzir 1 to 16 milligrams/day for 1 month to 2.75 years (Singer et al, 1986).

4.6.W.2 Schizophrenia

a) Haloperidol decanoate and fluphenazine decanoate were equally efficacious in an 8-month study in schizophrenic patients (Chouinard et al, 1984). Haloperidol decanoate was given in doses of 15 to 900 milligrams (median, 225 mg) every 2 to 4 weeks with fluphenazine decanoate administered in doses of 2 to 300 milligrams per injection (median, 75 mg) every 2 to 4 weeks. No significant differences between th 2 drugs were observed with regard to therapeutic efficacy; however, tardive dyskinetic movements of the tongue and jaw were more severe in haloperidol-treated patients.
b) Haloperidol decanoate was compared with fluphenazine decanoate in 38 schizophrenic inpatients in parallel, single-blind study which lasted for 60 weeks. Doses were based on standard relative potency assignments calculated from previous neuroleptic medication, and haloperidol and fluphenazine were considered equipotent. The haloperidol patients had better mental states but poorer ward behavior and lower parkinsonism scores compared with the fluphenazine group (McKane et al, 1987).

4.6.X Imipramine

4.6.X.1 Schizophrenia

a) Haloperidol was compared with placebo, chlorpromazine, diazepam, and imipramine as prophylactic agents to prevent relapse of schizophrenic patients. At the end of the three-year trial, haloperidol and chlorpromazine significantly prolonged remission as compared to the other three treatments. Daily doses haloperidol were 3 milligrams; chlorpromazine doses were 75 mg (Nishikawa et al, 1982).

4.6.Y Lithium

4.6.Y.1 Aggressive behavior

a) The same results of the same study were published in two different journals (Platt et al, 1984, 1984a) (Campbell et al, 1984). They compared the effects of lithium (mean dose 1,166 mg/day) to haloperidol (mean dose 2.95 mg/day) on cognition in hospitalized school-age children with conduct disorder. After a two week placebo period to eliminate placebo responders, 61 children were divided into haloperidol, lithium, or placebo groups. Both drugs gave better responses by a variety of tests and were equally effective. Haloperidol produced significantly more side effects.

4.6.Z Lorazepam

Agitation - Psychotic disorder

Delirium

4.6.Z.1 Agitation - Psychotic disorder

a) The combination of haloperidol and lorazepam was suggested to be more effective than lorazepam alone in agitated patients presenting to the psychiatric emergency service (Bieniek et al, 1998). Patients who met clinical criteria for the use of chemical restraints and had a minimum score of 4 on the Overt Aggression Scale received either lorazepam 2 milligrams (mg) (n=11) or haloperidol 5 mg and lorazepan mg (n=9). Combination therapy was significantly better than lorazepam alone after 1 hour according to th Overt Aggression Scale and the visual analog scale (p less than 0.05). However, on the Clinical Global Impressions severity scale, the comparison was not significant. With repeated measures of analyses of variance, both groups improved over time.

b) Repeated doses of either lorazepam 2 milligrams or haloperidol 5 milligrams were equally effective fo the early treatment of acute agitation in psychotic patients (Battaglia et al, 1997). In a double-blind, randomized study, 98 patients received either intramuscular lorazepam, haloperidol, or both. Patients received 1 to 6 injections in a 12-hour period depending upon clinical need. Effective symptom reduction was achieved in each treatment group with significant decreases from baseline at every hourly evaluatio (p less than 0.01). Mean differences on the Agitated Behavior Scale and modified Brief Psychiatric Ratin Scale suggested that tranquilization was most rapid in patients receiving the combination therapy (p less than 0.05).

4.6.Z.2 Delirium

a) Chlorpromazine (n=13) and haloperidol (n=11) were effective and had few side effects in the treatmer of delirium in AIDS patients in a double-blind study; lorazepam (n=6) was not effective and was associate with adverse effects (Breitbart et al, 1996). Average doses for the first 24 hours of treatment were lorazepam 3 mg, chlorpromazine 50 mg, and haloperidol 1.4 mg. There was significant improvement in t 2 neuroleptic-treated groups in the first 24 hours as measured by the Delirium Rating Scale scores (p les than 0.001 for both groups). Very little further improvement was seen after day 2. Delirium symptoms did not improve in the lorazepam-treated group. Cognitive status as measured by the Mini-Mental State scal improved in the chlorpromazine group (p less than 0.001) and haloperidol group (NS), but did not improv in the lorazepam group. Few extrapyramidal side effects were associated with either neuroleptic drug, bu all lorazepam-treated patients developed adverse effects that led to the removal of this drug from the protocol. Breitbart et al recommend further study to confirm their finding that early intervention with low-dose neuroleptics is effective in managing delirium in AIDS patients.

4.6.AA Loxapine

4.6.AA.1 Schizophrenia

a) Intramuscular loxapine and intramuscular haloperidol at the usual therapeutic doses were shown to b comparable in the initial management of hostile and aggressive schizophrenic patients. Both drugs resul in rapid improvement in symptoms of hostility and uncooperativeness, and produced desirable sedation. The maintenance of therapeutic response after conversion to oral medication was also comparable between the 2 drugs (Tuason, 1986).

4.6.AB Melperone

4.6.AB.1 Anxiety

a) The effects of melperone, chlorpromazine, haloperidol, and diazepam on artificially-induced anxiety were compared in normal subjects. Autonomic (skin conductance) response evoked during aversive classical conditioning was measured in eleven healthy subjects. Single oral doses of placebo, melperone 10 mg, melperone 50 mg, chlorpromazine 50 mg, diazepam 10 mg, and haloperidol were administered randomly to each member of the study group. There was a minimum of 10 days between tests. Judging from the data which indicates a subject's anxiety level in this experimental setting, ie, skin conductance level during habituation and reinforcement, its pattern of changes and fluctuations, etc, it may be conclud that diazepam, the higher (50 mg) dose of melperone and chlorpromazine are effective anxiolytics. Whereas melperone 50 mg reduced skin conductance level, and eliminated anticipatory responses, melperone 10 mg (as well as haloperidol) had no effect upon conditioned and unconditioned responses (Molander, 1982).

4.6.AC Mesoridazine

4.6.AC.1 Schizophrenia

a) Mesoridazine was compared with haloperidol in a group of 39 schizophrenic patients in an attempt to correlate the response seen in the first 48 hours, as measured by the Dysphoric Response Index (DRI) v ultimate outcome of therapy (White et al, 1981). The daily dosage of haloperidol was 2 to 100 milligrams (mean 28 mg) and of mesoridazine was 100 to 800 milligrams (mean 421 mg). The outcome as measure by BPRS (Brief Psychiatric Rating Scale and CGI (Clinical Global Impressions Scale), was equivalent fo the two regimens. Side effects for the two regimens were significantly different. Correlation of the DRI to ultimate outcome was poor.

4.6.AD Metoclopramide

4.6.AD.1 Chemotherapy-induced nausea and vomiting

a) Metoclopramide (2 mg/kg) was compared with haloperidol (3 mg total dose) for the control of cisplatir induced emesis (Grunberg et al, 1984). Both drugs were administered intravenously two hours for five doses beginning one-half hour before cisplatin therapy. Twenty-eight patients completed the cross-over study. Metoclopramide resulted in 1.92 vomiting episodes (range 0-5) with 36% exhibiting no vomiting. Haloperidol resulted in 3.04 vomiting episodes (range 0-8) with 20% having no vomiting. Metoclopramide showed a minor but not significant advantage.

4.6.AE Midazolam

4.6.AE.1 Psychotic disorder

a) A single-blind study of fifteen healthy male schizophrenic patients found intramuscular administration 250 milligrams (mg) of sodium amytal or 5 mg of midazolam significantly more effective than 10 mg of haloperidol in controlling motor agitation. Midazolam and sodium amytal were also more effective than haloperidol in controlling hostility, though this did not reach statistical significance. No significant differen in controlling auditory hallucinations or flight of ideas was noted (Wyant et al, 1990a).

4.6.AF Molindone

Psychotic disorder

Tardive dyskinesia

4.6.AF.1 Psychotic disorder

a) Molindone and haloperidol were comparable in a study of 24 acutely psychotic patients (Binder et al, 1981). The dose of molindone was 25 milligrams 2 to 4 times/day (+ as needed) the dose of haloperidol was 5 milligrams 2 to 4 times/day (+ as needed). Both drugs were given intramuscularly. Evaluation of results was based on Brief Psychiatric Rating Scale, Target Symptom Rating Scale, and Clinical Global Impression.

b) Molindone (up to 225 milligrams/day by injection followed by up to 500 mg/day orally) was compared with haloperidol (up to 45 milligrams/day by injection followed by 100 mg/day orally) in 35 acutely schizophrenic patients in a double-blind study. There were no significant differences in efficacy or safety over the 4 weeks of the study (Escobar et al, 1985).

4.6.AF.2 Tardive dyskinesia

a) Haloperidol was more effective than molindone at masking tardive dyskinesia which was exacerbatec by withdrawal of neuroleptic medication. Molindone was compared with haloperidol with regard to their ability to mask neuroleptic withdrawal-exacerbated tardive dyskinesia, using the theoretical proposition th agents less able to mask are less dyskinetogenic (Glazer et al, 1985). In a parallel, double-blind study, 1 patients were given either molindone or haloperidol in doses ranging from 50% to 200% dose equivalenc to the neuroleptics from which they had been removed, at a point after discontinuation where involuntary movements showed a significant increase. At doses that were equivalent to 200% of the prestudy neuroleptic dose, molindone was shown to be less able to mask neuroleptic withdrawal-exacerbated tarc dyskinesia than was haloperidol, thereby suggesting lower dyskinetogenic potential.

4.6.AG Olanzapine

Adverse reaction to cannabis - Drug-induced psychosis

Mania

Schizophrenia

Tardive dyskinesia

4.6.AG.1 Adverse reaction to cannabis - Drug-induced psychosis

a) Olanzapine was as effective as haloperidol in the treatment of cannabis-induced psychotic disorder (Berk et al, 1999). In a double- blind study, patients with a psychotic episode associated with cannabis u were randomized to receive either olanzapine 10 milligrams (n=15) or haloperidol 10 mg (n=15). After 4 weeks there was a significant improvement in both groups as compared to baseline measured on the Bri Psychiatric Rating Scale (p=0.0002 for olanzapine, p=0.0001 for haloperidol). There was no significant

difference between the 2 groups. Olanzapine was associated with fewer extrapyramidal side effects.

4.6.AG.2 Mania

a) Olanzapine and haloperidol therapies were similarly effective in the treatment of acute mania in patie with bipolar disorder. In a randomized, double-blind study, patients with bipolar I disorder, mixed or mani episode and a Young-Mania Rating Scale (Y-MRS) score of at least 20 received either olanzapine (5 to 2 milligram (mg)/day) or haloperidol (3 to 15 mg/day) at flexible doses for 6 weeks. Patients showing symptom improvement entered a 6-week continuation phase in which they received ongoing treatment. Symptomatic remission was defined as a Y-MRS score of 12 or less and a Hamilton Rating Scale for Depression score (HAM-D) of 8 or less at week 6. Symptomatic remission rates for patients in the olanzapine group were similar to those of patients in the haloperidol group at week 6 (52.1% vs 46.1%, respectively; p=NS) and week 12 (51.7% vs 43.8%, respectively; p=NS). However, olanzapine treatment produced greater improvements in health- related quality of life factors as compared with haloperidol treatment (Shi et al, 2002).

4.6.AG.3 Schizophrenia

a) SUMMARY: Olanzapine is more effective than haloperidol for the treatment of negative symptoms of schizophrenia; both agents are similarly effective in managing positive symptoms. Olanzapine is less like to induce extrapyramidal reactions or elevation of serum prolactin levels.

b) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine i patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvemer over time in global neurocognitive score was seen for olanzapine and risperidone. In general executive a perceptual organization and in processing speed and attention, improvement was seen with olanzapine. simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modes Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocationa functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002).

c) Olanzapine was at least as effective as and safer than haloperidol for the treatment of schizophrenia a large population of Japanese patients with positive and negative symptoms resistant to treatment with typical antipsychotics. In a randomized, double-blind trial, 182 patients were given olanzapine, starting at milligrams (mg) per day and increased to a maximum of 15 mg/day, or haloperidol, starting at 4 mg/day a increasing to 12 mg/day, for 8 weeks. Mean modal daily doses were 10.5 mg for olanzapine and 8 mg fo haloperidol. The proportion of olanzapine-treated patients who showed moderate to remarkable improvement was 44.5%, compared to 40.5% of haloperidol-treated patients. The 95% confidence interv was -8% to 16% favoring olanzapine. Thus, olanzapine was not inferior to haloperidol in efficacy. Total a subscale scores on the Positive and Negative Symptom Scale (PANSS) were numerically better in the olanzapine group than in the haloperidol group, but only on the negative symptoms subscale did the difference reach statistical significance (p=0.024). Eighty-one percent of olanzapine-treated patients and 66% of haloperidol-treated patients finished the study, with fewer dropping out of the olanzapine group because of adverse events or abnormal laboratory values (8 vs 22). Olanzapine-treated patients showe an improvement in extrapyramidal symptoms, whereas haloperidol-treated patients showed a worsening less than 0.001). Treatment-emergent parkinsonism occurred in 3.2% of the olanzapine group and 18.8% of the haloperidol group. By the end of treatment, parkinsonism had resolved in all patients in the olanzapine group but was sustained in 7.8% of the haloperidol group. There was a significantly greater incidence of insomnia, akathisia, tremor, anorexia, increased salivation, bradykinesia, abnormal gait, nausea, and weight decrease in haloperidol-treated patients than in olanzapine-treated patients. Only weight gain was significantly greater with olanzapine (0.96 kilogram vs -0.71 kilogram, p less than 0.001) Thirty-two percent of olanzapine-treated patients showed no adverse drug reaction and no laboratory abnormality, compared to 15.5% of haloperidol-treated patients (p=0.008) (Ishigooka et al, 2001).

d) Olanzapine has been at least as effective as haloperidol, each given for six weeks, in the treatment o schizophrenia (Tollefson et al, 1997); (Beasley et al, 1996)(Anon, 1996; Anon, 1995). Overall improveme based on Brief Psychiatric Rating Scale (BPRS) total scores, has been greater with olanzapine; this reached significance in the largest trial (Anon, 1996). Both agents have produced similar decreases in positive symptoms, and the superior overall improvement with olanzapine is attributed to a greater reduction in negative symptoms in these patients, particularly in higher dosages (12.5 to 17.5 mg daily); decreases in negative symptoms have been significantly greater with olanzapine on the Scale for the Assessment of Negative Symptoms (SANS) and Positive and Negative Syndrome Scale (PANSS), although significance was not achieved on the BPRS-negative scale in one study (Beasley et al, 1996). Significantly more patients have demonstrated greater than 80% improvement in BPRS-total scores with olanzapine, whereas the percentage with lower levels of improvement has not always differed significant

between drugs.
e) Intramuscular (IM) olanzapine successfully treated acutely agitated patients with schizophrenia in 3 clinical trials. Two open-label, single-blind trials evaluated 108 patients receiving fixed or variable doses 2.5, 5.0, 7.5, or 10.0 milligram (mg) given as 1 to 4 injections daily (QD) for 3 days, followed by 10 to 20 orally (PO) QD for 2 days. Response was assessed using the Brief Psychiatric Rating Scale (BPRS); the positive subscale improved during both IM and PO Administration (no statistical analysis was performed) The third study was a multicenter, double-blind, placebo-controlled trial that compared IM olanzapine wit IM haloperidol in the treatment of acute agitation. Patients (n=311) received up to 3 doses of olanzapine (10 mg), haloperidol (7.5 mg) or placebo in 24 hours. Thereafter, patients were treated with oral olanzapi (5 to 20 mg QD) or oral haloperidol (5 to 20 mg QD) for 4 days. Patients treated with IM olanzapine or haloperidol showed significantly greater improvement over placebo at 2 and 24 hours as measured by th BPRS positive subscale, but no differences were observed between olanzapine- and haloperidol-treated patients. Patients treated with intramuscular olanzapine continued to improve to day 5; but, there was nc significant difference between patients treated with IM drug between baseline and day 5 (Jones et al, 20
f) In a study of 300 patients with schizoaffective disorder, olanzapine treated patients showed significant greater improvement than haloperidol treated patients on the Brief Psychiatric Rating Scale (BPRS) total (p=0.002), Positive and Negative Syndrome Scale (PANSS) total (p=0.003), PANSS negative (p=0.006), and Montgomery-Asberg Depression Rating Scale (MADRS) total (p less than 0.001). Patients were take from a larger prospective, double blind study. Patients were assessed weekly for a six week acute phase with responders followed for up to 1-year. Among acute phase patients with bipolar subtype, olanzapine to 20 milligrams) was superior to haloperidol (5 to 20 milligrams) in the BPRS (p=0.012), PANSS negativ (p=0.031) and total (p=0.028), and MADRS (p less than 0.001); however, in depressed subtype patients, no significant differences were seen when compared to haloperidol treated patients. During the double-blind extension phase, the only significant difference between treatment groups was in the MADRS total score in favor of olanzapine (p=0.045). Extrapyramidal symptoms were less severe among olanzapine treated patients (p=0.016), but weight gain was more problematic (p=0.032) (Tran et al, 1997).
g) In a 6-week randomized study of 83 patients with first-episode psychosis (schizophrenia, schizophreniform disorder, or schizoaffective disorder), patients receiving olanzapine showed significantl greater improvement on the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Symptoms Scale (PANSS) as compared to patients receiving haloperidol. Patients greater than 45 years age at onset of symptoms with a disease duration of greater than 5 years received olanzapine or haloperidol 5 milligrams (mg) per day and adjusted every 7 days within the range of 5 to 20 mg per day. the BPRS, 67.2% of olanzapine treated patients experienced a 40% or greater improvement from baseli compared to 29.2% of haloperidol treated patients (p=0.003). Olanzapine treated patients also improved more on the PANSS total score (p=0.02) and positive symptom score (p=0.03) compared to haloperidol treated patients. Using the Simpson-Angus scale, olanzapine patients showed improvement in extrapyramidal symptoms, whereas haloperidol treated patients worsened (p less than 0.001). Somnoler was more common in olanzapine treated patients, whereas akathisia and hypertonia were more commor with haloperidol (Sanger et al, 1999).
h) Olanzapine showed a superior and broader spectrum of efficacy over haloperidol in the treatment of schizophrenia and also had a more favorable safety profile (Tollefson et al, 1997). In a large internationa multicenter double-blind trial, olanzapine (N=1336) was compared to haloperidol (N=660) over 6 weeks. Starting doses were 5 milligrams (mg) for both drugs which could be increased by 5 mg increments at th investigator's discretion to a maximum of 20 mg/day. Olanzapine was significantly superior to haloperido on the Brief Psychiatric Rating Scale (p less than 0.02), the Positive and Negative Syndrome Scale (p=0.05), the clinical Global Impression severity score (p less than 0.03), and the Montgomery-Asberg Depression Rating Scale total score (p=0.001). Significant advantages were also seen in the extrapyramidal profiles and effects on prolactin levels. Further analyses revealed that depressive signs a symptoms were also better controlled with olanzapine therapy (Tollefson et al, 1998). On the Montgomer Asberg Depression Rating Scale, olanzapine was significantly more effective than haloperidol (p = 0.001
i) In multiple clinical trials of olanzapine, the incidence of self-directed aggression among patients receiv olanzapine, haloperidol, or placebo, was not significantly different (Keck et al, 2000). These trials indicate a significantly greater improvement in suicidal thoughts in olanzapine-treated patients compared with haloperidol-treated patients. Another analysis demonstrated a 2.3-fold reduction in the annual suicide attempt rate among chronic psychotic patients receiving olanzapine versus haloperidol.

4.6.AG.4 Tardive dyskinesia
a) Olanzapine was associated with a lower incidence of tardive dyskinesia when compared to haloperid (Tollefson, 1997a). Data combined from 3 controlled and blinded studies evaluating patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder treated with olanzapine (n=707) or haloperidol (n=197) were compared. Patients had no evidence of tardive dyskinesia at baseline. At any v after baseline 7.1% of patients in the olanzapine group and 16.2% of patients in the haloperidol group manifested treatment-emergent tardive dyskinesia (p less than 0.001). At the last study visit, 2.3% of olanzapine patients and 7.6% of haloperidol patients manifested tardive dyskinesia (p equal to 0.001). Similar results have been reported (Beasley et al, 1999).
4.6.AG.5 Efficacy
a) Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rat of extrapyramidal symptoms (EPS) than haloperidol, but was similar to rates occurring with risperidone a

clozapine therapy. In a pooled analysis of 23 randomized, controlled clinical trials in 4611 patients with schizophrenia, frequency and severity of EPS associated with olanzapine therapy (2.5 to 20 milligrams (mg)/day) was compared with that of haloperidol (1 to 20 mg/day), risperidone (4 to 12 mg/day), clozapir (25 to 625 mg/day), and placebo. Dystonic events (ie, dystonia, oculogyric crisis, opisthotonos, torticollis occurred in significantly fewer patients during olanzapine treatment as compared with haloperidol (0.5% 5.6%, respectively; p less than 0.001) or risperidone (1% vs 3.2%, respectively; p=0.047) treatment, whil no significant difference was found between olanzapine- and clozapine-treated patients. As compared w olanzapine-treated patients, a significantly higher percentage of haloperidol-treated patients experiencec parkinsonian events (ie, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively; p less than 0.001) or akathisia events (ie, akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no significant difference was observed between the olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to the occurrence of parkinsonian or akathisia events. Overall, EPS occurred in significantly more patients treated with haloperidol as compared with olanzapine (44.4% vs 16.2%, respectively; p less than 0.001) and in fewer patients treated with clozapine as compared with olanzapine (2.6% vs 6.8%, respectively; p=0.047). The overall rate of EPS was similar between the placebo and risperidone groups as compared with olanzapine. Significantly fewer patients received anticholinergic medications in the olanzapine group as compared with the haloperidol (p less than 0.001) risperidone (p=0.018) groups. No difference was found between olanzapine-treated patients as compare with placebo or clozapine in regard to percentage of patients given anticholinergic drugs during therapy (Carlson et al, 2003).

b) Pooled safety results from 3 large double-blind, controlled trials in 2606 patients demonstrated that olanzapine had a significantly lower rate of any extrapyramidal symptoms (EPS) occurring versus haloperidol (p less than 0.001) (Tran et al, 1997). Also statistically fewer patients treated with olanzapine discontinued the study because of EPS (p less than 0.001). This suggests that the use of olanzapine ma be associated with better long-term compliance due to fewer adverse effects.

c) The risk of extrapyramidal adverse effects is lower with olanzapine compared to haloperidol, especial dystonic reactions. Increases in serum prolactin have been significantly less with olanzapine (Tollefson e al, 1997); (Beasley et al, 1996)(Anon, 1996; Anon, 1995).

4.6.AG.6 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidenc of PANCREATITIS than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean do 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003).

4.6.AH Oxazepam

4.6.AH.1 Dementia - Restlessness and agitation

a) Oxazepam, haloperidol, and diphenhydramine were equally efficacious in the treatment of agitated behavior in 59 elderly demented inpatients in an 8-week, double-blind study (Coccaro et al, 1990). The mean daily doses were oxazepam 30 +/- 19.4 milligrams, haloperidol 1.5 +/- 0.9 milligrams, and diphenhydramine 81.3 +/- 48.5 mg. Chloral hydrate was given if the study medication did not adequately control agitation. Ratings scale scores indicated that diphenhydramine and haloperidol were more effecti than oxazepam, but none of the differences in scores among the groups was significant. Only modest improvement was seen in terms of agitated behavior and activities of daily living. There was only a slight decrease in the use of chloral hydrate in all 3 groups during the study and no difference among the grou

4.6.AI Oxcarbazepine

4.6.AI.1 Bipolar disorder

a) Oxcarbazepine has been compared with with haloperidol in 42 patients with acute mania; mean dose used were 2400 mg/day and 42 mg/day respectively. Although the response to oxcarbazepine was slow by the end of the second week of treatment, results were similar in both treatment groups. Haloperidol-treated patients had a significantly higher incidence of adverse effects (Emrich, 1990).

4.6.AJ Penfluridol

Gilles de la Tourette's syndrome

Schizophrenia

4.6.AJ.1 Gilles de la Tourette's syndrome

a) Haloperidol has been the drug of choice for Tourette's syndrome for many years, producing beneficia effects in up to 90% of patients treated (Shapiro & Shapiro, 1981; Shapiro et al, 1983). However, advers effects with haloperidol, mainly extrapyramidal symptoms, have limited its use in many patients. Penfluri and pimozide have both been evaluated in the treatment of Tourette's syndrome, based upon animal studies suggesting that each drug has catecholamine blocking effects that differ from haloperidol (Nose Takemoto, 1975). Penfluridol is presumed to be a more specific blocker of dopamine than haloperidol. In addition, it is postulated that penfluridol produces less frequent and less severe extrapyramidal toxicity th haloperidol (Ayd, 1972). However, the differences in extrapyramidal symptoms between the 2 agents remain unclear.

b) Penfluridol was evaluated in the treatment of Tourette's syndrome (Shapiro et al, 1983). The study involved 8 patients with Tourette's syndrome and the results with penfluridol were compared to previous therapy with haloperidol or pimozide (6 of 8 patients). There were 7 males and 1 female aged 10 to 33 years. Penfluridol was given initially in oral doses of 10 mg weekly, increasing by 10 mg weekly for 3 to 1 months (mean, 10 months). Dosage during treatment ranged from 20 to 160 mg weekly, with penfluridol being taken every 3 to 7 days. The percent decrease in tic symptoms was significantly higher for penfluri (mean, 74.4%) than previous haloperidol treatment (mean, 61%). Penfluridol was considered to be slight superior to previous pimozide treatment, however, these differences were not considered significant. Sid effects, including extrapyramidal symptoms, were less in penfluridol patients as compared to previous pimozide or haloperidol therapy. The number of patients using antiparkinson drugs was less with penfluridol.

4.6.AJ.2 Schizophrenia

a) Penfluridol administered once weekly is probably as effective as haloperidol administered daily in the treatment of chronic schizophrenia as well as Tourette's syndrome. An investigational preparation of haloperidol decanoate (McNeil Laboratories) can be given IM and has a duration of action of 4 weeks. B haloperidol decanoate and oral penfluridol will have advantages over oral haloperidol for the manageme of chronic schizophrenia, each improving compliance significantly. Other controlled studies have also reported the equivalent efficacy of daily chlorpromazine as compared to weekly penfluridol (Chouinard e 1977; Chouinard & Annable, 1976; Claghorn et al, 1979). Thus, penfluridol appears to be as effective as chlorpromazine with the advantage of once weekly administration. The incidence of extrapyramidal reactions is greater with penfluridol. Penfluridol will be useful in the patients who are non-compliant on chlorpromazine given daily and in some patients who are not responding optimally to chlorpromazine alo

4.6.AJ.3 Efficacy

a) Although penfluridol is considered a diphenylbutylpiperidine derivative, it does have structural similarities to haloperidol, and both drugs have essentially indistinguishable pharmacologic effects (AMA Department of Drugs, 1986). However, the one-week duration of action of penfluridol is significantly long than haloperidol. Although there is some evidence that penfluridol produces a lower incidence of extrapyramidal side effects than haloperidol (Ayd, 1972; Shapiro et al, 1983), there are no direct comparative studies to support these claims.

4.6.AK Perazine

4.6.AK.1 Schizophrenia

a) High-dose haloperidol was not found to be more effective than standard-dose perazine in treating acutely psychotic schizophrenic patients in a double-blind randomized clinical trial of 32 male patients. Patients received between 15 to 45 milligrams (mg) daily of haloperidol or 300 to 900 mg/day of perazine According to the Clinical Global Impression scale 60% of all examined patients achieved satisfactory improvement after 4 weeks of therapy with an average 65% reduction in their symptoms. The number of responders in the haloperidol group (9 of 15) was not statistically different from the responders in the perazine group (9 of 17). Symptoms were measured according to the AMP scale. As expected, the high-dose haloperidol group reported a significantly higher frequency of extrapyramidal symptoms, rigor, and acute dyskinesia; the perazine group had a higher incidence of dry mouth. Overall 4 patients discontinue the study: 2 in the haloperidol group due to extrapyramidal symptoms and 2 in the perazine group who h to be switched to high-dose haloperidol therapy because of uncontrolled symptoms (Schmidt et al, 1982)

4.6.AL Periciazine

4.6.AL.1 Schizophrenia

a) Maintenance therapy with oral periciazine in doses of 10 to 60 milligrams daily has been less effectiv than haloperidol 1 to 6 mg daily in symptom-free schizophrenic patients. This was attributed in part to lac of dose-dependent decreases in relapse rates with periciazine; although the drug increased symptom-fre days over doses of 10 to 30 mg daily, a significant decrease in this parameter (placebo levels) was seen with 60 mg daily, in association with a high incidence of adverse effects (eg, dysarthria, malaise, hypersomnia). These combined results are suggestive of an inverted U-shaped dose-response curve for periciazine. In contrast, haloperidol significantly and dose-dependently increased symptom-free days ov the range of 1 to 6 mg daily, without an increase in adverse effects (Nishikawa et al, 1984).

4.6.AM Perphenazine

Psychotic disorder

Schizophrenia

4.6.AM.1 Psychotic disorder

a) One double-blind study reported the similar efficacy of intramuscular haloperidol 5 milligrams every 8 hours and intramuscular perphenazine 5 milligrams every 8 hours in the treatment of acute psychiatric episodes (Fitzgerald, 1969). Total doses (mean) of haloperidol and perphenazine were 26 mg and 27 mg respectively, over a period of 48 hours.

4.6.AM.2 Schizophrenia

a) Haloperidol decanoate (100 milligrams/4 weeks) was compared with perphenazine enanthate (100 milligrams/2 weeks) in 20 schizophrenic patients in a 48-week, double-blind crossover study. There were no significant differences in either safety or efficacy (Rapp et al, 1986).

b) Perphenazine decanoate and haloperidol decanoate were compared in a 51-week, randomized, double blind, cross-over, multicenter study. There were no significant differences between the two drugs in antipsychotic efficacy or side effects (Dencker et al, 1994).

4.6.AN Phenelzine

4.6.AN.1 Personality disorder

a) Haloperidol was compared to phenelzine in a placebo-controlled, randomized, double-blind study of 1 patients with borderline personality disorder over a 5 week period (Soloff et al, 1993). Thirty-six patients received 4 mg haloperidol, 38 received 60 mg phenelzine and 34 received look-alike placebo tablets. Several measures of effectiveness were evaluated. Haloperidol was found to be ineffective and phenelzi was effective in comparison to both placebo and haloperidol. This study was not able to establish a dissection of borderline personality disorders into affective and schizotypal subtypes.

4.6.AO Physostigmine

4.6.AO.1 Alzheimer's disease

a) Physostigmine was compared with haloperidol in the treatment of behavioral disturbances in 15 patie diagnosed with Alzheimer's disease (Gorman et al, 1993). Physostigmine 15 milligrams/day in two-hourly divided doses was compared to haloperidol to 3 milligrams/day. Both drugs were effective in controlling t behavioral disturbances. Haloperidol produced a high incidence of adverse effects.

b) Physostigmine 6 mg/day was compared with haloperidol 3 mg/day in a double-blind study of two patients with Alzheimer's Disease and prominent delusions. Both patients responded to each treatment with a decrease in delusions and associated hallucinations and agitated behavior. Physostigmine was w tolerated in both patients (Cummings et al, 1993).

4.6.AP Pimozide

Gilles de la Tourette's syndrome

Schizophrenia

4.6.AP.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 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, 1978). 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 me 5-minute tic counts, with no significant difference between the 2 drugs. Both haloperidol and pimozide w 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 haloperid 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 57 patients with Tourette's syndrome. The maximum dose of haloperidol was 10 milligrams (mg)/day, an 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 pimozid 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.AP.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 sma double-blind study. A subsequent report has indicated the equivalent efficacy of pimozide 10 to 60 mg da and haloperidol 10 to 60 mg daily in acute schizophrenia (Haas & Beckmann, 1982). In this study, howev extrapyramidal effects were more pronounced in patients using pimozide (Gowardman et al, 1973).

4.6.AQ Pramipexole

4.6.AQ.1 Schizophrenia

a) Haloperidol 15 mg daily has been superior to pramipexole (0.3, 0.75, or 3 mg daily) in the treatment o schizophrenia (Lecrubier, 1994).

4.6.AR Prochlorperazine

4.6.AR.1 Chemotherapy-induced nausea and vomiting

a) Butyrophenones such as haloperidol and droperidol are more effective than phenothiazines such as prochlorperazine in moderate to highly emetogenic chemotherapy, particularly when used in combinatior with steroids and antihistamines (Wood, 1993; Sridhar & Donnelly, 1988; Kelley et al, 1986); (Mason, 1982).

b) Haloperidol combined with dexamethasone was compared to prochlorperazine combined with dexamethasone in controlling nausea and vomiting in breast cancer patients (Silvey et al, 1988). The prospective study was nonblinded and randomized. The patients received either intravenous cyclophosphamide, doxorubicin, and fluorouracil (a chemotherapy regimen known as CAF) or cyclophosphamide, methotrexate, and fluorouracil) (a chemotherapy regimen known as CMF). Patients received either prochlorperazine 6 mg/m(2) plus dexamethasone 5 mg/m(2) or haloperidol 2 mg/m(2) plu dexamethasone 5 mg/m(2). The patients received the first dose intravenously 30 minutes before the administration of cytotoxic drug, the same dose orally 3.5 hours after therapy and then every 4 hours for hours. Neither the prochlorperazine plus dexamethasone or haloperidol plus dexamethasone was highly effective in preventing nausea and vomiting in the doses and schedules used, although the haloperidol a dexamethasone regimen did reduce the severity of vomiting and nausea to some extent. Based upon thi information, neither regimen can be recommended as standard antiemetic therapy for this patient population.

4.6.AS Quetiapine

4.6.AS.1 Schizophrenia

a) In a study involving 361 patients, quetiapine (across 5 fixed doses) was found to be superior to placel in improving depressive symptoms in schizophrenic patients, while haloperidol (12 milligrams/day) was r Additionally, depressive symptoms were improved in a greater proportion of patients treated with quetiap versus haloperidol or placebo. None of the quetiapine patients withdrew from the study due to extrapyramidal symptoms, while 4 haloperidol and 1 placebo patient withdrew (Keck et al, 2000a; Glazer 2000).

b) A 6-week, multicenter, double-blind trial comparing quetiapine and haloperidol (mean total daily dose of 455 milligrams and 8 milligrams, respectively) in the treatment of acute exacerbation of schizophrenia concluded that quetiapine in as effective and better tolerated than haloperidol. Both agents produced cle reductions in the Positive and Negative Syndrome Scale scores and Clinical Global Impression Severity

Illness and Global Improvement scores. Quetiapine was better tolerated in terms of extrapyramidal symptoms. In addition, mean serum prolactin concentration decreased in quetiapine patients and increas in haloperidol patients (Copolov et al, 2000).

4.6.AT Remoxipride

4.6.AT.1 Schizophrenia

a) SUMMARY: REMOXIPRIDE and HALOPERIDOL have been shown to achieve equal efficacy for the treatment of schizophrenia. In some studies, REMOXIPRIDE produced a lower frequency of extrapyrami or other adverse symptoms.

b) Controlled-release (CR) REMOXIPRIDE and HALOPERIDOL were shown to produce comparable efficacy in the treatment of chronic schizophrenia patients with a preponderance of negative symptoms (ratings based on the Positive and Negative Symptoms Scale (PANSS)) in a multi-center, double-blind tr Following a run-in period, patients were randomized to a 24-week course of remoxipride CR 150 to 600 milligrams (mg)/day (n=97) or haloperidol 5 to 20 mg/day (n=108), given in 2 divided doses. Mean daily doses were 334.1 mg for remoxipride and 10.44 mg for haloperidol during the last study-week. A reducti of 20% in the PANSS negative symptoms scores occurred in 49.4% and 47.6%, respectively, of remoxipride- and haloperidol-treated patients. Clinical Global Impression evaluations rated 33.7% of remoxipride and 30.8% of haloperidol patients much or very much improved. Tolerability was similar for both medications with the overall adverse effects profile of remoxipride not statistically different from haloperidol. The authors noted that the generally low-dosages of haloperidol used in this study may have enhanced its tolerability (Lapierre et al, 1999).

c) Remoxipride showed equal efficacy to haloperidol in a double-blind study using 80 patients with schizophrenia (Ahlfors et al, 1990). Remoxipride is a dopamine D2 receptor blocking agent that shows n effect on serotonin, noradrenaline, histamine, acetylcholine, or GABA receptors. Because remoxipride ha receptor specificity, it suggests low extrapyramidal side-effects. A total of 50 patients were used in the study and were then evaluated at the end of the treatment. The mean daily dose of remoxipride was 316 milligrams as opposed to 8.7 milligrams of haloperidol. The results showed comparable effectiveness in treating schizophrenia. Only 14 patients exhibited extrapyramidal effects, and of these, only three were remoxipride patients. The researchers conclude that remoxipride is a comparable antipsychotic to haloperidol. Similar results have been reported (Andersen et al, 1990; Deo et al, 1990; den Boer et al, 1990; den Boer & Westenberg, 1990); (Lindrom et al, 1990)(Mendlewicz et al, 1990).

d) Haloperidol and remoxipride were equally efficacious in one study (Laux et al, 1990). The study grou was divided into three groups: remoxipride (53 patients) twice daily, remoxipride (52 patients) three times daily, and haloperidol (52 patients) three times daily. The results showed no significant differences in effectiveness. No extrapyramidal effects were noticed in remoxipride patients opposed to 4% affected patients using haloperidol. The researchers' conclusion is that remoxipride is as effective as haloperidol i acute schizophrenia with fewer side-effects. Similar results have been reported by others (Lapierre et al, 1990; Patris et al, 1990).

e) A double-blind multicenter study of 150 schizophrenic or schizophreniform patients compared the efficacy and safety of oral forms of remoxipride immediate-release (IR), remoxipride controlled-release (CR), and haloperidol. Patients randomly received one of the three drugs in mean daily doses of 332 milligrams and 12.5 milligrams, respectively, and were evaluated for a four-week period using two standa neuroleptic efficacy scales as well as the Simpson & Angus scale for extrapyramidal symptoms. There were no statistically significant differences among the treatment groups. The authors concluded that the three drugs were equal in antipsychotic efficacy in treating schizophrenia or schizophreniform behavior while remoxipride, IR and CR had less frequent side effects than haloperidol in therapeutic doses (Hebenstreit et al, 1991).

f) In a four-week study involving 51 previously untreated patients with schizophrenia, remoxipride (mean dose 375 milligrams/day), haloperidol (mean dose 16 milligrams/day), and clozapine (mean dose 350 milligrams/day) were compared (Klieser et al, 1994). There was no significant difference in efficacy amor the three drugs. The incidence of extrapyramidal side effects (EPS) was most frequent with haloperidol a least frequent with clozapine, with remoxipride causing EPS with intermediate frequency.

4.6.AU Risperidone

Cognitive function finding

Dementia

Extrapyramidal disease

Mania

Schizophrenia

4.6.AU.1 Cognitive function finding

a) Results of a multicenter, randomized, double blind trial assessing cognitive function in patients experiencing their first schizophrenic episode or a related psychosis demonstrated that overall improvement in cognitive functioning was superior with risperidone than with haloperidol. Patients (n=53 were randomized to receive either risperidone or haloperidol on a one-to-one randomization basis for a period of 2 years or more. There were no significant differences in sex, race or ethnicity, age, diagnosis, previous neuroleptic treatment in either group. Dosing strategies were equivalent in both groups where patients were started on 1 milligram per day (mg/day) of the study drug and titrated up to 4 mg/day, or in some cases, to a maximum of 8 mg/day. Patients in the risperidone group received the trial medication (mean modal total dose 3.3 mg/day) for an average of 192 days while patients in the haloperidol group received treatment (mean modal total dose 2.9 mg/day) for an average of 218 days. Cognitive assessments, performed at several different follow-up intervals, included examinations of verbal and visuospatial episodic memory, vigilance, executive functioning, processing speed, and verbal fluency. Ar intention-to-treat analysis conducted with a focus on the 3-month assessment revealed that there was significant improvement from baseline in the risperidone group (n=169) for all measures except category verbal fluency and letter verbal fluency (p less than 0.05). In the haloperidol group (n=169), statistically significant improvements from baseline were noted in episodic memory, vigilance, and visuomotor speec but not in executive functioning and verbal fluency. Comparison between the two groups showed that, af 3 months of treatment, the risperidone group was significantly more beneficial than the haloperidol group on the composite measure of cognitive functioning. In addition, cognitive improvement as a result of treatment with risperidone was not affected by changes in symptoms. Risperidone therapy also proved t be superior than haloperidol in relapse prevention and extrapyramidal side effects (Harvey et al, 2005).

b) Risperidone therapy appeared to exert a more favorable effect on verbal working memory in treatmer resistant schizophrenic patients than did haloperidol therapy (Green et al, 1997). In a randomized, doubl blind comparison of treatment with risperidone (n = 30) and haloperidol (n = 29), verbal working memory was measured at baseline and after 4 weeks of both a fixed dose and flexible dose regimen. Risperidone patients showed a significant improvement in memory using a Digit Span Distractibility Test from baselin performance at both the fixed-dose (p less than 0.0001) and the flexible dose (p less than 0.0003) phase The haloperidol-treated patients did not change significantly. Results suggest that treatment of schizophrenia could be broadened to include the impact on neurocognitive abilities.

4.6.AU.2 Dementia

a) Some Chinese patients with dementia, who were non-responders to haloperidol, responded to risperidone with decreased behavioral disturbances and improved mood. Thirty-five Chinese patients wh had shown insufficient response to an 8- week trial with haloperidol (i.e., having a total score of more tha 10 on the Brief Psychiatric Rating Scale (BPRS) at the end of 8 weeks) (typical dose 1 gram/day) were switched abruptly from haloperidol to risperidone 0.5 milligrams (mg) at bedtime for weeks 1 to 4 and the (if tolerated) to 1 mg at bedtime for weeks 5 to 12. At week 13, the regimen was shifted again to haloperi at the dose used in the earlier trial. Twenty-nine patients completed the trial. Sixteen patients responded the end of the risperidone trial (response = a decrease of 25% in the BPRS score). After haloperidol resumption, the mean BPRS score stayed the same, but the number of responders decreased to 15. Patients with vascular dementia were almost 6 times more likely to respond to risperidone than patients with Alzheimer's disease. Mean scores on the Behavioral Pathology in Alzheimer's Disease Rating Scale decreased (6.1 at baseline to 1.9 at 12 weeks of risperidone treatment) and increased after switching ba to haloperidol (to 2.4 after 4 weeks of haloperidol). Thirty- four of the 35 patients tolerated both doses of risperidone and haloperidol 1 mg/day. One patient experienced moderate rigidity with risperidone 1 mg/c which was relieved by reduction of the dose to 0.5 mg/day. Patients experienced fewer extrapyramidal symptoms with risperidone than with haloperidol (Lane et al, 2002).

b) Both risperidone and haloperidol in low doses reduced the severity and frequency of behavioral and psychological symptoms of elderly Chinese patients with dementia. Risperidone was associated with les severe exacerbation of extrapyramidal symptoms (EPS). In a randomized, double-blind trial, 55 elderly Chinese patients (mean age 80 years) with Alzheimer's dementia or vascular dementia and with behavic disturbance, were given either risperidone or haloperidol for 12 weeks after a 2-week washout period for elimination of psychotropic and antiparkinsonian drugs. The starting dose for both treatment drugs was 0 milligrams (mg) at night; doses were adjusted individually in increments of 0.5 mg no faster than every other day, to a maximum of 2 mg/day. At 12 weeks, the mean daily dose of haloperidol was 0.9 mg, and that of risperidone, 0.85 mg. Significant improvements on the Cohen- Mansfield Agitation Inventory (CMA were evident in both groups (haloperidol, p less than 0.001; risperidone, p=0.002). Significant reduction was seen at 2 weeks in the risperidone group and at 4 weeks in the haloperidol group. With risperidone, there were significant improvements in scores for psychosis, activity disturbances, aggressiveness and diurnal rhythm disturbances, whereas with haloperidol, improvement in only the aggressiveness score reached statistical significance. However, none of the measures showed a significant difference betweer the treatment groups. With haloperidol, there was a significant worsening of EPS (p less than 0.001), whereas, with risperidone, EPS scores were only modestly worsened. Final EPS scores were significant higher for haloperidol (p=0.001) (Chan et al, 2001).

4.6.AU.3 Extrapyramidal disease

a) Data from a multicenter comparative study of risperidone, placebo, and haloperidol revealed that risperidone caused few or no extrapyramidal symptoms (Simpson & Lindenmayer, 1997). Mean changes Extrapyramidal Symptom Rating Scale (ESRS) scores from baseline to worst score were significantly lov in each risperidone group than the haloperidol group (P less than 0.001).

4.6.AU.4 Mania

a) A small, controlled study, compared the efficacy and safety of risperidone versus lithium and haloperi in mania and found comparable results with risperidone. Patients (n=45) were assigned to take risperido (as monotherapy), dosed at 6 mg per day, haloperidol at 10mg per day, or 800 to 1000 mg daily of lithiur All 3 groups showed a similar improvement on Brief Psychiatric Rating Scale and Young Mania Rating Scale scores. The EPS of risperidone and haloperidol were not significantly different and mania did not worsen in any of the risperidone treated patients (Segal et al, 1998).

4.6.AU.5 Schizophrenia

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine i patients with schizophrenia or schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients were given clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was insufficient, but sometimes reduced because of adverse effects). Improvemer over time in global neurocognitive score was seen for olanzapine and risperidone. In general executive a perceptual organization and in processing speed and attention, improvement was seen with olanzapine. simple motor function, there was improvement with clozapine. Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximately 8 to 9 "IQ equivalents") but large enough to be clinically significant. Beneficial changes with clozapine were modes Despite cognitive gains, patients still had significant impairments of cognitive ability and social/vocationa functioning. Improvements in neurocognitive deficits were associated with improvements in negative symptoms (Bilder et al, 2002a).

b) The risk of relapse of schizophrenia was significantly less with long-term treatment with risperidone th with haloperidol. In a randomized, double-blind study, 365 patients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder and in a stable condition were given flexible doses of either risperidone or haloperidol. The trial was continued until the last enrolled patient had completed one year treatment. Means of modal daily doses were 4.9 milligrams (mg) for risperidone and 11.7 mg for haloperidol. At the end of the study, 25% of the risperidone group and 40% of the haloperidol group had relapsed. The risk of relapse was significantly higher among patients assigned to haloperidol (risk ratio 1.93, p less than 0.001). The risk of premature discontinuation was greater for the haloperidol group thar for the risperidone group (risk ratio 1.52), mainly because of relapse. Median duration of treatment for th risperidone group was 364 days and for the haloperidol group, 238 days (p=0.02). The subtypes of relap (psychiatric hospitalization, clinical deterioration, increase in level of care, suicidal or homicidal ideation) were similar in the 2 groups. In the risperidone group, there were improvements from baseline in positive and negative symptoms, disorganized thoughts, and anxiety- depression, whereas symptoms were not improved with haloperidol. The severity of extrapyramidal symptoms was reduced from baseline in the risperidone group and increased in the haloperidol group. Differences between the groups were significa (p less than 0.02 for total score on the Extrapyramidal Symptom Rating Scale). The most frequent adver events were somnolence (14% with risperidone and 25% with haloperidol), agitation (10% and 18% respectively), and hyperkinesia (5% and 20%, respectively). Those taking risperidone had a mean increa in body weight of 2.3 kilograms (kg) and those taking haloperidol had a mean decrease of 0.73 kg (p less than 0.001) (Csernansky et al, 2002).

c) Risperidone was more efficacious and had fewer adverse effects than haloperidol when used to treat refractory schizophrenia in Chinese patients. Chinese patients, meeting DSM-III-R criteria for schizophre and having a history of treatment failure with 3 conventional neuroleptics given at least 3 months at full dose, were randomly assigned to receive risperidone (n=41) or haloperidol (n=37) for a 12-week, double blind trial. The dose of risperidone was increased during the first week to 6 milligrams (mg) per day, and dose of haloperidol to 20 mg/day. By the end of the study, the average score on the Positive and Negativ Syndrome Scale (PANSS) had decreased by 39.8% for the risperidone group and by 28.3% for the haloperidol group (p=0.03). The general psychopathology and negative subscores of the PANSS showe greater improvement with risperidone, but there was no difference between treatments in the positive subscore. The proportion of patients rated as responders was higher in the risperidone group (31 of 41 v 20 of 37, p=0.046). Total scores on the Treatment Emergent Symptoms Scale (TESS) were significantly lower with risperidone than with haloperidol (2.9 vs 6.9, p=0.01). Particular subscores significantly favori risperidone were those showing symptoms of the nervous system (rigidity, tremor, dystonia, and akathisi and of the cardiovascular system (hypotension, dizziness, tachycardia, hypertension and electrocardiogr abnormalities) (p=0.02 and p=0.04, respectively). Patients in the risperidone group required less medicat for extrapyramidal symptoms during the study than did patients in the haloperidol group. The authors mentioned that the dose of haloperidol was higher than the dose recommended in the United States and Europe and may have accounted for some of the difference between treatments in efficacy and adverse

effects (Zhang et al, 2001).
d) Results of a subanalysis of data from the multinational risperidone trial (double-blind, randomized, parallel-group) reported that the reduction in negative symptoms was significantly better in patients receiving risperidone 16 mg/day than haloperidol 10 mg/day (p less than 0.05) (Moller et al, 1997a). Patients with chronic schizophrenia (n=169) were treated with risperidone 1 mg, 4 mg, 8 mg, 12 mg, or 1 mg, or haloperidol 10 mg/day for 8 weeks. Improvement was noted in each group. Risperidone onset wa faster than haloperidol. An analysis of the Positive and Negative Syndrome Scale cluster scores revealed significantly greater improvement in the risperidone-treated patients than in the haloperidol group on 2 clusters: activity and anxiety/depression (p less than 0.05).
e) Risperidone was significantly better than haloperidol in the treatment of chronic schizophrenia using combined data from 2 studies (Chouinard et al, 1993; Marder & Meibach, 1994) to evaluate five factors o the Positive and Negative Syndrome Scale (Marder et al, 1997). Data from 513 patients showed that afte to 8 weeks of therapy, patients receiving risperidone 6 to 16 milligrams had significantly higher adjusted mean changes in total Positive and Negative Syndrome Scale than patients treated with haloperidol (p le than 0.01). The 5 specific symptom areas that risperidone was significantly superior to haloperidol includ negative symptoms (p less than 0.01), positive symptoms (p less than 0.05), disorganized thought (p les than 0.05), uncontrolled hostility/excitement (p less than 0.01), and anxiety/depression (p less than 0.01) One author, however, noted some positive symptoms that reemerged after an initial response to risperidone (Cung & Stimmel, 1997).
f) In a meta-analysis, risperidone (4 to 8 milligrams(mg)/day) was found to be more effective and produc fewer extrapyramidal effects than haloperidol (4 to 20 mg/day). Seven studies done in a double-blind, randomized fashion were included. The primary outcome measure was clinical improvement defined as a 20% reduction in the total scores on the Brief Psychiatric Rating Scale or the Positive and Negative Syndrome Scale. Results showed that patients identified as treatment failures were 50% of those taking risperidone, 66% on haloperidol, and 83% on placebo. There was a highly significant need for anticholinergic medication in the haloperidol-treated patients as compared to risperidone (P less than 0.00001) (de Oliveira et al, 1996).
g) Risperidone was more effective than haloperidol in a double-blind, placebo-controlled, multicenter stu (Marder & Meibach, 1994). 388 schizophrenic patients were randomly assigned to receive 4 fixed doses risperidone (2, 6, 10, and 16 milligrams/day, on a BID schedule), haloperidol 20 milligrams daily or place for 8-weeks (Marder and Meibach, 1994). Patients receiving risperidone 6 to 16 milligrams showed statistically greater improvement than placebo or haloperidol in Clinical Global Impression (CGI) and tota Positive and Negative Syndrome Scale (PANSS) scores. Of the four doses studied, the 6, 10, and 16 milligram doses were all effective with the 6 milligram dose being the most effective. Similar results have been reported (Chouinard et al, 1993; Marder, 1992).
h) In an 8-week, double-blind study, 1362 schizophrenic patients were randomly assigned to receive eit risperidone 1, 4, 8, 12, 16 milligrams/day, on a BID schedule, or haloperidol 10 milligrams daily (Muller-Spahn, 1992). Significantly greater improvement in Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) total score, the PANSS General Psychopathology subscale, the BPRS Activity and Anxiety/Depression cluster, was observed in the risperidone 4 milligram and 8 milligra groups versus the haloperidol-treated patients. In addition, a greater percentage of patients treated with risperidone 4 and 8 milligrams achieved clinical improvement on the PANSS and BPRS as compared wi the haloperidol group.
i) Risperidone was faster acting, more effective, and had fewer side effects than haloperidol in a study t determine efficacy in treating negative symptoms of schizophrenia (Claus et al, 1992). The multicenter double-blind study that took place over a period of 15 weeks included a two-week run-in period and a on week washout period. The patients (n=42) took one to 5 mg bid of either drug for a period of 12 weeks. T Positive and Negative Syndrome Scale for Schizophrenia was the key efficacy parameter. The Schedule for Affective Disorders and Schizophrenia Change Conversion was used as a diagnostic aid and sympto severity measure. The Clinical Global Impression Scale was complete as a global rating. In addition, the occurrence of extrapyramidal side effects was also monitored. The improvement in PANSS was approximately three times greater in the risperidone group, both at week six and at endpoint. In addition, the onset of therapeutic effects was quicker in the risperidone group. Finally, the risperidone group need 10 times less anticholinergic medication to control the extrapyramidal side effects than did the haloperido group. According to this study, risperidone showed a greater improvement in schizophrenic symptoms th haloperidol.
j) Risperidone was less effective as monotherapy when compared to combination therapy of haloperidol and amitriptyline in patients with coexisting psychotic and depressive disorders. In this double-blind multicenter study, 123 patients were randomized to receive either risperidone (dose titrated to 8 milligram (mg) by the end of week 1) or the combination of haloperidol and amitriptyline (doses titrated to 10 mg a 200 mg by the end of week 1). For all patients, doses were then adjusted under double blind conditions over the next 5 weeks based on response. At endpoint, the mean effective daily dose was 6.9 mg risperidone, and 9 mg haloperidol in combination with 180 mg amitriptyline. In the 98 patients who completed at least 3 weeks of treatment, Brief Psychiatric Rating Scale (BPRS) scores decreased in both treatment groups, but the reduction in the combination treatment group was significantly greater than the risperidone treated group (p=0.004). The proportion of patients achieving at least 50% improvement in BPRS scores was also significantly higher with combination therapy (p = 0.002). Greater benefit by combination therapy was still observed in an intent-to-treat analyses of the 123 patients. Use of

anticholinergic medication for extrapyramidal symptoms was higher in the risperidone group (Muller-Siecheneder et al, 1998)

4.6.AU.6 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidenc of PANCREATITIS than patients receiving a conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis were identified in patients taking clozapine (mean do 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) or haloperidol (mean dose, 8.2 mg/day). Of the identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications clozapine, olanzapine, or risperidone, respectively, compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most patients, time to onset of pancreatitis was within 6 months after initiation of treatment (Koller et al, 2003a

4.6.AV Sertindole

4.6.AV.1 Schizophrenia

a) Sertindole appears to be as effective as haloperidol in the treatment of schizophrenia. In a placebo-controlled, double-blind, multicenter trial involving 497 hospitalized patients, sertindole 12 milligrams (n=76), 20 mg (n=68), or 24 mg (n=72) was compared with haloperidol 4 mg (n=71), 8 mg (n=67), or 16 (n=70) and placebo (n=73). All doses of both sertindole and haloperidol were significantly more effective than placebo in treating the positive symptoms of schizophrenia (hallucinations, delusions and disorganiz thinking) as measured by Positive and Negative Symptom Scale (PANSS) scores. With negative sympto (emotional withdrawal and paucity of thoughts), only sertindole 20 mg was significantly more effective tha placebo in reducing PANSS negative scale scores. Extrapyramidal symptoms (EPS) were not observed with sertindole; in contrast, patients receiving any dose of haloperidol experienced significantly more EPS than patients receiving placebo or any dose of sertindole. The most common adverse effects associated with sertindole included nasal congestion and decreased ejaculatory volume, thought to be related to its alpha-1 activity; other adverse effects were mild prolongation and mild weight gain (Anon, 1996a; Anon, 1996b).

4.6.AW Sulpiride

4.6.AW.1 Schizophrenia

a) Sulpiride in doses of 300 to 1200 milligrams daily has been comparable in efficacy to chlorpromazine 150 to 675 mg daily (Peselow & Stanley, 1982; Bratfos & Haug, 1979), trifluoperazine 15 to 45 mg daily (Edwards et al, 1980), haloperidol 0.5 to 10.5 milligrams daily (Cassano et al, 1975), and perphenazine 4 80 mg daily) (Peselow & Stanley, 1982) in patients with acute or chronic schizophrenia. One study (Taverna et al, 1972) reported the superiority of sulpiride 200 to 800 mg/day over haloperidol 1 to 4 mg/d with regard to overall global improvement, as well as improvement of thought content and mood state; however, the doses of haloperidol in this study may have been too low to enable a fair comparison.

b) In patients with severe chronic schizophrenia, higher doses of sulpiride (800 to 3200 milligrams daily) were as effective as haloperidol 6 to 24 milligrams daily in controlling symptoms (Gerlach et al, 1985; Munk-Andersen et al, 1984). Median doses in these studies were 1600 to 2000 mg sulpiride and 12 mg haloperidol daily.

c) In some studies, greater benefits of sulpiride have been observed on certain target symptoms, includi more improvement in thought content and mood state as compared with haloperidol (Taverna et al, 1972 and greater reductions in aggressiveness and hyperactivity as compared with chlorpromazine (Peselow Stanley, 1982). However, haloperidol tended to be more effective than sulpiride in a subgroup of chronic disturbed patients who had received long-term neuroleptic therapy in one study (Munk-Andersen et al, 1984), and perphenazine had a greater effect on hallucinations in another (Peselow & Stanley, 1982).

4.6.AW.2 Adverse Effects

a) Haloperidol, chlorpromazine, and sulpiride were compared in normal volunteers to test mood state (McClelland et al, 1990). The twelve volunteers were assessed using sixteen visual analog scales such a elapsed time estimation, tapping rate, body sway and tremor, etc. The volunteers were divided into four groups: haloperidol (3 milligrams per day), chlorpromazine (50 mg per day), sulpiride (400 milligrams per day), and a placebo group. The results showed chlorpromazine and haloperidol users experienced reduc alertness and well-being. Haloperidol reduced feelings of "calmness" in the volunteers. Sulpiride did not significantly alter vision in the volunteers. Haloperidol affected the information processing function, but di not affect motor ability and speed in the group taking this drug.

4.6.AX Sultopride

4.6.AX.1 Psychotic disorder, acute

a) A double-blind, randomized, multicenter study was carried out in a total of 64 acutely psychotic inpatients (32 on sultopride 800 milligrams (mg), and 32 on haloperidol 20 mg daily) over a 15-day perio Efficacy of treatment was assessed using Diagnostic Statistical Manual (DSM) III criteria, a visual analog scale evaluating overall symptom severity, a positive symptom scale, the Arbeitsgemeinschaft fuer Methodik und Dokumentation in der Psychatrie (AMDP)-4 and -5 scales, and an alertness scale. At study end, both groups had improved significantly and comparably. Sultopride was more effective than

haloperidol after 3 days of treatment on several AMDP items, such as mental dissociation, anxiety, cognitive disturbances, depression and apathy. According to the CHESS list of somatic symptoms, haloperidol induced more extrapyramidal symptoms than sultopride (Ropert et al, 1989).

4.6.AY Tetrabenazine

4.6.AY.1 Tardive dyskinesia

a) Tetrabenazine and haloperidol were similarly effective in an 18-week randomized study (n=13); haloperidol tended to be more effective during the first two weeks of therapy (Kazamatsuri et al, 1973). T small patient population in this study limits adequate comparison.

4.6.AZ Tetrahydrocannabinol

4.6.AZ.1 Chemotherapy-induced nausea and vomiting

a) Tetrahydrocannabinol was compared with haloperidol in 52 patients experiencing nausea and vomitir resulting from cancer chemotherapy. Subjective evaluation was made by the patient with regard to numb of vomiting episodes, preference, "efficacy", and adverse reactions. Doses were 10 mg tetrahydrocannabinol and 2 mg haloperidol, given 2 hours prior and 30 minutes prior to cancer chemotherapy then at 1 hour and then 3 to 4 hour intervals times 8 doses after cancer chemotherapy. Efficacy was judged equal for the two regimens, and about one-half had relief with the crossover regime when the first regimen failed. Adverse effects were more frequent and more severe in the tetrahydrocannabinol group (Neidhart et al, 1981).

4.6.BA Thioridazine

4.6.BA.1 Psychotic disorder

a) In a single-blind, randomized parallel study lasting six weeks, haloperidol (mean dose of 2.9 milligrams/day) was compared with thioridazine (mean dose of 145 milligrams/day) in 13 patients with psychosis associated with HIV infection. Based on several scales for assessing psychoses, the two drug produced modest improvement, but were not statistically different in the outcomes produced. All haloperidol-treated patients developed extrapyramidal side effects, while 60% of those taking thioridazin developed them (Sewell et al, 1994).

4.6.BB Thiothixene

4.6.BB.1 Psychotic disorder

a) Thiothixene is not as useful as haloperidol in the treatment of psychotic symptomatology including schizophrenia, manic-depression, psychotic reactions secondary to trauma, and psychosis with mental deficiencies (Howard, 1974).

b) A single-blind study compared the efficacy of haloperidol and thiothixene in the treatment of acute organic mental syndromes in 14 patients in a general hospital setting (Peterson & Bongar, 1989). The do of haloperidol was 4.8 to 15 milligrams and for thiothixene, 2 to 7 milligrams. Evaluations were performed using the Brief Psychiatric Rating Scale (BPRS). There was a trend toward greater reductions in magnitu of BPRS scores in patients treated with thiothixene. Symptoms most affected by treatment included: anergia, thought disturbance, level of activity, hostility, and suspicion. The small sample size was a limitation of this study and larger studies are needed to adequately compare the 2 agents.

c) In a double-blind study of borderline and schizotypal patients treated with thiothixene or haloperidol, 84% of patients improved markedly or moderately by 3 months (Serban & Siegel, 1984). A better respon was seen in those patients receiving thiothixene as compared with haloperidol. Mean dosages were 9.4 7.6 milligrams/day for thiothixene and 3 +/- 0.8 milligrams/day for haloperidol.

d) A 24-week, double-blind study compared the safety and efficacy of haloperidol and thiothixene in 46 schizophrenic outpatients (Abuzzahab & Zimmerman, 1982). Mean dosages used were 17.5 milligrams/ for haloperidol and 31.8 milligrams/day for thiothixene. Haloperidol was equal to, and in some parameter superior to, thiothixene in these patients. Haloperidol also appeared to produce fewer central nervous system adverse effects.

4.6.BC Timiperone

4.6.BC.1 Schizophrenia

a) Haloperidol (maximum dose 18 mg/day) was compared with timiperone (maximum dose 12 mg/day) i 206 patients treated for schizophrenia for up to 12 weeks. The authors concluded that timiperone was superior to haloperidol in efficacy and that the drugs were comparable in safety (Kariya et al, 1983).

4.6.BD Trifluoperazine

4.6.BD.1 Psychotic disorder

a) Trifluoperazine 1 mg milligram orally twice a day was reported similarly effective as haloperidol 0.5 milligram orally twice a day in the treatment of behavioral symptoms associated with chronic brain

syndrome and senile psychosis in a controlled study involving 54 elderly patients (Lovett et al, 1987). Based upon CGI scores, improvement was observed in 86% and 90% of patients receiving trifluoperazin and haloperidol, respectively. Several other rating scales demonstrated significant advantages of trifluoperazine. Due to the small number of patients in this trial, it is unclear if these findings are significa and more studies are required in larger patient populations.

4.6.BE Trimethobenzamide

4.6.BE.1 Vomiting

a) SUMMARY: Trimethobenzamide does not appear to be as effective as the phenothiazines for reducti of nausea and vomiting (Purkis, 1965; Bardfeld, 1966; Shields et al, 1971).

b) Trimethobenzamide was compared with haloperidol and prochlorperazine for emesis. In this study of males, aged 17 to 49 years, 6 patients received trimethobenzamide in a dose of 2.5 mg/kg IM as a single dose. Emesis was induced with a threshold emetic dose of apomorphine. Trimethobenzamide was found be effective in only 50% of the cases at the recommended dose. All patients responded to prochlorperaz 0.1 mg/kg and haloperidol 0.007 mg/kg (Shields et al, 1971).

4.6.BF Valproic Acid

4.6.BF.1 Mania

a) Divalproex and haloperidol were found to be equally efficacious in the management of acute psychoti mania in patients with bipolar disorder. In this study, patients (n=36) were randomized to therapy with divalproex (20 mg/kg/day) or haloperidol (0.2 mg/kg/day) for a period of six days. Divalproex was given a dosage considered to be a loading dose to produce valproate concentrations of approximately 80 mg/L after one day of treatment. Improvement was greatest during the first three days of treatment; extrapyramidal side effects were observed much more often in patients treated with haloperidol (McElroy al, 1996).

4.6.BG Ziprasidone

Chronic schizophrenia

Schizophrenic episode, acute

4.6.BG.1 Chronic schizophrenia

a) Ziprasidone was as effective as haloperidol in treating overall symptomatology, was more effective in the treatment of negative symptoms, and was better tolerated, in the long-term treatment of outpatients v stable schizophrenia. In a 28-week, double-blind, flexible-dose, parallel-group clinical trial, ziprasidone a haloperidol both improved overall symptomatology in 227 patients with chronic or subchronic schizophrenia. Patients who received ziprasidone had a significantly higher rate of improvement in the treatment of negative symptoms (48% of patients showed improvement) compared to patients who received haloperidol (33% of patients showed improvement). For patient assessment, the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions-Severity of Illness scale (CGI-S), a the Montgomery-Asberg Depression Rating Scale (MADRS) were used at baseline and weeks 3, 6, 16, a 28. In the ziprasidone group, patients received a starting dose of 40 milligrams per day (mg/d) on the firs days and 80 mg/d on day 3. The ziprasidone dose could be increased to a maximum of 120 mg/d in the second week and up to 160 mg/d in the third week. For the haloperidol group, patients received a startin dose of 5 mg/d, which could be increased to a maximum of 10 mg/d during the second week and 15 mg/ during the third week of treatment. At week 28, the mean doses of ziprasidone and haloperidol were 116 mg/d and 8.6 mg/d, respectively. Adverse events were evaluated using the Simpson-Angus scale, the Barnes Akathisia scale, and the Abnormal Involuntary Movement Scale (AIMS). Adverse events were reported in 85% of patients in the haloperidol group and 77% in the ziprasidone group; twice as many patients receiving haloperidol (16%) compared to ziprasidone (8%) discontinued the study due to treatment-related adverse events. There was also a distinct difference in the percentage of patients who developed movement disorders; 41% in the haloperidol group compared to 15% in the ziprasidone group although this difference was not statistically significant (Hirsch et al, 2002).

4.6.BG.2 Schizophrenic episode, acute

a) Acute exacerbations: ziprasidone 160 mg daily, haloperidol 15 mg daily comparable in efficacy (reduction of BPRS scores). Ziprasidone 4 to 40 mg/day less effective (Anon, 1996a).

b) Ziprasidone 160 milligrams (mg) and haloperidol 15 mg were both effective in improving overall psychopathology in patients with an acute exacerbation of schizophrenia or schizoaffective disorder (Go et al, 1998). In a double-blind, dose-ranging study, patients received either haloperidol 15 mg/day (n=17) or ziprasidone 4 mg (n=19), ziprasidone 10 mg (n=17), ziprasidone 40 mg (n=17), or ziprasidone 160 mg (n=20). Despite 46 patients failing to complete the study, intention-to-treat analysis showed a trend towa

significance for the ziprasidone dose response on the Brief Psychiatric Rating scale (p=0.08) and a statistically significant dose response for the Clinical Global Impression (CGI) scale (p less than 0.001). Changes in the CGI severity score were significantly changed from baseline as compared to the ziprasidone 4 mg group for both the haloperidol group (p less than 0.01) and the ziprasidone 160 mg gro (p=0.001). Study termination was due to 18 patients having a lack of efficacy (4 in the haloperidol group) due to liver transaminase elevations in ziprasidone groups, and 23 for unrelated reasons.
c) In hospitalized patients, the mean reductions in BPRS total, BPRS agitation items, and CGI were statistically greater after INTRAMUSCULAR (IM) ziprasidone than IM haloperidol, and this continued following conversion to oral treatment. The study was a multicenter, 7-day, randomized, open-label, parallel-group study in 7 countries (n=132). Patients received either an initial dose of ziprasidone 10 milligrams (mg) IM, followed by up to 3 days of flexible-dose IM ziprasidone (5 mg to 20 mg every 4 to 6 hours prn) and continued with oral treatment (80 mg to 200 mg/day) to day 7 (n = 90), or haloperidol IM (2.5 mg to 10 mg) on entry, followed by 2.5 mg to 10 mg IM every 4 to 6 hours prn up to 3 days followed oral haloperidol 10 mg/day to 80 mg/day to day 7 (n = 32). Ziprasidone was associated iwth a lower incidence of movement disorders compared to haloperidol (Brook et al, 2000).

4.6.BH Zotepine

Delusional disorder - Depression

Schizophrenia

4.6.BH.1 Delusional disorder - Depression

a) Zotepine 150 to 200 mg/day was as effective as a butyrophenone (haloperidol or bromperidol) approximately 10 mg/day, and had a better adverse effect profile than the butyrophenones, in two open, four-week studies of 31 patients with delusional depression (Wolfersdorf et al, 1994). All patients receive an antidepressant (maprotiline or amitriptyline, 150 mg/day) in addition to zotepine or the butyrophenone According to a 24-item version of the Hamilton depression scale, significant overall improvement was obtained with both zotepine and haloperidol or bromperidol. After one and two weeks of treatment, the improvement was significantly greater with zotepine. For a six-item list of delusional symptoms alone, bo groups improved significantly, and for the remaining non-delusional symptoms, the improvement was significant for both groups again (with significantly greater improvement with zotepine in the first two weeks). Zotepine, with its greater tolerability, is thus in many instances a viable alternative to highly pote butyrophenones in the treatment of delusional depression.

4.6.BH.2 Schizophrenia

a) There was no difference in efficacy between zotepine 50 milligrams (mg) 3 times daily and haloperido mg 3 times daily in the treatment of positive symptoms of schizophrenia in Chinese patients. After a washout period, patients (n=70) were randomly assigned to double-blind treatment with fixed doses of zotepine or haloperidol for 6 weeks. Although all of the efficacy measures tended to have greater score changes for haloperidol than for zotepine, there were no statistically significant differences between grou The greater score changes with haloperidol may have represented a lack of equivalency of doses. Dizziness, weight gain, and pulse rate were significantly higher with zotepine than with haloperidol, while the haloperidol group reported significantly more akathisia (Hwang et al, 2001).
b) Zotepine (mean dosage 309 mg/day) was as effective as haloperidol (mean dosage 14.5 mg/day) ora for six weeks in a randomized, double-blind study of 40 schizophrenics, and had a better side effect profi than haloperidol. Improvement measured according to the Brief Psychiatric Rating Scale (BPRS) total score reached statistical significance for both drugs on day 3, and at no point was there a significant difference between the two groups. For the individual BPRS factors, anxiety/depression was significantly improved in the zotepine group on day 14, as compared to haloperidol. Clinical Global Impression scores decreased similarly for both groups. Anticholinergic and extrapyramidal side effects were more common the haloperidol group. Liver function abnormalities were recorded in 12 and 6 patients from the zotepine and haloperidol groups, respectively, with one zotepine patient withdrawing from the study due to elevate liver enzymes (Fleischhacker et al, 1989).
c) Zotepine was more effective than haloperidol in controlling the negative effects of schizophrenia, and demonstrated better tolerability than haloperidol in a randomized, double-blind study of thirty schizophrer patients with similar characteristics (Barnas et al, 1992). The patients randomly received either zotepine to 150 mg/day (mean 94.4 mg/day) or haloperidol 2 to 6 mg/day (mean 4.2 mg/day) in oral capsule form the study period of seven weeks. Only zotepine significantly decreased schizophrenic behavior scores in the rating scales. Eight haloperidol patients did not complete the course due to side effects, while none o the zotepine patients experienced significant adverse effects. The authors noted that as most improved symptomatology was seen in the zotepine group after many haloperidol patients had already dropped ou of the study, longer therapy with haloperidol may have been more effective. However, zotepine was mor useful as it was better tolerated, and this must be recognized as a benefit of zotepine over haloperidol.
d) Similar advantages for zotepine (150 to 300 mg/day) versus haloperidol (10 to 20 mg/day) were

obtained in an 8-week, randomized, double-blind study of 126 schizophrenic patients. The mean reductic in Brief Psychiatric Rating Scale score was greater for zotepine compared to haloperidol (17.03 vs 13.45 not statistically significant). According to the Scale for Assessment of Negative Symptoms, zotepine was significantly more effective (p less than 0.05), and the adverse effect profile favored zotepine, particularly with respect to extrapyramidal symptoms. There were no occurrences of akathisia in patients treated wit zotepine compared with seven for haloperidol (Petit et al, 1996). Fixed doses of zotepine (225 mg/day) a haloperidol (12 mg/day) for four weeks in 26 schizophrenic patients resulted in comparable therapeutic efficacy with a clear advantage for zotepine with respect to global tolerability and extrapyramidal adverse effects (Klieser et al, 1991).

4.6.BI Zuclopenthixol

Dementia

Psychotic disorder

Tardive dyskinesia

4.6.BI.1 Dementia

a) Zuclopenthixol 4 to 5 milligrams orally daily was at least as effective as the combination of haloperido to 1.5 milligrams daily plus levomepromazine 6 to 8 milligrams daily in the treatment of elderly demented patients (over 80 years of age) with primary symptoms of agitation and aggressiveness in a 4-week, double-blind study (Fuglum et al, 1989). Zuclopenthixol was significantly superior to the combination at 2 weeks of treatment, but not at 4 weeks.

b) In an earlier double-blind study, oral zuclopenthixol 5 milligrams daily and oral haloperidol 0.5 milligra daily were associated with similar but minimal improvement in several rating scales (Clinical Global Impressions, Gottfries-Cronholm geriatric rating scale, Crichton geriatric rating scale) in elderly patients with dementia (Gotestam et al, 1981). Trends toward the superiority of zuclopenthixol were reported in some areas but these differences are of doubtful clinical significance.

4.6.BI.2 Psychotic disorder

a) Oral zuclopenthixol was similarly as effective as oral haloperidol in the treatment of chronic schizophrenia in a double-blind study involving 63 inpatients (Heikkila et al, 1981a). Mean daily doses of zuclopenthixol at week 1 and week 12 of therapy were 36 mg and 40 mg, respectively; corresponding doses of haloperidol were 7 mg and 10 mg, respectively. Adverse effects occurred with similar frequency although there was a trend toward a lower incidence of extrapyramidal effects in zuclopenthixol-treated patients. Similar findings were reported in another controlled study comparing oral haloperidol and zuclopenthixol in acute psychosis (Wistedt et al, 1991).

b) In 1 randomized study, intramuscular zuclopenthixol acetate was reported comparable in efficacy to parenteral haloperidol in treating patients with acute psychosis or an exacerbation of chronic psychosis; extrapyramidal symptoms were more frequent in haloperidol-treated patients (Bobon & De Bleeker, 1989

c) Intramuscular zuclopenthixol decanoate and haloperidol decanoate were similarly effective in the maintenance treatment of chronic schizophrenia in a 9-month double-blind study involving 64 patients (Wistedt et al, 1991). The average doses of zuclopenthixol decanoate and haloperidol decanoate at wee 36 of treatment were 284 milligrams and 92 milligrams, respectively; most patients received injections every 4 weeks. The incidence of extrapyramidal reactions was similar with both agents in this study, whic is in contrast to studies comparing shorter-acting formulations of haloperidol and zuclopenthixol. Other adverse effects also occurred with similar frequency; however, autonomic symptoms (eg, orthostatic dizziness, palpitations) tended to decrease with zuclopenthixol decanoate over the 9 months of treatmen whereas they increased with haloperidol decanoate during this period.

d) A double-blind, randomized study in 49 hospitalized patients with acute psychosis or exacerbation of chronic psychosis compared the clinical profile and frequency and severity of unwanted effects of oral zuclopenthixol and haloperidol (Heikkila et al, 1992). Patients initially received one of the two drugs with average daily dose of 33.5 milligrams or 7.6 milligrams, respectively, with doses titrated depending on patient response. Clinical efficacy scales and a side effect monitor were employed to evaluate efficacy a safety at baseline, one, two, four, six, and eight weeks with four weeks being the minimum study period analyzed. Both drugs were found to be effective in controlling psychotic episodes with no significant difference, and no difference in the incidence of side effects was seen. Zuclopenthixol had a slightly mor rapid onset of action as well as an earlier onset and elimination of extrapyramidal symptoms. Zuclopenthixol also appeared to have a stronger anxiolytic-antidepressant effect than haloperidol. The authors suggested that this study confirmed previous studies that both zuclopenthixol and haloperidol ar very efficacious and equally safe in treating acute psychoses.

e) Haloperidol (53 to 120 milligrams intramuscularly or orally over 6 days), zuclopenthixol (64 to 259 milligrams intramuscularly and orally over 6 days) and zuclopenthixol acetate (162 to 220 milligrams intramuscularly over 6 days) were compared in the treatment of acute psychoses (48 patients), mania (2

patients) and exacerbation of chronic psychoses (73 patients). Several measures of effectiveness, differi according to the initial diagnosis, were evaluated. The number of doses administered was significantly different in the zuclopenthixol acetate group (1 to 4) versus the haloperidol group (1 to 26) and the zuclopenthixol group (1 to 22). There was no significant difference in efficacy among any treatment regimens or initial diagnoses. Haloperidol caused significantly more hypokinesia during the first 24 hours but after that period there were no significant differences in any adverse effects. Based on the decreased number of doses administered, the authors concluded that zuclopenthixol acetate would be a useful addition to the therapeutic armamentarium (Baastrup et al, 1993).

4.6.BI.3 Tardive dyskinesia

a) It has been hypothesized that neuroleptics with both D1 and D2 antagonist activity are better drugs fo suppressing tardive dyskinesia than pure D2 antagonists. A study compared the effects of the mixed D1/ antagonist zuclopenthixol to that of the pure D2 antagonist haloperidol (Lublin et al, 1991). The double-blind crossover study consisted of 15 patients, who took each drug for three weeks. There was a six wee washout period. The subjects took either oral haloperidol 0.5 milligram twice a day, or oral zuclopenthixo milligrams twice a day. During treatment, benzodiazepines were prescribed on a prn basis for anxiety. Tardive dyskinesia and Parkinson-like symptoms were recorded on video tape and were scored by two raters. The changes and differences in the two groups regarding aggravation and suppression of tardive dyskinesia and Parkinson-like symptoms were compared using a paired t-test. There was no significant difference in the induction of tardive dyskinesia suppression and tardive dyskinesia withdrawal. Both drug induced or aggravated Parkinson-like symptoms. There were no differences between the groups. This study did not support the animal findings that a D1 component in a neuroleptic drug would lead to a stronger tardive dyskinesia suppression and to less withdrawal tardive dyskinesia.

6.0 References

1. .. ., .
2. .. Goodman and Gilman"s the pharmacologic basis of therapeutics. 8th ed., 1990.
3. .. Haldol Decanoate package insert (McNeil)., 1986.
4. AMA Department of Drugs: AMA Drug Evaluations, 4th. American Medical Association, Chicago, IL, 1980.
5. AMA Department of Drugs: AMA Drug Evaluations, 6th. American Medical Association, Chicago, IL, 1986.
6. AMA Department of Drugs: AMA Drug Evaluations, 6th. American Medical Association, Chicago, IL, 1986a.
7. AMA Department of DrugsAMA Department of Drugs: AMA Drug Evaluations, . American Medical Association, 5th ed, 5th. American Medical Association, Chicago, IL, 1983.
8. Abramson LB, Brown AJ, & Sitaram N: A cardioacceleratory response to low-dose arecoline infusion during sle in patients with major depressive disorder: relationship to REM sleep induction. Psych Res 1985; 16:189-198.
9. Absher JR & Bale JF Jr: Aggravation of myasthenia gravis by erythromycin. J Pediatr 1991; 119:155-156.
10. Abuzzahab FS & Zimmerman RL: Psychopharmacological correlates of post-psychotic depression: a double-blind investigation of haloperidol vs thiothixene in outpatient schizophrenia. J Clin Psychiatry 1982; 43:105-110
11. Adams F, Fernandez F, & Andersson BS: Emergency pharmacotherapy of delirium in the critically ill cancer patient. Psychosomatics 1986; 27(suppl):33-37.
12. Adams S & Fernandez F: Intravenous use of haloperidol.. Hospital Pharmacy 1987; 22:306-7.
13. Adams SL, Mathews J, & Grammer LC: Drugs that may exacerbate myasthenia gravis. Ann Emerg Med 1984; 13:532-538.
14. Addonizio G, Roth SD, Stokes PE, et al: Increased extrapyramidal symptoms with addition of lithium to neuroleptics. J Nerv Ment Dis 1988; 176:682-685.
15. Addonizio G, Roth SD, Stokes PE, et al: Increased extrapyramidal symptoms with addition of lithium to neuroleptics. J Nerv Ment Dis 1988a; 176:682-685.
16. Agelink MW, Majewski T, Wurthmann C, et al: Effects of newer atypical antipsychotics on autonomic neurocardiac function: a comparison between amisulpride, olanzapine, sertindole, and clozapine. J Clin Psychopharmacol 2001o; 21(1):8-13.
17. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001; 5:33-40.
18. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001a; 5:33-40.
19. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001aa; 5:33-40.
20. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001b; 5:33-40.
21. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001c; 5:33-40.
22. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001d; 5:33-40.
23. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001e; 5:33-40.
24. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001f; 5:33-40.

25. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001g; 5:33-40.
26. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001h; 5:33-40.
27. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001i; 5:33-40.
28. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001j; 5:33-40.
29. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001k; 5:33-40.
30. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001l; 5:33-40.
31. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001m; 5:33-40.
32. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001n; 5:33-40.
33. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001p; 5:33-40.
34. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001q; 5:33-40.
35. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001r; 5:33-40.
36. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001s; 5:33-40.
37. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001t; 5:33-40.
38. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001u; 5:33-40.
39. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001v; 5:33-40.
40. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001w; 5:33-40.
41. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001x; 5:33-40.
42. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001y; 5:33-40.
43. Agelink MW, Zeit T, Baumann B, et al: In vivo cardiovascular effects of the new atypical neuroleptic sertindole. J Psychiatry Clin Pract 2001z; 5:33-40.
44. Ahlfors UG, Rimon R, Appelberg B, et al: Remoxipride and haloperidol in schizophrenia: a double-blind multicentre study. Acta Psychiatr Scand 1990; 82(suppl 358):99-103.
45. Alessi NE, Walden M, & Hsieh PS: Nifedipine-haloperidol combination in the treatment of Gilles de la Tourette' syndrome: A case study. J Clin Psychiatry 1989; 50:103-104.
46. Alexander HE, McCarty K, & Giffen MB: Hypotension and cardiopulmonary arrest associated with concurrent haloperidol and propranolol therapy. JAMA 1984; 252(1):87-88.
47. Allwood MC: The compatibility of high-dose diamorphine with cyclizine or haloperidol in plastic syringes. Int Pharm J 1991; 5:120.
48. Allwood MC: The compatibility of high-dose diamorphine with cyclizine or haloperidol in plastic syringes. Int Pharm J 1991a; 5:120.
49. Amdisen A: Lithium and drug interactions. Drugs 1982; 24:133-139.
50. Amdurski S, Radwan M, Levi A, et al: A therapeutic trial of amantadine in haloperidol-induced malignant neuroleptic syndrome. Curr Ther Res 1983; 33:225-229.
51. Amiel JM, Mangurian CV, Ganguli R, et al: Addressing cardiometabolic risk during treatment with antipsychotic medications. Curr Opin Psychiatry 2008; 21(6):613-618.
52. Ananth J: Tardive dyskinesia: myths and realities. Psychosomatics 1980; 21:394-396.
53. Andersen J, Korner A, Ostergaard P, et al: A double blind comparative multicentre study of remoxipride and haloperidol in schizophrenia. Acta Psychiatry Scand 1990; 82:(suppl 358):104-107.
54. Anderson BG, Reker D, & Cooper TB: Prolonged adverse effects of halperidol in normal subjects. N Engl J Me 1981; 305:643-644.
55. Anderson KE, Bloomer JR, Bonkovsky HL, et al: Recommendations for the diagnosis and treatment of the acu porphyrias. Ann Intern Med 2005; 142(6):439-450.
56. Anderson LT, Campbell M, Grega DM, et al: Haloperidol in the treatment of infantile autism: effects on learning and behavioral symptoms. Am J Psychiatry 1984; 141:1195-1202.
57. Anderson RJ, Gambertoglio JG, & Schrier RW: Clinical Use of Drugs in Renal Failure, Charles C Thomas, Springfield, IL, 1976.
58. Anderson RJ, Gambertoglio JG, & Schrier RWAnderson RJ, Gambertoglio JG, & Schrier RW: Clinical Use of Drugs in Renal Failure, Charles C Thomas, Springfield, IL, 1976a.
59. Anon: ASHP Therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. Am J Health-Syst Pharm

1999; 56:729-764.
60. Anon: American academy of pediatrics committee on drugs: transfer of drugs and other chemicals into human milk. Pediatrics 2001; 108(3):776-789.
61. Anon: An expanding range of atypical antipsychotic agents to choose from (review). Drugs Ther Perspect 1996 8:1-5.
62. Anon: Antiemesis Clinical Practice Panel: NCCN Antiemesis practice guidelines. ; version 1, 2003.
63. Anon: Aripiprazole. Drugs Fut 2000; 25(9):961.
64. Anon: Boston Collaborative Drug Surveillance Program: Drug-Induced Extrapyramidal Symptoms. A Cooperati Study. JAMA 1973a; 224:889-891.
65. Anon: Boston Collaborative Surveillance Program: Drug-induced extrapyramidal symptoms. A cooperative stuc JAMA 1973; 224:889-891.
66. Anon: Breastfeeding and Maternal Medication. World Health Organization, Geneva, Switzerland, 2002.
67. Anon: Department of Health and Human Services; Substance abuse and mental health services administratior 42 CFR Part 8. Opioid drugs in maintenance and detoxification treatment of opiate addiction; addition of buprenorphine and buprenorphine combination to list of approved opioid treatment medications. Federal Regis 2003a; 68:27937-27939.
68. Anon: F-D-C Reports: The Pink Sheet. ; T&G#10, December 18, 1995.
69. Anon: FDC Reports: The Pink Sheet. ; 58:T&G 3, January 15, 1996a.
70. Anon: Food and drug administration center for drug evaluation and research psychopharmacologic drugs advisory committee. U.S. Food and Drug Administration. Rockville, MD, USA. 2000. Available from URL: http://www.fda.gov/OHRMS/DOCKETS/AC/00/transcripts/ 3619t1.rtf. As accessed Accessed December 2000.
71. Anon: Ketek myasthenia gravis warning. SCRIP (World Pharmaceutical News) 2003b; 2842(April 18):23.
72. Anon: Nordic Dyskinesia Study Group: Effect of different neuroleptics in tardive dyskinesia and parkinsonism. Psychopharmacology 1986; 90:423-429.
73. Anon: Practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry 1997; 154(suppl):1-6
74. Anon: SCRIP World Pharmaceutical News. PJB Publications Ltd, London, UK; No 2093, p 27, January 12, 199
75. Anon: Sertindole therapy is effective in patients with schizophrenia. Am Fam Physician 1996b; 53:939-940.
76. Appleton WS et al: Before drug therapy begins, choosing an antipsychotic and principles of prescribing antipsychotics. In: Appleton WS, ed. Practical Clinical Psychopharmacology, 2nd ed, Williams & Wilkins, Baltimore, MD, 1980, p 1, 1980.
77. Arana GW, Goff DC, Friedman H, et al: Does carbamazepine-induced reduction of plasma haloperidol levels worsen psychotic symptoms?. Am J Psychiatry 1986; 143:650-651.
78. Arana GW, Goff DC, Friedman H, et al: Does carbamazepine-induced reduction of plasma haloperidol levels worsen psychotic symptoms?. Am J Psychiatry 1986a; 143:650-651.
79. Argov Z & Mastaglia FL: Disorders of neuromuscular transmission caused by drugs. N Engl J Med 1979; 301:409-413.
80. Asnis GM, Sachar EJ, Langer G, et al: Prolactin responses to haloperidol in normal young women. Psychoneuroendocrinology 1988; 13:515-520.
81. Australian Drug Evaluation Committee: Prescribing medicines in pregnancy: An Australian categorisation of ris of drug use in pregnancy. Therapeutic Goods Administration. Australian Capital Territory, Australia. 1999. Available from URL: http://www.tga.gov.au/docs/html/medpreg.htm.
82. Awad AG & Hogan TP: Early treatment events and prediction of response to neuroleptics in schizophrenia. Pro Neuropsychopharmacol Biol Psychiatry 1985; 9:585-588.
83. Ayd F: Penfluridol: a long-acting oral neuroleptic. Int Drug Ther Newsletter 1972; 7:13.
84. Ayd FJ Jr: Haloperidol: twenty years' clinical experience. J Clin Psychiatry 1978; 39:807-814.
85. Ayd FJ Jr: Respiratory dyskinesias in patients with neuroleptic-induced extrapyramidal reactions. Int Drug Ther Newslett 1979; 14:1-3.
86. Ayd FJ: Psychotropic drug therapy during pregnancy. Int Drug Ther Newsletter 1976; 11:5.
87. Baastrup PC, Alhfors UG, Bjerkenstedt L, et al: A controlled nordic multicentre study of zuclopenthixol acetate oil solution, haloperidol and zuclopenthixol in the treatment of acute psychosis. Acta Psychiatr Scand 1993; 87:48-58.
88. Backonja M, Beinlich B, Dulli D, et al: Haloperidol and lorazepam for the treatment of nausea and vomiting associated with the treatment of intractable migraine headaches (letter). Arch Neurol 1989; 46:724.
89. Bamrah JS, Kumar V, Krska J, et al: Interactions between procyclidine and neuroleptic drugs: some pharmacological and clinical aspects. Br J Psychiatry 1986; 149:726-733.
90. Barbhaiya RH, Shukla UA, Greene DS, et al: Investigation of pharmacokinetic and pharmacodynamic interacti after coadministration of nefazodone and haloperidol. J Clin Psychopharmacol 1996; 16:26-34.
91. Barcai A: Acta Psychiatr Scand 1977; 55:97-101. Acta Psychiatr Scand 1977; 55:97-101.
92. Bardfeld PA: A controlled double-blind study of trimethobenzamide, prochlorperazine, and placebo. JAMA 196 196:796-798.
93. Barnas C, Stuppaeck C, Miller C, et al: Zotepine in the treatment of schizophrenic patients with prevailingly negative symptoms: a double-blind trial vs haloperidol. Int Clin Psychopharmacol 1992; 7:23-27.
94. Barton MD, Libonati M, & Cohen PJ: The use of haloperidol for treatment of postoperative nausea and vomiting a double-blind placebo-controlled trial. Anesthesiology 1975; 42:508-512.
95. Batey SR: Schizophrenic disorders In: DiPiro JT, Talbert RL, Hayes PE, et al (Eds): Pharmacotherapy A Pathophysiologic Approach, Elsevier, New York, NY, 1989.
96. Batey SR: Schizophrenic disorders In: DiPiro JT, Talbert RL, Hayes PE, et al (Eds): Pharmacotherapy A Pathophysiologic Approach, Elsevier, New York, NY, 1989a.

97. Battaglia J, Moss S, Rush J, et al: Haloperidol. lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. Am J Emerg Med 1997; 15:335-340.
98. Benazzi F: Urinary retention with fluoxetine-haloperidol combination in a young patient. Can J Psychiatry 1996 41:606-607.
99. Benazzi F: Urinary retention with fluoxetine-haloperidol combination in a young patient. Can J Psychiatry 1996 41:606-607.
100. Bennett WM, Aronoff GR, Golper TA, et al: Drug Prescribing in Renal Failure, American College of Physicians, Philadelphia, PA, 1994.
101. Berciano J, Oterino A, Rebollo M, et al: Myasthenia gravis unmasked by cocaine abuse (letter). N Engl J Med 1991; 325:892.
102. Beresford R & Ward A: Haloperidol decanoate. A preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in psychosis.. Drugs 1987; 33:31-49.
103. Beresford R & Ward A: Haloperidol decanoate: a preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in psychosis. Drugs 1987a; 33:31-49.
104. Berk M, Brook k S, & Trandafir AI: A comparison of olanzapine with haloperidol in cannabis-induced psychotic disorder: a double-blind randomized controlled trial. Int Clin Psychopharmacol 1999; 14:177-180.
105. Berkow R (Ed): Merck Manual, Rahway: Merck and Co, Inc, 1982; 14:1301, Merck and Co, Inc, Merck Manual Rahway, 1982, pp 14:1301.
106. Berkowitz RL, Coustan DR, & Mochizaki TKBerkowitz RL, Coustan DR, & Mochizaki TK: Handbook for Prescribing Medications During Pregnancy, 1st. Little Brown & Company, Boston, MA, 1981.
107. Bescansa E, Nicolas M, Aguado C, et al: Myasthenia gravis aggravated by pyrantel pamoate. J Neurol Neuros Psychiatry 1991; 54:563.
108. Bieniek SA, Ownby RL, Penalver A, et al: A double-blind study of lorazepam versus the combination of haloperidol and lorazepam in managing agitation. Pharmacotherapy 1998; 18:57-62.
109. Bilder RM, Goldman RS, Volavka J, et al: Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 2002; 159(6):10 1028.
110. Bilder RM, Goldman RS, Volavka J, et al: Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 2002a; 159 (6):1018-1028.
111. Bilder RM, Goldman RS, Volavka J, et al: Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry 2002b; 159 (6):1018-1028.
112. Binder R & Jonelis F: Seborrheic dermatitis in neuroleptic-induced parkinsonism. Arch Dermatol 1983; 119:473 475.
113. Binder R, Glick I, & Rice M: A comparative study of parenteral molindone and haloperidol in the acutely psych patient. J Clin Psychiatry 1981; 42:203-206.
114. Bjorndal N, Bjerre M, Gerlach J, et al: High dosage haloperidol therapy in chronic schizophrenic patients: a double blind study of clinical response, side effects, serum haloperidol and serum prolactin. Psychopharmacol 1980; 67:17-23.
115. Blake LM, Marks RC, & Luchins DJ: Reversible neurologic symptoms with clozapine and lithium. J Clin Psychopharmacol 1992; 12:297-299.
116. Blasing J, Herz A, & Gramsch C: Effects of depletion of brain catecholamines during the development of morphine dependence on precipitated withdrawal in rats. Naughyn-Schmiedeberg's Arch Pharmacol 1975; 286:325-336.
117. Blumenthal, M, Busse WR, et alBlumenthal, M, Busse WR, et al (Eds): The Complete German Commission E Monographs, 1st. American Botanical Council, Austin, TX, 1998, pp 87-88.
118. Boachie A, Goldfield GS, & Spettigue W: Olanzapine use as an adjunctive treatment for hospitalized children v anorexia nervosa: case reports. Int J Eat Disord 2003; 33:98-103.
119. Bobon D & De Bleeker E: Zuclopenthixol acetate and haloperidol in acute psychotic patients. A randomized multicentre study (abstract), ECNP Congress, Gothenburg, Sweden, 1989.
120. Bollini P, Pampallona S, Orza MJ, et al: Antipsychotic drugs: is more worse? A meta-analysis of the published randomized control trials. Psychol Med 1994; 24:307-316.
121. Borson S & Raskind MA : Clinical features and pharmacologic treatment of behavioral symptoms of Alzheimer' disease. Neurology 1997; 48(5 Suppl 6):S17-S24.
122. Bostwick JR, Guthrie SK, & Ellingrod VL: Antipsychotic-induced hyperprolactinemia. Pharmacotherapy 2009; 2 (1):64-73.
123. Bransgrove LL & Kelly MW: Movement disorders in patients treated with long-acting injectable antipsychotic drugs. Am J Hosp Pharm 1994; 51:895-899.
124. Bratfos O & Haug JO: Comparison of sulpiride and chlorpromazine in psychosis: a double-blind multicenter stu Acta Psychiatr Scand 1979; 60:1-9.
125. Brayley J & Yellowlees P: An interaction between haloperidol and carbamazepine in a patient with cerebral pal Aust N Z J Psychiatry 1987; 21:605-607.
126. Bregni M, Siena S, Di Nicola M, et al: Tropisetron plus haloperidol to ameliorate nausea and vomiting associat with high-dose alkylating agent cancer chemotherapy. Eur J Cancer 1991; 27:561-565.
127. Breitbart W, Marotta R, Platt MM, et al: A double-blind trial of haloperidol, chlorpromazine, and lorazepam in th treatment of delirium in hospitalized AIDS patients. Am J Psychiatry 1996; 153:231-237.
128. Breitbart W, Marotta R, Platt MM, et al: A double-blind trial of haloperidol, chlorpromazine, and lorazepam in th

treatment of delirium in hospitalized AIDS patients. Am J Psychiatry 1996a; 153:231-237.
129. Breitbart W, Marotta R, Platt MM, et al: A double-blind trial of haloperidol, chlorpromazine, and lorazepam in th treatment of delirium in hospitalized AIDS patients. Am J Psychiatry 1996b; 153:231-237.
130. Bristol JH: Haloperidol and phobias. Am J Psychiatry 1982; 139:1373-1374.
131. Brook S, Lucey JV, & Gunn KP: Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. J Clin Psychiatry 2000; 61:933-941.
132. Brotman AW & McCormick S III: A role for high-dose antipsychotics. J Clin Psychiatry 1990; 51:164-166.
133. Brown K, Levy H, Brenner C, et al: Overdose of risperidone. Ann Emerg Med 1993; 22:1908-1910.
134. Brown K, Levy H, Brenner C, et al: Overdose of risperidone. Ann Emerg Med 1993a; 22:1908-1910.
135. Brown LA & Levin GM: Sertindole, a new atypical antipsychotic for the treatment of schizophrenia. Pharmacotherapy 1998a; 18(1):69-83.
136. Brown LA & Levin GM: Sertindole, a new atypical antipsychotic for the treatment of schizophrenia. Pharmacotherapy 1998b; 18(1):69-83.
137. Brown LA & Levin GM: Sertindole, a new atypical antipsychotic for the treatment of schizophrenia. Pharmacotherapy 1998c; 18(1):69-83.
138. Brown LA & Levin GM: Sertindole, a new atypical antipsychotic for the treatment of schizophrenia. Pharmacotherapy 1998d; 18(1):69-83.
139. Brown LA & Levin GM: Sertindole, a new atypical antipsychotic for the treatment of schizophrenia. Pharmacotherapy 1998e; 18(1):69-83.
140. Brown LA & Levin GM: Sertindole: a new atypical antipsychotic for the treatment of schizophrenia. Pharmacotherapy 1998; 18(1):69-83.
141. Bruun R: Dysphoric phenomena associated with haloperidol treatment of Tourette's syndrome In: Bruun R: Friedhoff AJ & Chase TN: Gilles de la Tourette syndrome, Raven Press, New York, NY, 1982, pp 433-436.
142. Bucci L & Marini S: Haloperidol decanoate in chronic schizophrenic patients. Curr Ther Res 1985; 37:1091-109
143. Burke AM, White AB, & Brill N: Baclofen for intractable hiccups. N Engl J Med 1988; 319(20):1354.
144. Bush SE, Hatton RC, Winterstein AG, et al: Effects of concomitant amiodarone and haloperidol on Q-Tc interva prolongation. Am J Health Syst Pharm 2008; 65(23):2232-2236.
145. Butterworth AT: Inhibition of extrapyramidal side effects of haloperidol through the joint use of imipramine-type drugs. Psychosomatics 1972; 13:328-332.
146. Cadisch R, Streit E, & Hartmann K: Exazerbation einer Myasthenia gravis pseudoparalytica nach Azithromycin (Zithromax(R)). Schweiz Med Wochenschr 1996; 126:308-310.
147. Caine ED & Polinsky RJ: Haloperidol-induced dysphoria in patients with tourette syndrome. Am J Psychiatry 1979; 136:1216-1217.
148. Campbell M, Anderson CT, Small AM, et al: The effects of haloperidol on learning and behavior in autistic children. J Autism Dev Disord 1982a; 12:167-175.
149. Campbell M, Small AM, Green WH, et al: Behavioral efficacy of haloperidol and lithium carbonate. Arch Gen Psychiatry 1984; 41:650-656.
150. Cardoni AA & Myer S: Sertindole: an atypical antipsychotic for the treatment of schizophrenia. Formulary 1997 32:907-925.
151. Cardoni AA & Myer S: Sertindole: an atypical antipsychotic for the treatment of schizophrenia. Formulary 1997 32:907-925.
152. Cardoni AA & Myer S: Sertindole: an atypical antipsychotic for the treatment of schizophrenia. Formulary 1997 32:907-925.
153. Carli M, Anand-Srivastava MB, Molina-Holgado E, et al: Effects of chronic lithium treatments on central dopaminergic receptor systems: G proteins as possible targets. Neurochem Int 1994; 24:13-22.
154. Carlson CD, Cavazzoni PA, Berg PH, et al: An integrated analysis of acute treatment-emergent extrapyramida syndrome in patients with schizophrenia during olanzapine clinical trials: comparisons with placebo, haloperidc risperidone, or clozapine. J Clin Psychiatry 2003; 64(8):898-906.
155. Carriere P, Bonhomme D, & Leperiere T: Amisulpride has a superior benefit/risk profile to haloperidol in schizophrenia: results of a multicentre, double-blind study (the Amisulpride Study Group). Eur Psychiatry 2000 15:321-329.
156. Carter JG: Intravenous haloperidol in the treatment of acute psychosis (letter). Am J Psychiatry 1986; 143:131 1317.
157. Cassano GB, Castrogiovanni P, & Conti L: Sulpiride versus haloperidol in schizophrenia: a double-blind comparative trial. Curr Ther Res 1975; 17:189-701.
158. Cassano GB, Miniati M, Pini S, et al: Six-month open trial of haloperidol as an adjunctive treatment for anorexi nervosa: a preliminary report. Int J Eat Disord 2003; 33:172-177.
159. Cavanaugh JJ & Finlayson RE: Rhabdomyolysis due to acute dystonic reaction to antipsychotic drugs. J Clin Psychiatry 1984; 45:356-357.
160. Cersosimo RJ & Brophy MT: Hiccups with high dose dexamethasone administration: a case report. Cancer 19 82(2):412-414.
161. Chan WC, Lam LCW, Choy CNP, et al: A double-blind randomised comparison of risperidone and haloperidol the treatment of behavioral and psychological symptoms in Chinese dementia patients. Int J Geriatr Psychiatry 2001; 16:1156-1162.
162. Charney DS: The clinical use of clonidine in abrupt withdrawal from methadone. Arch Gen Psychiatry 1981; 38:1273.
163. Chen B & Cardasis W: Delirium induced by lithium and risperidone combination (letter). Am J Psychiatry 1996; 153:1233-1234.

164. Cheng YF, Paalzow LK, Bondesson U, et al: Pharmacokinetics of haloperidol in psychotic patients. Psychopharmacology 1987; 91:410-414.
165. Chiang E, Pitts WM Jr, & Rodriguez-Garcia M: Respiratory dyskinesia: review and case reports. J Clin Psychia 1985; 46:232-234.
166. Chien CP: Past history of drug and somatic treatments in tardive dyskinesia In: Fann WE, Smith RC, David JM al (Eds): Tardive Dyskinesia. Research and Treatment, SP Medical & Scientific Books, New York, NY, 1980, p 315-324.
167. Chisholm CA & Kuller JA: A guide to the safety of CNS-active agents during breastfeeding. Drug Saf 1997; 17 (2):127-142.
168. Chouinard G & Annable L: Penfluridol in the treatment of newly admitted schizophrenic patients in brief therapy unit. Am J Psychiatry 1976; 133:820-823.
169. Chouinard G, Annable L, & Kolivakis TN: Penfluridol in the maintenance treatment of schizophrenic patients newly discharged from a brief therapy unit. J Clin Pharmacol 1977; 17:162-167.
170. Chouinard G, Annable L, Campbell W, et al: A double-blind, controlled clinical trial of haloperidol decanoate an fluphenazine decanoate in the maintenance treatment of schizophrenia. Psychopharmacol Bull 1984; 20:108-109.
171. Chouinard G, Annable L, Turnier L, et al: A double-blind randomized clinical trial of rapid tranquilization with IM clonazepam and IM haloperidol in agitated psychotic patients with manic symptoms. Can J Psychiatry 1993a; 38:S114-S121.
172. Chouinard G, Jones BJ, Remington G, et al: A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol 1993; 1 (1):25-40.
173. Chouinard G, Pinard G, Serrano M, et al: Potentiation of haloperidol by alpha-methyldopa in the treatment of schizophrenic patients. Curr Ther Res 1973; 15:473-483.
174. Christensen DB & Benfield WR: Alprazolam as an alternative to low-dose haloperidol in older, cognitively impaired nursing facility patients. J Am Geriatr Soc 1998; 46:620-625.
175. Christman RS, Weinstein RA, & Larose JB: Low-dose haloperidol as antiemetic treatment in gastrointestinal disorders: a double-blind study. Curr Ther Res 1974; 16:1171-1176.
176. Chu NS: Sympathetic response to betel chewing. J Psychoact Drugs 1995; 27(2):183-186.
177. Citrome L, Volavka J, Czobar P, et al: Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia. Psych Serv 2001; 52(11):1510-1514.
178. Claghorn JL, Mathew RJ, & Mirabi M: Penfluridol: a long acting oral antipsychotic drug. J Clin Psychiatry 1979; 40:107-109.
179. Clarke DJ & Ford R: Treatment of refractory Tourette syndrome with haloperidol decanoate. Acta Psychiatr Scand 1988; 77:495-496.
180. Class CA, Schneider L, & Farlow MR: Optimal management of behavioural disorders associated with dementia Drugs Aging 1997; 10(2):95-106.
181. Claus A, Bollen J, De Cuyper H, et al: Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: A multicentre double-blind comparative study. Acta Psychiatr Scand 1992; 85:295-305.
182. Clinton JE, Sterner S, Stelmachers Z, et al: Haloperidol for sedation of disruptive emergency patients. Ann Em Med 1987; 16:319-322.
183. Coccaro EF, Kramer E, Zemishlany Z, et al: Pharmacologic treatment of noncognitive behavioral disturbances elderly demented patients. Am J Psychiatry 1990; 147:1640-1645.
184. Coccaro EF, Kramer E, Zemishlany Z, et al: Pharmacologic treatment of noncognitive behavioral disturbances elderly demented patients. Am J Psychiatry 1990a; 147:1640-1645.
185. Cohen IL, Campbell M, & Posner D: A study of haloperidol in young autistic children: a within-subjects design using objective rating scales. Psychopharmacol Bull 1980; 16:63-65.
186. Cohen WJ & Cohen NH: Lithium carbonate, haloperidol and irreversible brain damage. JAMA 1974; 230:1283-1287.
187. Cohen WJ & Cohen NH: Lithium carbonate, haloperidol and irreversible brain damage. JAMA 1974a; 230:1283 1287.
188. Cohen-Mansfield J, Lipson S, Werner P, et al: Withdrawal of haloperidol, thioridazine, and lorazepam in the nursing home. Arch Intern Med 1999; 159:1733-1740.
189. Cole DR & Duffy DF: Haloperidol for radiation sickness. control of associated nausea, vomiting, and anorexia. Y J Med 1974; 74:1553.
190. Collins K & Comer J: Maternal haloperidol therapy associated with dyskinesia in a newborn. Am J Health-Syst Pharm 2003; 60:2253-2255.
191. Colonna L, Saleem P, Dondey-Nouvel L for the Amisulpride Study, et al: Long-term safety and efficacy of amisulpride in subchronic or chronic schizophrenia. Int Clin Psychopharmacol 2000; 15:13-22.
192. Colvin CL & Tankanow RM: Pimozide: Use in Tourette's syndrome. Drug Intell Clin Pharm 1985; 19:421-424.
193. Copolov DL, Link CGG, & Kowalcyk B: A multicentre, double-blind, randomized comparison of quetiapine (ICI 204,636, 'Seroquel') and haloperidol in schizophrenia. Psychological Med 2000; 30:95-105.
194. Coryell W, Miller DD, & Perry PJ: Haloperidol plasma levels and dose optimization. Am J Psychiatry 1998; 155:48-53.
195. Craig TJ: Swallowing, tardive dyskinesia, and anticholinergics. Am J Psychiatry 1982; 139:1083.
196. Crane GE: Persistant dyskinesia. Br J Psychiatry 1973; 122:395-405.
197. Cressman WA, Bianchine JR, Slotnick VB, et al: Plasma level profile of haloperidol in man following IM administration. Eur J Clin Pharmacol 1974a; 7:99-103.

198. Cressman WA, Bianchine JR, Slotnick VB, et al: Plasma level profile of haloperidol in man following intramuscular administration.. Eur J Clin Pharmacol 1974; 7:99-103.
199. Crisp AH, Lacey JH, & Crutchfield M: Clomipramine and "drive" in people with anorexia nervosa: an in-patient study. Br J Psychiatry 1987; 150:355-358.
200. Cruz FG, Thiagarajan D, & Harney JH: Neuroleptic malignant syndrome after haloperidol therapy. South Med J 1983; 76:684-685.
201. Csernansky JG, Mahmoud R, Brenner R, et al: A comparison of risperidone and haloperidol for the prevention relapse in patients with schizophrenia. New Engl J Med 2002; 346:16-22.
202. Cummingham DG & Challapalli M: Hypertension in acute haloperidol poisoning. J Pediatr 1979; 95:489-490.
203. Cummings JL, Gorman DG, & Shapira J: Physostigmine Ameliorates the delusions of alzheimer's disease. Bio Phychiatry 1993; 33:536-541.
204. Cung DD & Stimmel GL: Reemergence of positive symptoms after initial response to risperidone. Pharmacotherapy 1997; 17:383-386.
205. Cutler R & Heiser JF: Leukopenia following treatment with thiothixene and haloperidol. JAMA 1979; 242:2872.
206. D'Arcy PF & Griffin JP: Iatrogenic Diseases, 2nd. Oxford University Press, New York, 1979.
207. Daniel DG, Randolph C, Jaskiw G, et al: Coadministration of fluvoxamine increases serum concentrations of haloperidol. J Clin Psychopharmacol 1994; 14:340-343.
208. Daniel DG, Randolph C, Jaskiw G, et al: Coadministration of fluvoxamine increases serum concentrations of haloperidol. J Clin Psychopharmacol 1994a; 14:340-343.
209. Daras M, Samkoff LM & Koppel BS: Exacerbation of myasthenia gravis associated with cocaine use. Am Acad Neurol 1996; 271-272, 1996.
210. Das Gupta V & Stewart KR: Stability of haloperidol in 5% dextrose injection. Am J Hosp Pharm 1982; 39:292-294.
211. Davies DM: Textbook of Adverse Drug Reactions, 2nd. Oxford University Press, New York, 1981.
212. Davis TME, Dembo LG, Kaye-Eddie SA, et al: Neurological, cardiovascular and metabolic effects of mefloquin in healthy volunteers: a double-blind, placebo-controlled trial. Br J Clin Pharmacol 1996; 42:415-421.
213. Davison K: Pharmacological treatment for intractable sneezing. Br Med J 1982; 284:1163-1164.
214. Daw JL & Cohen-Cale SA: Haloperidol analgesia. South Med J 1981; 74:364-365.
215. De Maio D: Withdrawal syndrome after neuroleptics. Br J Psychiatry 1973; 123:377-378.
216. DeVane CL: Nefazodone--pharmacology and efficacy of a new antidepressant agent: formulary considerations and T 1995; 20:363-374.
217. Deahl M: Betel nut-induced extrapyramidal syndrome: an unusual drug interaction. Movement Disord 1989; 4 (4):330-333.
218. Deahl M: Betel nut-induced extrapyramidal syndrome: an unusual drug interaction. Movement Disord 1989a; 4 (4):330-333.
219. Debray H & Galland A: Haloperidol poisoning at therapeutic doses in children. Ann Pediatr 1970; 17(6):498-50
220. Delamere JP, Jobson S, Mackintosh LP, et al: Penicillamine-induced myasthenia in rheumatoid arthritis: its clinical and genetic features. Ann Rheum Dis 1983; 42:500-504.
221. Delcker A, Schoon ML, Oczkowski B, et al: Amisulpride versus haloperidol in treatment of schizophrenic patier - results of a double-blind study. Pharmacopsychiatry 1990; 23:125-130.
222. Dencker SJ, Gios I, Martensson E, et al: A long-term cross-over pharmacokinetic study comparing perphenazi decanoate and haloperidol decanoate in schizophrenic patients. Psychopharmacology 1994; 114:24-30.
223. Denijs EL: Clinical evaluation of bromperidol versus haloperidol in psychotic patients. Int Pharmacopsychiatry 1980; 15:309-317.
224. Deo R, Soni S, Rastogi SC, et al: Remoxipride and haloperidol in the acute phase of schizophrenia: a double-blind comparison. Acta Psychiatry Scand 1990; 82(suppl 358):120-124.
225. Devanand DP, Marder K, Michaels KS, et al: A randomized, placebo-controlled dose-comparison trial of haloperidol for psychosis and disruptive behaviors in alzheimer's disease. Am J Psychiatry 1998; 155(11):1512 1520.
226. Devanand DP, Sackeim HA, Brown RP, et al: A pilot study of haloperidol treatment of psychosis and behavior disturbance in Alzheimer's disease. Arch Neurol 1989; 46:854-857.
227. Diav-Citrin O, Shechtman S, Ornoy S, et al: Safety of haloperidol and penfluridol in pregnancy: a multicente, prospective, controlled study. J Clin Psychiatry 2005; 66:3:317-322.
228. Dincsoy HP & Saelinger DA: Haloperidol-induced chronic cholestatic liver disease. Gastroenterology 1982; 83:694-700.
229. Doenecke AL & Heuermann RC: Treatment of haloperidol abuse with diphenhydramine. Am J Psychiatry 1980 137:487-488.
230. Dole UP, Nyswander ME, & Kreek MS: Narcotic blockade. Arch Intern Med 1966; 118:304.
231. Donlon PT, Hopkin JT, Tupin JP, et al: Haloperidol for acute schizophrenic patients. Arch Gen Psychiatry 1980 37:691-695.
232. Dorevitch A, Katz N, Zemishlany Z, et al: Intramuscular flunitrazepam versus intramuscular haloperidol in the emergency treatment of aggressive psychotic behavior. Am J Psychiatry 1999; 156(1):142-144.
233. Dosani RA: Haloperidol-induced neuroleptic malignant syndrome. South Med J 1983; 76:546.
234. Dr Paparno, McNeil Pharmaceuticals, Professional Services, 5
235. Drachman DB: Myasthenia gravis (part I). N Engl J Med 1978; 298:136-142.
236. Drachman DB: Myasthenia gravis (part II). N Engl J Med 1978a; 298:186-193.
237. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999; 37(7):893-894.

238. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999aa; 37(7):893-894.
239. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999ab; 37(7):893-894.
240. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999b; 37(7):893-894.
241. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999c; 37(7):893-894.
242. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999d; 37(7):893-894.
243. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999e; 37(7):893-894.
244. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999f; 37(7):893-894.
245. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999g; 37(7):893-894.
246. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999h; 37(7):893-894.
247. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999i; 37(7):893-894.
248. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999j; 37(7):893-894.
249. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999k; 37(7):893-894.
250. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999l; 37(7):893-894.
251. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999m; 37(7):893-894.
252. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999n; 37(7):893-894.
253. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999o; 37(7):893-894.
254. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999p; 37(7):893-894.
255. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999q; 37(7):893-894.
256. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999r; 37(7):893-894.
257. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999s; 37(7):893-894.
258. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999t; 37(7):893-894.
259. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999u; 37(7):893-894.
260. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999v; 37(7):893-894.
261. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999w; 37(7):893-894.
262. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999x; 37(7):893-894.
263. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999y; 37(7):893-894.
264. Duenas-Laita A, Castro-Villamor MA, Martin-Escudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999z; 37(7):893-894.
265. Duenas-Laita A, Castro-Villamor MA, Martin-Excudero JC, et al: New clinical manifestations of acute risperidor poisoning (letter). Clin Toxicol 1999a; 37(7):893-894.
266. Dukes MNG: Side Effects of Drugs, 8, American Elsevier Publishing Co, New York, 1975.
267. Dupont H, Timsit JF, Souweine B, et al: Torsades de pointes probably related to sparfloxacin. Eur J Clin Microl Infect Dis 1996; 15:350-351.
268. Eberhard G & Hellbom E: Haloperidol decanoate and flupenthixol decanoate in schizophrenia. Acta Psychiatr Scand 1986; 74:255-262.
269. Edwards J, Alexander JR, Alexander MS, et al: Controlled trial of sulpiride in chronic schizophrenic patients. Bı Psychiatry 1980; 137:522-529.
270. Ehmann TS, Delva NJ, & Beninger RJ: Flupenthixol in chronic schizophrenic inpatients: a controlled comparisc with haloperidol. J Clin Psychopharmacol 1987; 3:173-175.
271. Emrich HM: Studies with oxcarbazine (Trileptal-) in acute mania. Int Clin Psychopharmacol 1990; 5(suppl 1):83 88.
272. Erenberg G: Treatment of tourette syndrome with neuroleptic drugs In: Erenberg G: Advance Neurology, 58,

Raven Press, Ltd, New York, NY, 1992.
273. Ereshefsky L & Richards A: Psychoses In: Ereshefsky L & Richards A: Young LY & Koda-Kimble MA: Applied Therapeutics The Clinical Use of Drugs, 4th. Applied Therapeutics Inc, Vancouver, WA, 1988a.
274. Ereshefsky L & Richards A: Psychoses In: Young LY & Koda-Kimble MA (Eds): Applied Therapeutics The Clin Use of Drugs, 4th. Applied Therapeutics, Inc, San Francisco, CA, 1988.
275. Ereshefsky L, Saklad SR, Tran-Johnson T, et al: Kinetics and clinical evaluation of haloperidol decanoate load dose regimen. Psychopharmacol Bull 1990; 26:108-114.
276. Ereshefsky L, Toney G, Saklad SR, et al: A loading-dose strategy for converting from oral to depot haloperidol. Hosp Comm Psychiatry 1993; 44:1155 1161.
277. Ericksen SE, Hurt SW, & Chang S: Haloperidol dose, plasma levels, and clinical response: a double-blind stud Psychopharmacology Bull 1978; 14:15-16.
278. Escobar JI, Mann JJ, Keller J, et al: Comparison of injectable molindone and haloperidol followed by oral dosa forms in acutely ill schizophrenics. J Clin Psychiatry 1985; 46:15-19.
279. European Porphyria Initiative: Recommendations for the use of drugs in the acute porphyrias (AIP, HCP, VP). European Porphyria Initiative. Available from URL: www.porphyria-europe.org. As accessed 2/13/06.
280. Extein I, Pottash ALC, & Gold MS: Therapeutic window for plasma haloperidol in acute schizophrenic psychosi Lancet 1983; 1:1048-1049.
281. Faheem AD, Brightwell DR, Burton GC, et al: Respiratory dyskinesia and dysarthria from prolonged neurolepti use: tardive dyskinesia?. Am J Psychiatry 1982; 139:517-518.
282. Falaschi P, del Pozo E, Rocco A, et al: Prolactin release in polycystic ovary. Obstet Gynecol 1980; 55:579-582
283. Fast DK, Jones BD, Kusalic M, et al: Effect of carbamazepine on neuroleptic plasma levels and efficacy (letter) Am J Psychiatry 1986; 143:117-118.
284. Fawcett JP, Woods DJ, & Munasiri B: Compatibility of cyclizine lactate and haloperidol lactate. Am J Hosp Pha 1994; 51:2292.
285. Fernandez F, Holmes VF, Adams F, et al: Treatment of severe, refractory agitation with a haloperidol drip. J Cl Psychiatry 1988; 49:239-241.
286. Fernandez F, Levy JK, & Mansell PWA: Management of delirium in terminally ill AIDS patients. Int J Psychiatr Med 1989; 19:165-172.
287. Finch JW: Rapid control of persistent hiccups by orphenadrine citrate. Med Times 1966; 94:485-488.
288. Fines RE, Brady WJ, & Martin ML: Acute laryngeal dystonia related to neuroleptic agents. Am J Emerg Med 1999; 17(3):319-320.
289. Fisher H: A new approach to emergency department therapy of migraine headache with intravenous haloperid a case series. J Emerg Med 1995; 13:119-122.
290. Fitzgerald CH: A double-blind comparison of haloperidol with perphenazine in acute psychiatric episodes. Curr Ther Res 1969; 11:515-519.
291. Fleischhacker WW, Barnas C, Stuppaeck CH, et al: Zotepine vs haloperidol in paranoid schizophrenia: a doub blind trial. Psychopharmacol Bull 1989; 25:97-100.
292. Forsman A & Ohman R: Pharmacokinetic studies on haloperidol in man. Curr Ther Res 1976; 20:319.
293. Forsman A & Ohman R: Studies on serum protein binding of haloperidol. Curr Ther Res 1977; 21:245.
294. Forsman A, Larsson M, Lundborg H, et al: On the metabolism of haloperidol. Curr Ther Res 1977; 21:606.
295. Forsman A: Pharmacokinetics of haloperidol in man.. Curr Ther Res (Sep) 1976; 20(3):319-36.
296. Fraser GL & Riker RR: Visual compatibility of haloperidol lactate with injectable solutions. Am J Hosp Pharm 1994; 51:905-906.
297. Fraser GL & Riker RR: Visual compatibility of haloperidol lactate with injectable solutions. Am J Hosp Pharm 1994a; 51:905-906.
298. Fraser GL & Riker RR: Visual compatibility of haloperidol lactate with injectable solutions. Am J Hosp Pharm 1994b; 51:905-906.
299. Fraser GL & Riker RR: Visual compatibility of haloperidol lactate with injectable solutions. Am J Hosp Pharm 1994c; 51:905-906.
300. Fraser GL & Riker RR: Visual compatibility of haloperidol lactate with injectable solutions. Am J Hosp Pharm 1994d; 51:905-906.
301. Fraser GL & Riker RR: Visual compatibility of haloperidol lactate with injectable solutions. Am J Hosp Pharm 1994e; 51:905-906.
302. Fried MJ & Protheroe DT: D-penicillamine induced myasthenia gravis, its relevance for the anaesthetist. Br J Anaesth 1986; 58:1191-1193.
303. Friedgood CE & Ripstein CB: Chlorpromazine (Thorazine) in the treatment of intractable hiccups. JAMA 1955; 157(4):309-310.
304. Friedman NL: Hiccups: a treatment review. Pharmacotherapy 1996; 16(6):986-995.
305. Froemming JS, Lam YW, & Jann MW: Pharmacokinetics of haloperidol.. Clin Pharmacokinet 1989; 17(6):396-423.
306. Froemming JS, Lam YWF, Jann MW, et al: Pharmacokinetics of haloperidol. Clin Pharmacokinet 1989a; 17:39 423.
307. From Phenothiazines (Systemic), USP DI 1989. Reference is: Lamy P, Zuckerman IH. Pharmacologic considerations in the treatment of Alzheimer"s disease.. The Maryland Pharmacist 63(3): 10-2., 1987 Mar.
308. Fuglum E, Schillinger A, Andersen JB, et al: Zuclopenthixol and haloperidol/levomepromazine in the treatment elderly patients with symptoms of aggressiveness and agitation: a double-blind, multi-centre study. Pharmatherapeutica 1989; 5:285-291.
309. Gardos G, Cole JO, Matthews JD, et al: The acute effects of a loading dose of phenylalanine in unipolar

depressed patients with and without tardive dyskinesia. Neuropsychopharmacology 1992; 6(4):241-247.
310. Gardos G, Cole JO, Matthews JD, et al: The acute effects of a loading dose of phenylalanine in unipolar depressed patients with and without tardive dyskinesia. Neuropsychopharmacology 1992a; 6(4):241-247.
311. Gardos G: Dr Gardos and associates reply. Am J Psychiatry 1980; 137:261.
312. Geller B & Greydanus DE: Haloperidol-induced comatose state with hyperthermia and rigidity in adolescence: Two case reports with a literature review. J Clin Psychiatry 1979; 40:102-103.
313. Gerlach J, Behnke K, Heltberg J, et al: Sulpiride and haloperidol in schizophrenia: a double-blind cross-over study of therapeutic effect, side effects and plasma concentrations. Br J Psychiatry 1985; 147:283-288.
314. Gerra G, Zaimovic A, Giusti F, et al: Lofexidine versus clonidine in rapid opiate detoxification. J Substance Abu Treat 2001; 21:11-17.
315. Gesell LB & Stephen M: Toxicity following a single dose of risperidone for pediatric attention deficit hyperactivit disorder (ADHD) (abstract). J Toxicol Clin Toxicol 1997; 35:549.
316. Gesell LB & Stephen M: Toxicity following a single dose of risperidone for pediatric attention deficit hyperactivit disorder (ADHD) (abstract). J Toxicol Clin Toxicol 1997a; 35:549.
317. Gessa R, Tagliamonte A, & Gessa GL: Blockade by apomorphine of haloperidol-induced dyskinesia in schizophrenic patients. Lancet 1972; 2:981-982.
318. Giannini AJ & Eighan MS: Comparison of haloperidol and chlorpromazine in the treatment of phencyclidine psychosis. J Clin Pharmacol 1984; 24:202-204.
319. Giannini AJ, Loiselle RH, DiMarzio LR, et al: Augmentation of haloperidol by ascorbic acid in phencyclidine intoxication. Am J Psychiatry 1987; 144:1207-1209.
320. Gill SS, Bronskill SE, Normand SL, et al: Antipsychotic drug use and mortality in older adults with dementia. Ar Intern Med 2007; 146(11):775-786.
321. Gilman AG, Goodman LS, Rall TW, et al (Eds): Goodman & Gilman's The Pharmacological Basis of Therapeutics, 7th. Macmillan Publishing Co, New York, NY, 1985.
322. Gilman AG, Goodman LS, Rall TW, et al: Goodman and Gilman's The Pharmacologic Basis of Therapeutics, 7 ed. Macmillan Publishing, New York, NY, 1985. Jeste DV & Wyatt RJ: Changing epidemiology of tardive dyskinesia: an overview. Am J Psychiatry 1981; 138:297-309.
323. Glazer WM, Hafez HM, Benarroche CL, et al: Molindone and haloperidol in tardive dyskinesia. J Clin Psychiatr 1985; 46:4-7.
324. Glazer WM, Hafez HM, Benarroche CL, et al: Molindone and haloperidol in tardive dyskinesia. J Clin Psychiatr 1985a; 46:4-7.
325. Glazer WM: Extrapyramidal side effects, tardive dyskinesia, and the concept of atypicality. J Clin Psychiatry 2000; 61(suppl 3):16-21.
326. Goff DC, Arana GW, Greenblatt DJ, et al: The effect of benztropine on haloperidol-induced dystonia, clinical efficacy and pharmacokinetics: a prospective, double-blind trial. J Clin Psychopharmacol 1991b; 11:106-112.
327. Goff DC, Midha KK, Brotman AW, et al: Elevation of plasma concentrations of haloperidol after the addition of fluoxetine. Am J Psychiatry 1991; 148:790-792.
328. Goff DC, Midha KK, Brotman AW, et al: Elevation of plasma concentrations of haloperidol after the addition of fluoxetine. Am J Psychiatry 1991a; 148:790-792.
329. Goff DC, Posever T, Herz L, et al: An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 1998; 18(4):296-304.
330. Gohn DC & Simmons TW: Polymorphic ventricular tachycardia (torsade de pointes) associated with the use of probucol (letter). New Eng J Med 1992; 326:1435-1436.
331. Gold MS, Pottash AL, Sweeney DR, et al: Effect of methadone dosage on clonidine detoxification efficacy. Am Psychiatry 1980; 137:375-376.
332. Goldberg TE, Bigelow LB, Weinberger DR, et al: Cognitive and behavioral effects of the coadministration of dextramphetamine and haloperidol in schizophrenia. Am J Psychiatry 1991; 148:78-84.
333. Goldney RD & Spence ND: Safety of the combination of lithium and neuroleptic drugs. Am J Psychiatry 1986; 143:882-884.
334. Goldsmith S: A treatment for hiccups.. JAMA 1983; 249(12):1566.
335. Gomberg RF: Interaction between olanzapine and haloperidol (letter). J Clin Psychopharmacol 1999; 19:272-2
336. Gomberg RF: Interaction between olanzapine and haloperidol (letter). J Clin Psychopharmacol 1999a; 19:272-273.
337. Gomez EA: Neuroleptic-induced priapism. Tex Med 1985; 81:47-48.
338. Goodman: Goodman and Gilman's the pharmacologic basis of therapeutics 8th ed, Pergamon Press, New Yor NY, 1990.
339. Gorman DG, Read S, & Cummings JL: Cholinergic therapy of behavioral disturbances in Alzheimer's disease. Neuropsychiatry Neuropsychol Behavior Neurol 1993; 6:229-234.
340. Gotestam KG, Ljunghall S, & Olsson B: A double-blind comparison of the effects of haloperidol and cis(Z)-clopenthixol in senile dementia. Acta Psychiatr Scand 1981; 64(suppl 294):46-53.
341. Gowardman M, Barrer B, & Brown RA: Pimozide (R6238) in chronic schizophrenia: double-blind trial. N Z Med 1973; 78:487-491.
342. Gralla RJ, Osoba D, Kris MG, et al: Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. American Society of Clinical Oncology. J Clin Oncol 1999; 17(9):2971-2994.
343. Green MF, Marshall BD Jr, Wirshing WC, et al: Does risperidone improve verbal working memory in treatment resistant schizophrenia?. Am J Psychiatry 1997; 154:799-804.
344. Greenberg DB & Murray GB: Hyperventilation as a variant of tardive dyskinesia. J Clin Psychiatry 1981; 42:40

403.
345. Greenberg WM & Lee KK: Priapism treated with benztropine. Am J Psychiatry 1987; 144:384-385.
346. Gregory RP, Smith PT, & Rudge P: Tardive dyskinesia presenting as severe dysphagia. J Neurol, Neurosurg, Psychiatry 1992; 55:1203- 1204.
347. Grimaldi MG & Bergonzi M: Haloperidol in rheumatoid arthritis: objective measurement using proximal interphalangeal joints technetium index. Curr Ther Res 1980; 27:565.
348. Grimaldi MG: Serum sulfhydryl levels in rheumatoid arthritis patients treated with haloperidol. Scand J Rheuma 1980; 9:225-228.
349. Gross HA: J Clin Psychopharmacol 1981; 1:376-381. J Clin Psychopharmacol 1981; 1:376-381.
350. Grossman F: A review of anticonvulsants in treating agitated demented elderly patients. Pharmacotherapy 199 18(3):600-606.
351. Grunberg SM, Gala KV, Lampenfeld M, et al: Comparison of the antiemetic effect of high-dose intravenous metoclopramide and high-dose intravenous haloperidol in a randomized double-blind crossover study. J Clin Oncol 1984; 2:782-787.
352. Gualtieri CT & Patterson DR: Neuroleptic-induced tics in two hyperactive children. Am J Psychiatry 1986; 143:1176-1177.
353. Haas S & Beckmann H: Pimozide versus haloperidol in acute schizophrenia: a double blind controlled study. Pharmacopsychiatry 1982; 15:70-74.
354. Haldol (McNeil—US) package insert. Rev Rec 11/29/88., 6/3/87.
355. Haldol Decanoate Injection (McNeil—US) package insert. Rev Rec 10/30/89., 2/15/89.
356. Halmi KA, Eckert E & Falk JR: Cyproheptadine, an antidepressant and weight-inducing drug for anorexia nervosa. Psychopharmacol Bull; 19:103-105. 8. Halmi, 1983.
357. Haloperidol product monograph.. Kenral—Canada., Rev 2/20/89, Rec 3/22/90.
358. Hamadah K & Teggin AG: Haloperidol, thyrotoxicosis, and neurototoxicity. Lancet 1974; 2:1019-1020.
359. Hamann GL, Egan TM, Wells BG, et al: Injection site reactions after intramuscular administration of haloperido decanoate 100 mg/mL. J Clin Psychiatry 1990; 51:502-504.
360. Hanks GW, Thomas PF, Trueman T, et al: The myth of haloperidol potentiation. Lancet 1983; 2:523-524.
361. Hanley SP & Hampton JR: Ventricular arrhythmias associated with lidoflazine: side effects observed in a randomized trial. Eur Heart J 1983; 4:889-893.
362. Hansen LM, Megerian G, & Donnenfeld AE: Haloperidol overodse during pregnancy. Obstet Gynecol 1997; 90:659-661.
363. Harder A, Modestin J, & Steiner H: Body temperature changes during parenteral courses of neuroleptics. retrospective statistical evaluation. Schweiz Med Wschr 1971; 101:828-831.
364. Harrison AM, Lugo RA, Lee WE, et al: The use of haloperidol in agitated critically ill children. Clin Pediatr (Phila 2002; 41(1):51-54.
365. Harry P: Acute poisoning by new psychotropic drugs. Rev Prat 1997a; 47:731-735.
366. Harry P: Acute poisoning by new psychotropic drugs. Rev Prat 1997b; 47:731-735.
367. Harry P: Acute poisoning of new psychotropic drugs. Rev Prat 1997; 47:731-735.
368. Harvey AM, Johns RJ, McKusick VA, et al (Eds): The Principles and Practice of Medicine, Appleton & Lange, Norwalk, CT, 1988.
369. Harvey PD, Rabinowitz J, Eerdekens M, et al: Treatment of cognitive impairment in early psychosis: A comparison of risperidone and haloperidol in a large long-term trial. Am J Psychiatry 2005; 162(10:1888-1895.
370. Hasnain M, Vieweg WV, Fredrickson SK, et al: Clinical monitoring and management of the metabolic syndrom patients receiving atypical antipsychotic medications. Prim Care Diabetes 2008; Epub:1-.
371. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003; 10(1):58-60.
372. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003a; 10(1):58-60.
373. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003b; 10(1):58-60.
374. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003c; 10(1):58-60.
375. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003d; 10(1):58-60.
376. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003e; 10(1):58-60.
377. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003f; 10(1):58-60.
378. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003g; 10(1):58-60.
379. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003h; 10(1):58-60.
380. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003i; 10(1):58-60.
381. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003j; 10(1):58-60.
382. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003k; 10(1):58-60.

383. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003l; 10(1):58-60.
384. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003m; 10(1):58-60.
385. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003n; 10(1):58-60.
386. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003o; 10(1):58-60.
387. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003p; 10(1):58-60.
388. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003q; 10(1):58-60.
389. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003r; 10(1):58-60.
390. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003s; 10(1):58-60.
391. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003t; 10(1):58-60.
392. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003u; 10(1):58-60.
393. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003v; 10(1):58-60.
394. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003w; 10(1):58-60.
395. Hassaballa HA & Balk RA: Torsade de pointes associated with the administration of intravenous haloperidol. A J Ther 2003x; 10(1):58-60.
396. Hebenstreit GF, Laux G, Schubert H, et al: A double-blind comparative multicentre study of controlled-release remoxipride, immediate-release remoxipride and haloperidol in schizoprenia. Pharmacopsychiatry 1991; 24:15 158.
397. Heikkila L, Eliander H, Vartiainen H, et al: Zuclopenthixol and haloperidol in patients with acute psychotic state A double-blind, multi-centre study. Curr Med Res Opin 1992; 12:594-603.
398. Heikkila L, Laitinen J, & Vartiainen H: Cis(Z)-clopenthixol and haloperidol in chronic schizophrenia patients - a double-blind clinical multicentre investigation. Acta Psychiatr Scand 1981a; 64(suppl 294):30-38.
399. Heird SB, Rhoads JE Jr, & Agarwal NN: Neuroleptic malignant syndrome in a trauma patient: case report. J Trauma 1989; 29:1595-1597.
400. Hemstrom CA, Evans RL, & Lobeck FG: Haloperidol decanoate: A depot antipsychotic. Drug Intell Clin Pharm 1988; 22:290-295.
401. Hemstrom CA, Evans RL, & Lobeck FG: Haloperidol decanoate: a depot antipsychotic.. Drug Intell Clin Pharm 1988a; 22:290-5.
402. Henderson RA, Lane S, & Henry JA: Life-threatening ventricular arrhythmia (Torsades de Pointes) after haloperidol overdose. Hum Exp Toxicol 1991; 10:59-62.
403. Henderson VW & Wooten GF: Neuroleptic malignant syndrome: A pathogenetic role for dopamine receptor blockade. Neurology 1981; 31:132-137.
404. Hermesh H, Huberman M, Radvan N, et al: Recurrent neuroleptic malignant syndrome due to tiapride and haloperidol: The possible role of D-2 dopamine receptors. J Nerv Ment Dis 1984; 172:692-695.
405. Herrmann N: Valproic acid treatment of agitation in dementia. Can J Psychiatry 1998; 43:69-72.
406. Hershey L & Weintraub M: Easing morphine withdrawal in children. Drug Ther 1980; 10:57.
407. Hesslinger B, Normann C, Langosch JM, et al: Effects of carbamazepine and valproate on haloperidol plasma levels and on psychopathologic outcome in schizophrenic patients. J Clin Psychopharmacol 1999; 19:310-315
408. Hesslinger B, Normann C, Langosch JM, et al: Effects of carbamazepine and valproate on haloperidol plasma levels and on psychopathologic outcome in schizophrenic patients. J Clin Psychopharmacol 1999a; 19:310-31
409. Hirsch SR, Kissling W, Bauml J, et al: A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. J Clin Psychiatry 2002; 63(6):516-523.
410. Hoffman L & Halmi K: Psychopharmacology in the treatment of anorexia nervosa and bulimia nervosa. Psychia Clin North Am 1993; 16:767-778.
411. Holley FO, Magliozzi JR, & Stanski DR: Haloperidol kinetics after oral and intravenous doses. Clin Pharmacol Ther 1983a; 33:477-484.
412. Holley FO, Magliozzi JR, Stanski DR, et al: Haloperidol kinetics after oral and intravenous doses.. Clin Pharma Ther (Apr) 1983; 33(4):477-84.
413. Hollister LE: Disorders of the nervous system due to drugs In: Meyler L & Peck HM (Eds): Drug-Induced Disea 4, Excerpta Medica, Amsterdan, 1972.
414. Howard JE: Severe psychosis and the adrenal androgens. Integr Physiol Behav Sci 1992; 27:209-215.
415. Howard JE: Severe psychosis and the adrenal androgens. Integr Physiol Behav Sci 1992a; 27:209-215.
416. Howard JS: Haloperidol for chronically hospitalized psychotics: a double-blind comparison with thiothixene anc placebo; a follow-up open evaluation. Dis Nerv Syst 1974; 35:458.
417. Huang V, Figge H, & Demling R: Haloperidol complications in burn patients. J Burn Care Rehab 1987; 8:269-2
418. Hummer M, Kemmler G, Kurz M, et al: Sexual distrubances during clozapine and haloperidol treatment for schizophrenia. Am J Psychiatry 1999; 156:631-633.

419. Hummer M, Kurz M, Kurzthaler I, et al: Hepatotoxicity of clozapine. J Clin Psychopharmacol 1997; 17(4):314-3
420. Hunt TL, Cramer M, Shah A, et al: A double-blind, placebo-controlled, dose-ranging safety evaluation of single dose intravenous dolasetron in healthy male volunteers. J Clin Pharmacol 1995; 35:705-712.
421. Husband C, Mai FM, & Carruthers G: Syndrome of inappropriate secretion of antidiuretic hormone in a patient treated with haloperidol. Can J Psychiatry 1981; 26:196-197.
422. Huyse F & Van Schijndel RS: Haloperidol and cardiac arrest. Lancet 1988; 2:568-569.
423. Hwang TJ, Lin SK, & Lin HN: Efficacy and safety of zotepine for the treatment of Taiwanese schizophrenic patients: a double-blind comparison with haloperidol. J Formos Med Assoc 2001; 100(12):811-816.
424. Iqbal MM, Gundlapalli SP, Ryan WG, et al: Effects of antimanic mood-stabilizing drugs on fetuses, neonates, a nursing infants. South Med J 2001; 94(3):304-322.
425. Isaac NE, Walker AM, Jick H, et al: Exposure to phenothiazine drugs and risk of cataract. Arch Ophthalmol 19 109:256-260.
426. Ishigooka J, Inada T, & Miura S: Olanzapine versus haloperidol in the treatment of patients with chronic schizophrenia: results of the Japan multicenter, double-blind olanzapine trial. Psychiatry Clin Neurosci 2001; 55:403-414.
427. Itoh H: A comparison of the clinical effects of bromperidol, a new butyrophenone derivative, and haloperidol on schizophrenia using a double-blind technique. Psychopharmacol Bull 1985; 21:120-122.
428. Ives TJ, Fleming MF, Weart CW, et al: Treatment of intractable hiccups with intramuscular haloperidol. Am J Psychiatry 1985; 142(11):1368-1369.
429. Jackson IV, Volavka J, James B, et al: The respiratory components of tardive dyskinesia. Biol Psychiatry 1980 15:485-487.
430. Jacobson PL, Messenheimer JA, & Farmer TW: Treatment of intractable hiccups with valproic acid. Neurology 1981; 31:1458-1460.
431. James DH: Neuroleptics and epilepsy in mentally handicapped patients. J Ment Defic Res 1986; 30:185-189.
432. Jamieson DD, Duffield PH, Cheng D, et al: Comparison of the central nervous system activity of the aqueous a lipid extract of kava (Piper methysticum). Arch Int Pharmacodyn Ther 1989; 301:66-80.
433. Janicak PG, Javaid JI, Sharma RP, et al: A two-phase, double-blind randomized study of three haloperidol plasma levels for acute psychosis with reassignment of initial non-responders. Acta Psychiatr Scand 1997; 95:343-350.
434. Jann MW & Bitar AH: Respiratory dyskinesia. Psychosomatics 1982; 23:764-765.
435. Jann MW, Ereshefsky L, & Saklad SR: Clinical pharmacokinetics of the depot antipsychotics.. Clin Pharmacokinetics 1985; 10:315-53.
436. Jarry H, Leonhardt S, Gorkow C, et al: In vitro prolactin but not LH and FSH release is inhibited by compounds extracts of Agnus castus: direct evidence for a dopaminergic principle by the dopamine receptor assay. Exp Cl Endocrinol 1994; 102:448-454.
437. Jarry H, Leonhardt S, Gorkow C, et al: In vitro prolactin but not LH and FSH release is inhibited by compounds extracts of Agnus castus: direct evidence for a dopaminergic principle by the dopamine receptor assay. Exp Cl Endocrinol 1994a; 102:448-454.
438. Jasinski DR: Therapeutic usefulness of propoxyphene napsylate in narcotic addiction. Arch Gen Psychiatry 19 34:227.
439. Jimenez-Jimenez FJ, Garcia-Ruiz PJ, & Molina JA: Drug-induced movement disorders. Drug Saf 1997; 16 (3):180-204.
440. Jin H, Meyer JM, & Jeste DV: Atypical antipsychotics and glucose dysregulation: a systematic review. Schizop Res 2004; 71(2-3):195-212.
441. Johanson AJ & Knorr NJ: L-Dopa as treatment for anorexia nervosa In: Vigersky RA (Ed): Anorexia Nervosa, Raven Press, New York, NY, 1977, pp 363-372.
442. Johnson PC Jr, Charalampous KD, & Braun GA: Absorption and excretion of tritiated haloperidol in man (a preliminary report). Int J Neuropsychiatry 1967; 3(suppl):24.
443. Jones B, Taylor CC, & Meehan K: The efficacy of a rapid-acting intramuscular formulation of olanzapine for positive symptoms. J Clin Psych 2000; 62(suppl 2):22-24.
444. Joshi PT, Capozzoli JA, & Coyle JT: Low-dose neuroleptic therapy for children with childhood-onset pervasive developmental disorder. Am J Psychiatry 1988; 145:335-338.
445. Kahn EM, Schulz SC, Perel JM, et al: Change in haloperidol level due to carbamazepine - a complicating facto combined medication for schizophrenia. J Clin Psychopharmacol 1990; 10:54-57.
446. Kahn EM, Schulz SC, Perel JM, et al: Change in haloperidol level due to carbamazepine - a complicating facto combined medication for schizophrenia. J Clin Psychopharmacol 1990a; 10:54-57.
447. Kane J, Ingenito G, & Ali M: Efficacy of aripiprazole in psychotic disorders: comparison with haloperidol and placebo. Schizophr Res 2000; 41(1):39.
448. Kane JM, Marder SR, Schooler NR, et al: Clozapine and haloperidol in moderately refractory schizophrenia. A Gen Psychiatry 2001; 58(10):965-972.
449. Kariya T, Shimazono Y, Itoh H, et al: A comparison of the clinical effects of timiperone, a new butyrophenone derivative, and haloperidol on schizophrenia using a double-blind technique. J Int Med Res 1983; 11:66-77.
450. Kaye WH, Weltzin TE, Hsu LK, et al: An open trial of fluoxetine in patients with anorexia nervosa. J Clin Psychiatry 1991; 52:464-471.
451. Kazamatsuri H, Chien C-P, & Cole JO: Long-term treatment of tardive dyskinesia with haloperidol and tetrabenazine. Am J Psychiatry 1973; 130:479-483.
452. Keck PE Jr, Strakowski SM, & McElroy SL: The efficacy of atypical antipsychotics in the treatment of depressiv symptoms, hostility, and suicidality in patients with schizophrenia. J Clin Psychiatry 2000; 61(suppl 3):4-9.

453. Keck PE Jr, Strakowski SM, & McElroy SL: The efficacy of atypical antipsychotics in the treatment of depressiv symptoms, hostility, and suicidality in patients with schizophrenia. J Clin Psychiatry 2000a; 61(suppl 3):4-9.
454. Keitner GI & Rahman S: Reversible neurotoxicity with combined lithium-haloperidol administration. J Clin Psychopharmacol 1984; 4:104-105.
455. Kelley SL, Braun TJ, Meyer TJ, et al: Trial of droperidol as an antiemetic in cisplatin chemotherapy. Cancer Tre Rep 1986; 70:469-472.
456. Ketai R, Matthews J, & Mozdzen JJ Jr: Sudden death in a patient taking haloperidol. Am J Psychiatry 1979; 136:112-113.
457. Khakee A & Hess GF: Mellaril(R) in the treatment of chronically disturbed patients. Am J Psychiatry 1960; 116:1029.
458. Khazan M & Mathis AS: Probable cause of torsades de pointes induced by fluconazole. Pharmacotherapy 200 22(12):1632-1637.
459. Kiloh LG, Smith JS, & Williams SE: Antiparkinson drugs as causal agents in tardive dyskinesia. Med J Aust 19 2:591-593.
460. Kleber HD, Riodian CE, Rounsville B, et al: Clonidine in outpatient detoxification from methadone maintenance Arch Gen Psychiatry 1985; 42:391-394.
461. Kleber HD, Topazian M, Gaspari J, et al: Clonidine and naltrexone in the outpatient treatment of heroin withdrawal. Am J Drug Alcohol Abuse 1987; 13:1-17.
462. Klein E, Bental E, Lerer B, et al: Carbamazepine and haloperidol v placebo and haloperidol in excited psychos a controlled study. Arch Gen Psychiatry 1984; 41:165-170.
463. Klein E, Bental E, Lerer B, et al: Carbamazepine and haloperidol vs placebo and haloperidol in excited psychoses. Arch Gen Psychiatry 1984a; 41:165-170.
464. Klieser E, Lehmann E, & Tegeler J: Doppelblindvergleich von 3 x 75 mg Zotepin und 3 x 4 mg Haloperidol bei akut schizophrenen Patienten. Fortschr Neurol Psychiatr 1991; 59(suppl 1):14-17.
465. Koller EA, Cross JT, Doraiswamy PM, et al: Pancreatitis associated with atypical antipsychotics: from the food and drug administration¿s medwatch surveillance system and published reports. Pharmacotherapy 2003; 23 (9):1123-1130.
466. Koller EA, Cross JT, Doraiswamy PM, et al: Pancreatitis associated with atypical antipsychotics: from the food and drug administration¿s medwatch surveillance system and published reports. Pharmacotherapy 2003a; 23 (9):1123-1130.
467. Koller EA, Cross JT, Doraiswamy PM, et al: Pancreatitis associated with atypical antipsychotics: from the food and drug administration¿s medwatch surveillance system and published reports. Pharmacotherapy 2003b; 23 (9):1123-1130.
468. Koller EA, Cross JT, Doraiswamy PM, et al: Pancreatitis associated with atypical antipsychotics: from the food and drug administration¿s medwatch surveillance system and published reports. Pharmacotherapy 2003c; 23 (9):1123-1130.
469. Kopelman AE, McCullar FW, & Heggeness L: Limb malformations following maternal use of haloperidol. JAMA 1975; 321:62-4.
470. Kris MG, Grunberg SM, Gralla RJ, et al: Dose-ranging evaluation of the serotonin antagonist dolasetron mesyl in patients receiving high-dose cisplatin. J Clin Oncol 1994; 12:1045-1049.
471. Kris MG, Hesketh PJ, Somerfield MR, et al: American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. J Clin Oncol 2006; 24(18):2932-2947.
472. Kriwisky M, Perry GY, Tarchitsky D, et al: Haloperidol-induced torsades de pointes. Chest 1990; 98:482-484.
473. Kubota T, Ishikura T, & Jibiki I: Alopecia areata associated with haloperidol. Jpn J Psychiatry Neurol 1994; 48:579-581.
474. Kudo S & Ishizaki T: Pharmacokinetics of Haloperidol: an update. Clin Pharmacokinet 1999; 37(6):435-456.
475. Kumor K, Sherer M, & Jaffe J: Haloperidol-induced dystonia in cocaine addicts. Lancet 1986; 2:1341-1342.
476. Lake CR & Fann WE: Possible potentiation of haloperidol neurotoxicity in acute hyperthyrodism. Br J Psychiatı 1973; 123:523-525.
477. Lanctot KL, Best TS, Mittmann N, et al: Efficacy and safety of neuroleptics in behavioral disorders associated v dementia. J Clin Psychiatry 1998; 59(10):550-561.
478. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992; 11:629-635.
479. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992a; 11:629-635.
480. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992aa; 11:629-635.
481. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992ab; 11:629-635.
482. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992ac; 11:629-635.
483. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992b; 11:629-635.
484. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992c; 11:629-635.
485. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992d; 11:629-635.
486. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular

electrophysiological correlation. Ann Fr Anesth Reanim 1992e; 11:629-635.
487. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992f; 11:629-635.
488. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992g; 11:629-635.
489. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992h; 11:629-635.
490. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992i; 11:629-635.
491. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992j; 11:629-635.
492. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992k; 11:629-635.
493. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992l; 11:629-635.
494. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992m; 11:629-635.
495. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992n; 11:629-635.
496. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992o; 11:629-635.
497. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992p; 11:629-635.
498. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992q; 11:629-635.
499. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992r; 11:629-635.
500. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992s; 11:629-635.
501. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992t; 11:629-635.
502. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992u; 11:629-635.
503. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992v; 11:629-635.
504. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992x; 11:629-635.
505. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992y; 11:629-635.
506. Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. Ann Fr Anesth Reanim 1992z; 11:629-635.
507. Lande G, Drouin E, Gauthier C, et al: effects of sultopride chlorhydrate: clinical and cellular electrophysiologica correlation. Ann Fr Anesth Reanim 1992w; 11:629-635.
508. Lane HY, Chang YC, Su MY, et al: Shifting from haloperidol to risperidone for behavioral disturbances in dementia: safety, response predictors, and mood effects. J Clin Psychopharmacol 2002; 22(1):4-10.
509. Lapierre YD, Angus C, Awad AG, et al: The treatment of negative symptoms: a clinical and methodological stu Int Clin Psychopharmacol 1999; 14(2):101-112.
510. Lapierre YD, Nair NPV, Chouinard G, et al: A controlled dose-ranging study of remoxipride and haloperidol in schizophrenia - a Canadian multicentre trial. Acta Psychiatr Scand 1990; 82(suppl 358):72-76.
511. Larochelle P, Belanger L, Lemire F, et al: Dose-response effect of propafenone in patients with ventricular arrhythmias. Curr Ther Res 1984; 36:959-969.
512. Lauritzen C, Reuter HD, Repges R, et al: Treatment of premenstrual tension syndrome with Vitex agnus castus controlled, double-blind study versus pyridoxine. Phytomedicine 1997; 4:183-189.
513. Lauritzen C, Reuter HD, Repges R, et al: Treatment of premenstrual tension syndrome with Vitex agnus castus controlled, double-blind study versus pyridoxine. Phytomedicine 1997a; 4:183-189.
514. Laux G, Klieser E, Schroder HG, et al: A double-blind multicentre study comparing remoxipride, two and three times daily, with haloperidol in schizophrenia. Acta Psychiatr Scand 1990; 82(suppl 358):125-129.
515. Lavin MJ & Andrews V: Is topical haloperidol a useful glaucoma treatment?. Br J Ophthalmol 1986; 70:448-45(
516. Lawrence KR & Nasraway SA: Conduction disturbances associated with administration of butyrophenone antipsychotics in the critically ill: a review of the literature. Pharmacotherapy 1997; 17(3):531-537.
517. Lecrubier Y: A dose-response study of SND#919 vs haloperidol in the treatment of schizophrenia (abstract). Neuropsychopharmacol 1994; 10(suppl Part 1):124.
518. Leucht S, Corves C, Arbter D, et al: Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2008; 373(9657):31-41.
519. Lieberman J: Cholinergic rebound in neuroleptic withdrawal syndrome. Psychosomatics 1981; 22:253-254.
520. Lieberman JA, Stroup TS, McEvoy JP, et al: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353(12):1209-1223.
521. Lin KM, Poland RE, Fu P, et al: Serum haloperidol and desipramine concentrations and the treatment of

psychotic depression: two case reports. J Nerv Ment Dis 1989; 177:431-432.
522. Lindsay J Jr, Smith MA, & Light JA: Torsades de pointes associated with antimicrobial therapy for pneumonia. Chest 1990; 98:222-223.
523. Linnoila M, Viukari M, Vaisanen K, et al: Effect of anticonvulsants on plasma haloperidol and thioridazine levels Am J Psychiatry 1980; 137:819-821.
524. Linnoila M, Viukari M, Vaisanen K, et al: Effect of anticonvulsants on plasma haloperidol and thioridazine levels Am J Psychiatry 1980a; 137:819-821.
525. Linnoila M, Viukari M, Vaisanen K, et al: Effect of anticonvulsants on plasma haloperidol and thioridazine levels Am J Psychiatry 1980b; 137:819-821.
526. Lipps DC, Jabbari B, Mitchell MH, et al: Nifedipine for intractable hiccups. Neurology 1990; 40:531-532.
527. Litt IF, Colli AS, & Cohen MI: Diazepam in the management of heroin withdrawal in adolescents: preliminary report. J Pediatr 1971; 78:692-696.
528. Lo Vecchio F, Hamilton RJ, & Hoffman RJ: Risperidone overdose. Am J Emerg Med 1996; 14:95-96.
529. Lo Vecchio F, Hamilton RJ, & Hoffman RJ: Risperidone overdose. Am J Emerg Med 1996a; 14:95-96.
530. Lober CA & Dollard PA: Visual compatibility of gallium nitrate with selected drugs during simulated Y-site injection. Am J Hosp Pharm 1993; 50:1208-1210.
531. Loeser EA, Bennett G, Stanley TH, et al: Comparison of droperidol, haloperidol and prochlorperazine as postoperative anti-emetics. Can Anaesth Soc J 1979; 26:125-127.
532. Lohr JB, Caligiuri MP, Edson R, et al: Treatment predictors of extrapyramidal side effects in patients with tardiv dyskinesia: results from Veterans Affairs Cooperative Study 394. J Clin Psychopharmacol 2002; 22(2):196-200
533. Longwell B, Betz T, Horton H, et al: Weight gain and edema on methadone maintenance therapy. Int J Addict 1979; 14:329.
534. Lopez JA, Harold JG, Rosenthal MC, et al: QT prolongation and torsades de pointes after administration of trimethoprim-sulfamethoxazole. Am J Cardiol 1987; 59:376-377.
535. Lor E & Takagi J: Visual compatibility of foscarnet with other injectable drugs. Am J Hosp Pharm 1990; 47:157 159.
536. Lor E, Sheybani T, & Takagi J: Visual compatibility of fluconazole with commonly used injectable drugs during simulated Y-site administration. Am J Hosp Pharm 1991; 48:744-746.
537. Lossos IS: Comment: drug-induced hiccups. Ann Pharmacother 1997; 31(10):1264-1265.
538. Loudon JB & Waring H: Toxic reactions to lithium and haloperidol (letter). Lancet 1976; 2:1088.
539. Lovett WC, Stokes DK, Taylor LB, et al: Management of behavioral symptoms in disturbed elderly patients: comparison of trifluoperazine and haloperidol. J Clin Psychiatry 1987; 48:234-236.
540. Lowinson JH: Commonly asked clinical questions about methadone maintenance. Int J Addict 1977; 12:821.
541. Lublin H, Gerlach J, Hagert U, et al: Zuclopenthixol, a combined dopamine D1/D2 antagonist, versus haloperid a dopamine D2 antagonist, in tardive dyskinesia. Eur Neuropsychopharmacol 1991; 1:541-548.
542. Maany I: Adverse interaction of tacrine and haloperidol (letter). Am J Psychiatry 1996; 153:1504.
543. Maany I: Adverse interaction of tacrine and haloperidol (letter). Am J Psychiatry 1996a; 153:1504.
544. Madanagopolan N: Metoclopramide in hiccup. Curr Med Res Opin 1975; 3(6):371-374.
545. Magliozzi JR, Hollister LE, Arnold KV, et al: Relationship of serum haloperidol levels to clinical response in schizophrenic patients. Am J Psychiatry 1981; 138:365-367.
546. Mahr GC, Berchou R, & Balon R: A grand mal seizure associated with desipramine and haloperidol. Can J Psychiatry 1987; 32:463-464.
547. Mahutte CK: Haloperidol and sudden death due to pulmonary edema. Arch Intern Med 1982; 142:1951-1952.
548. Malina A, Gaskill J, McConaha C, et al: Olanzapine treatment of anorexia nervosa: a retrospective study. Int J Eat Disord 2003; 33:234-237.
549. Maloney MJ & Farrell MK: Treatment of severe weight loss in anorexia nervosa with hyperalimentation and psychotherapy. Am J Psychiatry 1980; 137:310-314.
550. Maltbie AA, Cavenar JO Jr, Sullivan JL, et al: Ileus complicating haloperidol therapy. Psychosomatics 1981; 22:158-159.
551. Maltbie AA, Sullivan JL, Cavenar JO, et al: Haloperidol treatment of a sixty-year narcotic addiction: case report Milit Med 1979; 144:251.
552. Maltbie AA, Varia IG, & Thomas NU: Analgesia and haloperidol: A hypothesis. J Clin Psychiatry 1979a; 40:323 326.
553. Marder SR & Meibach RC: Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994; 151:825-835
554. Marder SR, Davis JM, & Chouinard G: The effects of risperidone on the five dimensions of schizophrenia deriv by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997; 58:538-546.
555. Marder SR, Essock SM, Miller AL, et al: Physical health monitoring of patients with schizophrenia. Am J Psychiatry 2004; 161(8):1334-1349.
556. Marder SR: Risperidone: Clinical development: North American Results. Proceedings of the 18th Collegium Internationale Neuro- Psychopharmacologicum Congress: S-20-58, 1992.
557. Marechal R, Berghmans T, & Sculier JP: Successful treatment of intractable hiccup with methylphenidate in a lung cancer patient. Support Care Cancer 2003; 11:126-128.
558. Marjerrison G, Bowman R, & Keogh RP: A comparison of chlorprothixene and haloperidol in acute schizophrer Can Psychiatr Assoc J 1971; 16:533-536.
559. Markowitz JC & Brown RP: Seizures with neuroleptics and antidepressants. Gen Hosp Psychiatry 1987; 9:135 141.
560. Marshall JB & Forker AD: Cardiovascular effects of tricyclic antidepressant drugs: therapeutic usage, overdose and management of complications. Am Heart J 1982; 103:401-414.

561. Matsuno H, Uematsu T, & Nakashima M: The measurement of haloperidol and reduced haloperidol in hair as a index of dosage history. Br J Clin Pharmacol 1990; 29:187-194.
562. Matthews SJ & Cersosimo RJ: Haloperidol induced neuroleptic malignant syndrome. Clin Res Prac Drug Reg Affairs 1986; 4:33-41.
563. Matuk F & Kalyanaraman K: Syndrome of inappropriate secretion of antidiuretic hormone in patients treated wi psychotherapeutic drugs. Arch Neurol 1977; 34:374-375.
564. Mauro VF, Bingle JF, Ginn SM, et al: Torsade de pointes in a patient receiving intravenous vasopressin. Crit C Med 1988; 16:200-201.
565. Mavroidis ML, Kanter DR, Hirschowitz, et al: Clinical response and plasma haloperidol levels in schizophrenia. Psychopharmacology 1983; 81:354-356.
566. Maxa JL, Taleghani AM, Ogu CC, et al: Possible toxic encephalopathy following high-dose intravenous haloperidol. Ann Pharmacother 1997; 31:736-737.
567. May EF & Calvert PC: Aggravation of myasthenia gravis by erythromcin. Ann Neurol 1990; 28:577-579.
568. May PRA: Prediction of schizophrenic patients' response to pharmacotherapy In: Lipton MA & eds: Psychopharmacology: A Generation of Progress, Raven Press, New York, 1978, pp 1139.
569. McClelland GR, Cooper SM, & Pilgrim AJ: A comparison of the central nervous system effects of haloperidol, chlorpromazine and sulpiride in normal volunteers. Br J Clin Pharmacol 1990; 30:795-803.
570. McClelland GR, Cooper SM, & Pilgrim AJ: A comparison of the central nervous system effects of haloperidol, chlorpromazine and sulpiride in normal volunteers. Br J Clin Pharmacol 1990a; 30:795-803.
571. McConville BJ, Fogelson MH, Norman AB, et al: Nicotine potentiation of haloperidol in reducing tic frequency i Tourette's disorder. Am J Psychiatry 1991; 148:793-794.
572. McCullar FW & Heggeness L: Limb malformations following maternal use of haloperidol. JAMA 1975; 231:62-6
573. McDougle CJ, Goodman WK, Leckman JF, et al: Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder. Arch Gen Psychiatry 1994; 51:302-308.
574. McElroy SL, Keck PE Jr, Stanton SP, et al: A randomized comparison of Divalproex oral loading versus Haloperidol in the initial treatment of acute psychotic mania. J Clin Psychiatry 1996; 57:142-146.
575. McKane JP, Robinson ADT, Wiles DH, et al: Haloperidol decanoate v fluphenazine decanoate as maintenance therapy in chronic schizophrenic in-patients. Br J Psychiatry 1987; 151:333-336.
576. McSwain ML & Forman LM: Severe parkinsonian syndrome development on combination treatment with tacrin and haloperidol (letter). J Clin Psychopharmacol 1995; 15:284.
577. McSwain ML & Forman LM: Severe parkinsonian syndrome development on combination treatment with tacrin and haloperidol (letter). J Clin Psychopharmacol 1995a; 15:284.
578. Meeks TW & Jeste DV: Beyond the Black Box: What is The Role for Antipsychotics in Dementia?. Curr Psychi 2008; 7(6):50-65.
579. Mehta D, Mehta S, Petit J, et al: Cardiac arrhythmia and haloperidol. Am J Psychiatry 1979; 136:1468-1469.
580. Mehta R & Reilly JJ: Manganese levels in a jaundiced long-term total parenteral nutrition patient: potentiation c haloperidol toxicity? Case report and literature review. J Parenteral Enteral Nutr 1990; 14:428-430.
581. Mendlewicz J, de Bleeker E, Cosyns P, et al: A double-blind comparative study of remoxipride and haloperidol schizophrenic and schizophreniform disorders. Acta Psychiatr Scand 1990; 82(suppl 358):138-141.
582. Menuck M: Laryngeal-pharyngeal dystonia and haloperidol. Am J Psychiatry 1981; 138:394-395.
583. Menza MA, Murray GB, Holmes VF, et al: Controlled study of extrapyramidal reactions in the management of delirious, medically ill patients: intravenous haloperidol versus intravenous haloperidol plus benzodiazepines. Heart Lung 1988; 17:238-241.
584. Menza MA, Murray GB, Holmes VF, et al: Decreased extrapyramidal symptoms with intravenous haloperidol. J Clin Psychiatry 1987; 48:278-280.
585. Metzger E & Friedman R: Polongation of the corrected QT and torsade de pointes cardiac arrhythmia associat with intravenous hlaoperidol in the medically ill. J Clin Psychopharmacol 1993; 13:128-132.
586. Metzger E & Friedman R: Prolongation of the corrected QT and torsade de pointes cardiac arrhythmia associa with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 1993a; 13:128-132.
587. Metzger E & Friedman R: Prolongation of the corrected QT and torsade de pointes cardiac arrhythmia associa with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 1993b; 13:128-132.
588. Metzger E & Friedman R: Prolongation of the corrected QT and torsade de pointes cardiac arrhythmia associa with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 1993c; 13:128-132.
589. Metzger E & Friedman R: Prolongation of the corrected QT and torsade de pointes cardiac arrhythmia associa with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 1993d; 13:128-132.
590. Metzger E & Friedman R: Prolongation of the corrected QT and torsade de pointes cardiac arrhythmia associa with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 1993e; 13:128-132.
591. Metzger E & Friedman R: Prolongation of the corrected QT and torsade de pointes cardiac arrhythmia associa with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 1993f; 13:128-132.
592. Metzger E & Friedman R: Prolongation of the corrected QT and torsade de pointes cardiac arrhythmia associa with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 1993g; 13:128-132.
593. Metzger E & Friedman R: Prolongation of the corrected QT and torsade de pointes cardiac arrhythmia associa with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 1993h; 13:128-132.
594. Metzger E & Friedman R: Prolongation of the corrected QT and torsade de pointes cardiac arrhythmia associa with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 1993i; 13:128-132.
595. Metzger E & Friedman R: Prolongation of the corrected QT and torsade de pointes cardiac arrhythmia associa with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 1993j; 13:128-132.
596. Metzger E & Friedman R: Prolongation of the corrected QT and torsade de pointes cardiac arrhythmia associa

with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 1993k; 13:128-132.
597. Metzger E & Friedman R: Prolongation of the corrected QT and torsade de pointes cardiac arrhythmia associa with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 1993l; 13:128-132.
598. Midha KK, Chakraborty BS, Ganes DA, et al: Intersubject variation in the pharmacokinetics of haloperidol and reduced haloperidol. J Clin Psychopharmacol 1989; 9:98-104.
599. Mielke DH & Gallant DM: Prolactin blood levels in response to varying doses of haloperidol. Curr Ther Res 198 31:90-94.
600. Mihara K, Otani K, Yasui N, et al: No pharmacokinetic but pharmacodynamic interactions between cisapride ar bromperidol or haloperidol. Ther Drug Monit 1999; 21:297-300.
601. Mihara K, Otani K, Yasui N, et al: No pharmacokinetic but pharmacodynamic interactions between cisapride ar bromperidol or haloperidol. Ther Drug Monit 1999a; 21:297-300.
602. Mihara K, Suzuki A, Kondo T, et al: Effect of a genetic polymorphism of CYP1A2 inducibility on the steady stat plasma concentrations of haloperidol and reduced haloperidol in japanese patients with schizophrenia. Ther D Monit 2000; 22:245-249.
603. Mikkelson EJ, Detlor J, Cohen DJ, et al: School avoidance and social phobia triggered by haloperidol in patien with Tourette's disorder. Am J Psychiatry 1981; 138:1572-1576.
604. Milewicz A, Gejdel E, Sworen H, et al: Vitex agnus castus extract in the treatment of luteal phase defects due t latent hyperprolactinemia. Results of a randomized placebo-controlled double-blind study (Article in German). Arzneimittelforschung 1993; 43(7):752-756.
605. Milewicz A, Gejdel E, Sworen H, et al: Vitex agnus castus extract in the treatment of luteal phase defects due t latent hyperprolactinemia. Results of a randomized placebo-controlled double-blind study (Article in German). Arzneimittelforschung 1993a; 43(7):752-756.
606. Miller F & Menninger J: Correlation of neuroleptic dose and neurotoxicity in patients given lithium and a neuroleptic. Hosp Comm Psychiatr 1987; 38:1219-1221.
607. Min DI, Brown T, & Hwang GC: Visual compatibility of tacrolimus with commonly used drugs during simulated site injection. Am J Hosp Pharm 1992; 49:2964-2966.
608. Mintzer JE, Hoernig KS, & Mirski DF: Treatment of agitation in patients with dementia. Clin Geriatr Med 1998; (1):147-175.
609. Miyaoka H & Kamijima K: Perphenazine-induced hiccups. Pharmacopsychiatry 1999; 32(2):81.
610. Modestin J, Krapf R, & Boker W: A fatality during haloperidol treatment: mechanism of sudden death. Am J Psychiatry 1981; 138:1616-1617.
611. Molander L: Effect of melperone, chlorpromazine, haloperidol, and diazepam on experimental anxiety in norma subjects. Psychopharmacology 1982; 77:109-113.
612. Moline RA: Atypical tardive dyskinesia. Am J Psychiatry 1975; 132:534-535.
613. Moller HJ, Boyer P, Fleurot O, et al: for the Prod-aslp Study Group: Improvement of acute exacerbations of schizophrenia with amisulpride: a comparison to haloperidol. Psychopharmacology 1997; 132(4):396-401.
614. Moller HJ, Kissling W, Riehl T, et al: Doubleblind evaluation of the antimanic properties of carbamazepine as a comedication to haloperidol. Prog Neuropsychopharmacol Biol Psychiatry 1989; 13:127-136.
615. Moller JH, Bauml J, Ferrero F, et al: Risperidone in the treatment of schizophrenia: results of a study of patient from Germany, Austria, and Switzerland. Eur Arch Psychiatry Clin Neurosci 1997a; 247:291-296.
616. Montaz L, Varache N, Harry P, et al: Torsades de pointes during sultopride poisoning. J Toxicol Clin Exp 1992 12:481-496.
617. Montaz L, Varache N, Harry P, et al: Torsades de pointes during sultopride poisoning. J Toxicol Clin Exp 1992 12:481-496.
618. Moore DC: Amitriptyline therapy in anorexia nervosa. Am J Psychiatry 1977a; 134:1303-1304.
619. Moore DP: Rapid treatment of delirium in critically ill patients.. Am J Psychiatry 1977; 132(12):1431-2.
620. Moore DP: Rapid treatment of psychosis with haloperidol.. South Med J 1979; 72(3):337-8.
621. Moore MR & Hift RJ: Drugs in the acute porphyrias--toxicogenetic diseases. Cell Mol Biol (Noisy-le-grand) 199 43(1):89-94.
622. Moore R: Naloxone in the treatment of anorexia nervosa: Effect on weight gain and lipolysis. J Royal Soc Med 1981; 74:129-131.
623. Morselli PL, Bianchetti G, Dugas M, et al: Haloperidol plasma level monitoring in neuropsychiatric patients. The Drug Monit 1982; 4(1):51-58.
624. Moskowitz D: Use of haloperidol to reduce LSD flashbacks. Mil Med 1971; 135:754-756.
625. Mukhopadhyay P, Osman MP, Wajima T, et al: Nifedipine for intractable hiccups. N Engl J Med 1986; 314:125
626. Muller-Siecheneder F, Muller MJ, Hillert A, et al: Risperidone versus haloperidol and amitriptyline in the treatm of patients with a combined psychotic and depressive syndrome. J Clin Psychopharmacol 1998; 18(2):111-11120.
627. Muller-Spahn F: Risperidone in the treatment of chronic schizophrenic patients: an international double-blind parallel group study versus haloperidol. Clin Neuropharm 1992; 15(suppl 1):90A-91A.
628. Munk-Andersen E, Behnke K, Heltberg J, et al: Sulpiride versus haloperidol, a clinical trial in schizophrenia: a preliminary report. Acta Psychiatr Scand 1984; 313(suppl):31-41.
629. Nadel I & Wallach M: Drug interaction between haloperidol and methyldopa (letter). Br J Psychiatry 1979; 135:484.
630. Nadel I & Wallach M: Drug interaction between haloperidol and methyldopa (letter). Br J Psychiatry 1979a; 135:484.
631. Nair NPV, Syranyi-Cadotte B, Schwartz G, et al: A clinical trial comparing intramuscular haloperidol decanoate and oral haloperidol in chronic schizophrenic patients: efficacy, safety, and dosage equivalence. J Clin

Psychopharmacol 1986; 6:30S-37S.
632. National Comprehensive Cancer Network: Antiemesis. National Comprehensive Cancer Network. Jenkintown, PA. 2006. Available from URL: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf.
633. Nayak RK, Doose DR, & Vasavan Nair NP: The bioavailability and pharmacokinetics of oral and depot intramuscular haloperidol in schizophrenic patients. J Clin Pharmacol 1987; 27:144-150.
634. Neidhart JA, Gagen M, Young D, et al: Specific antiemetics for specific cancer chemotherapeutic agents: haloperidol versus benzquinamide. Cancer 1981; 47:1439-1443.
635. Neidhart JA, Gagen M, Young D, et al: Specific antiemetics for specific cancer chemotherapeutic agents: haloperidol versus benzquinamide. Cancer 1981a; 47:1439-1443.
636. Neidhart JA, Gagen MM, Wilson HE, et al: Comparative trial of the antiemetic effects of THC and haloperidol. . Clin Pharmacol 1981b; 21(suppl):385-425.
637. Newcomer JW: Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. Clin Psychiatry 2007a; 68(Suppl 1):20-27.
638. Newcomer JW: Metabolic syndrome and mental illness. Am J Manag Care 2007; 13(7 Suppl):S170-S177.
639. Newport DJ, Calamaras MR, DeVane CL, et al: Atypical antipsychotic administration during late pregnancy: placental passage and obstetrical outcomes. Am J Psychiatry 2007; 164(8):1214-1220.
640. Nishikawa T, Tsuda A, Tanaka M, et al: Prophylactic effect of neuroleptics in symptom-free schizophrenics. Psychopharmacology 1982; 77:301-304.
641. Nishikawa T, Tsuda A, Tanaka M, et al: Prophylactic effect of neuroleptics in symptom-free schizophrenics. Psychopharmacology 1982a; 77:301-304.
642. Nishikawa T, Tsuda A, Tanaka M, et al: Prophylactic effect of neuroleptics in symptom-free schizophrenics. Psychopharmacology 1982b; 77:301-304.
643. Nishikawa T, Tsuda A, Tanaka M, et al: Prophylactic effects of neuroleptics in symptom-free schizophrenics: a comparative dose-response study of haloperidol and propericiazine. Psychopharmacology 1984; 82:153-156.
644. None Listed: Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004; 27(2):596-601.
645. Nose T & Takemoto H: The effect of penfluridol and some psychotropic drugs on monoamine metabolism in central nervous system. Eur J Pharmacol 1975; 31:351-359.
646. Nutt JG, Rosin A, & Chase TN: Treatment of Huntington disease with a cholinergic agonist. Neurology 1978; 28:1061-1064.
647. Nutt JG, Rosin A, & Chase TN: Treatment of Huntington disease with a cholinergic agonist. Neurology 1978a; 28:1061-1064.
648. Nyth AL & Gottfries CG: The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders: a Nordic multicentre study. Br J Psychiatry 1990; 157:894-901.
649. Nyth AL, Gottfries CG, Lyby K, et al: A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. Acta Psychiatr Scand 1992; 86:138-145.
650. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999; 33:10 1050.
651. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999a; 33 (10):1046-1050.
652. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999b; 33:1046-1050.
653. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999c; 33:1046-1050.
654. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999d; 33:1046-1050.
655. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999e; 33:1046-1050.
656. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999f; 33:1046-1050.
657. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999g; 33:1046-1050.
658. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999h; 33:1046-1050.
659. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999i; 33:1046-1050.
660. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999j; 33:1046-1050.
661. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999k; 33:1046-1050.
662. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999l; 33:1046-1050.
663. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999m; 33:1046-1050.
664. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999n; 33:1046-1050.
665. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999o; 33:1046-1050.

666. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999p; 33:1046-1050.
667. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999q; 33:1046-1050.
668. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999r; 33:1046-1050.
669. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999s; 33:1046-1050.
670. O'Brien JM, Rockwood RP, & Suh KI: Haloperidol-induced torsade de pointes. Ann Pharmacother 1999t; 33:1046-1050.
671. Oberg KC & Bauman JL: QT interval prolongation and torsades de pointes due to erythromycin lactobionate. Pharmacotherapy 1995; 15(6):687-692.
672. Oberg KC & Bauman JL: QT interval prolongation and torsades de pointes due to erythromycin lactobionate. Pharmacotherapy 1995a; 15(6):687-692.
673. Ohman R: Prolactin response to haloperidol after a single dose and during prolonged administration. Curr Ther Res 1980; 27:137.
674. Osser DN & Stewart TD: Agitation associated with dementia: neuroleptic malignant syndrome and fatal outcom in an 84-year-old man. J Clin Psychopharmacol 1988; 8:443-444.
675. Outman WR & Monolakis J: Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. Am J Hosp Pharm 1991; 48:1539-1541.
676. Outman WR & Monolakis J: Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. Am J Hosp Pharm 1991a; 48:1539-1541.
677. Outman WR & Monolakis J: Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. Am J Hosp Pharm 1991b; 48:1539-1541.
678. Outman WR & Monolakis J: Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. Am J Hosp Pharm 1991c; 48:1539-1541.
679. Outman WR & Monolakis J: Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. Am J Hosp Pharm 1991d; 48:1539-1541.
680. Outman WR & Monolakis J: Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. Am J Hosp Pharm 1991e; 48:1539-1541.
681. Outman WR & Monolakis J: Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. Am J Hosp Pharm 1991f; 48:1539-1541.
682. Outman WR & Monolakis J: Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. Am J Hosp Pharm 1991g; 48:1539-1541.
683. Outman WR & Monolakis J: Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. Am J Hosp Pharm 1991h; 48:1539-1541.
684. Outman WR & Monolakis J: Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. Am J Hosp Pharm 1991i; 48:1539-1541.
685. Outman WR & Monolakis J: Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. Am J Hosp Pharm 1991j; 48:1539-1541.
686. Outman WR & Monolakis J: Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. Am J Hosp Pharm 1991k; 48:1539-1541.
687. Outman WR & Monolakis J: Visual compatibility of haloperidol lactate with 0.9% sodium chloride injection or injectable critical-care drugs during simulated Y-site injection. Am J Hosp Pharm 1991l; 48:1539-1541.
688. Owen RR Jr & Cole JO: Molindone hydrochloride: a review of laboratory and clinical findings. J Clin Psychopharmacol 1989; 9:268-276.
689. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001; 21(3):310-319.
690. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001a; 21(3):310-319.
691. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001aa; 21(3):310-319.
692. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001ab; 21(3):310-319.
693. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001ac; 21(3):310-319.
694. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001ad; 21(3):310-319.
695. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001b; 21(3):310-319.
696. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001c; 21(3):310-319.
697. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001d; 21(3):310-319.
698. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001e; 21(3):310-319.
699. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001f; 21(3):310-319.

700. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001g; 21(3):310-319.
701. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001h; 21(3):310-319.
702. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001i; 21(3):310-319.
703. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001j; 21(3):310-319.
704. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001k; 21(3):310-319.
705. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001l; 21(3):310-319.
706. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001m; 21(3):310-319.
707. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001n; 21(3):310-319.
708. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001o; 21(3):310-319.
709. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001p; 21(3):310-319.
710. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001q; 21(3):310-319.
711. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001r; 21(3):310-319.
712. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001s; 21(3):310-319.
713. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001t; 21(3):310-319.
714. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001u; 21(3):310-319.
715. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001v; 21(3):310-319.
716. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001w; 21(3):310-319.
717. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001x; 21(3):310-319.
718. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001y; 21(3):310-319.
719. Owens R: Risk assessment for antimicrobial agent-induced QTc prolongation and torsades de pointes. Pharmacother 2001z; 21(3):310-319.
720. Pacher P & Kecskemeti V: Cardiovascular side effects of new antidepressants and antipsychotics: new drugs, concerns?. Curr Pharm Des 2004; 10(20):2463-2475.
721. Panel comment, 10/1991.
722. Parent M & Toussaint C: Flupenthixol versus haloperidol in acute psychosis. Pharmatherapeutica 1983; 3:354-364.
723. Parkin L, Skegg DC, Herbison GP, et al: Psychotropic drugs and fatal pulmonary embolism. Pharmacoepidemi Drug Saf 2003; 12(8):647-652.
724. Parlow JL, Costache I, Avery N, et al: Single-dose haloperidol for the prophylaxis of postoperative nausea and vomiting after intrathecal morphine. Anesth Analg 2004; 98:1072-1076.
725. Pary RJ, Klontz W, & Foxworth JM: Cholinergic rebounds and withdrawal syndromes (letter). Am J Psychiatry 1980; 137:261.
726. Pascuzzi RM: Medications and myasthenia gravis.. Available at http://www.myasthenia.org/drugs/reference.htr (cited 6/2001), October, 2000.
727. Patris M, Agussol P, Alby JM, et al: A double-blind multicentre comparison of remoxipride, at two dose levels, a haloperidol. Acta Psychiatr Scand 1990; 82(suppl 358):78-82.
728. Peabody CA, Brody D, & Warner MD: Tardive dyskinesia after low-dose haloperidol. Biol Psychiatry 1987; 22:111-117.
729. Peck V & Shenkman L: Haloperidol-induced syndrome of inappropriate secretion of antidiuretic hormone. Clin Pharmacol Ther 1979; 26:442-444.
730. Perry PJ, Alexander B, & Liskow BIPerry PJ, Alexander B, & Liskow BI: Psychotropic Drug Handbook, 6th. Harvey Whitney Books Company, Cincinnati, OH, 1991.
731. Perry R, Campbell M, Green WH, et al: Neuroleptic-related dyskinesias in autistic children. A prospective study Psychopharmacol Bull 1985; 21:140-143.
732. Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical Spring House, PA, November 6, 1990.
733. Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical Spring House, PA, November 6, 1990a.
734. Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical

Spring House, PA, November 6, 1990b.
735. Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical Spring House, PA, November 6, 1990c.
736. Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical Spring House, PA, November 6, 1990d.
737. Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical Spring House, PA, November 6, 1990e.
738. Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical Spring House, PA, November 6, 1990f.
739. Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical Spring House, PA, November 6, 1990g.
740. Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical Spring House, PA, November 6, 1990h.
741. Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical Spring House, PA, November 6, 1990i.
742. Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical Spring House, PA, November 6, 1990j.
743. Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical Spring House, PA, November 6, 1990k.
744. Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical Spring House, PA, November 6, 1990l.
745. Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical Spring House, PA, November 6, 1990m.
746. Pert CB, Kuhar MJ, & Snyder SH: Opiate receptor: autoradiographic localization in rat brain. Proc Natl Acad S USA 1976; 73:3729-3733.
747. Pertel P & Till M: Intractable hiccups induced by the use of megestrol acetate. Arch Intern Med 1998; 158(7):8 810.
748. Peselow ED & Stanley M: Clinical trials of benzamides in psychiatry. Adv Biochem Psychopharmacol 1982; 35:163-194.
749. Peterson LG & Bongar B: Navane(R) versus haldol: treatment of acute organic mental syndromes in the gener hospital. Gen Hosp Psychiatry 1989; 11:412-417.
750. Petit M, Raniwalla J, Tweed J, et al: A comparison of an atypical and typical antipsychotic, zotepine versus haloperidol in patients with acute exacerbation of schizophrenia: a parallel-group double-blind trial. Psychopharmacol Bull 1996; 32:81-87.
751. Phenothiazines monograph.. USP DI., 5/89.
752. Pichot P & Boyer P: A controlled double-blind multi-centre trial of high dose amisulpride versus haloperidol in acute psychotic states. Ann Psychiatr 1988; 3:83-92.
753. Pina Latorre MA & Cobeta JC Rodilla F: Influence of calcium antagonist drugs in myasthenia gravis in the elde J Clin Pharm Ther 1998; 23(5):399-401.
754. Plotkin DA, Plotkin D, & Okun R: Haloperidol in the treatment of nausea and vomiting due to cytotoxic drug administration. Curr Ther Res 1973; 15:599-602.
755. Plotnick EK & Brown GR: Intravenous haloperidol treatment of severely regressed, nonviolent psychiatric inpatients. Gen Hosp Psychiatry 1991; 13:385-390.
756. Poeldinger W, Bures E, & Haage H: Clinical study with bromperidol, a new butyrophenone derivative. Int Pharmacopsychiatry 1977; 12:20-24.
757. Pollock BG & Mulsant BH: Behavioral disturbances of dementia. J Geriatr Psychiatry Neurol 1998; 11:206-212
758. Prakash R: Lithium-haloperidol combination and brain damage (letter). Lancet 1982; 1:1468-1469.
759. Prieto IJ, Guerrero RP, Fernadez R, et al: Ultrarapid high-dose methadone detoxification. Psychopharmacol 2003; 165:430.
760. Product Information: Aloprim(TM), allopurinol sodium for injection. Nabi, Boca Raton, FL, USA, 1999.
761. Product Information: Anzemet(R), dolasetron. Hoechst Marion Roussel, Kansas City, MO, 1997.
762. Product Information: Anzemet(R), dolasetron. Hoechst Marion Roussel, Kansas City, MO, 1997a.
763. Product Information: Aralen(R), chloroquine phosphate. Sanofi Pharmaceuticals, New York, NY, 2001.
764. Product Information: Ativan(R) Injection compatibility charts. Wyeth-Ayerst Laboratories, Philadelphia, PA, 198
765. Product Information: Biaxin(R), clarithromycin. Abbott Laboratories, North Chicago, IL, 2002.
766. Product Information: Cogentin(R), benztropine. Merck & Co., Inc., West Point, PA, 1994.
767. Product Information: Compazine(R), prochlorperazine maleate spansule. GlaxoSmithKline, Research Triangle Park, NC, 2002.
768. Product Information: Dicumarol. Abbott Laboratories, North Chicago, IL, 1995.
769. Product Information: Dostinex(R), cabergoline. Pharmacia & Upjohn Company, Kalamazoo, MI, 1996.
770. Product Information: DynaCirc(R), isradipine. Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2000.
771. Product Information: Effexor(R) XR, venlafaxine hydrochloride extended-release. Wyeth Laboratories, Philadelphia, PA, 2003.
772. Product Information: Effexor(R) XR, venlafaxine hydrochloride extended-release. Wyeth Laboratories, Philadelphia, PA, 2003a.
773. Product Information: FANAPT(TM) oral tablets, iloperidone oral tablets. Vanda Pharmaceuticals, Rockville, MD 2009.
774. Product Information: Factive(R), gemifloxacin. Genesoft Pharmaceuticals, Seoul, Korea, 2003.

775. Product Information: Foscavir(R), foscarnet. AstraZeneca, Inc., Alexandria, VA, 1998.
776. Product Information: GEODON(R) intramuscular injection, oral capsule, ziprasidone hydrochloride oral capsule ziprasidone mesylate intramuscular injection. Pfizer Inc, NY, NY, 2005.
777. Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002.
778. Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002a.
779. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002.
780. Product Information: Geodon(TM), ziprasidone. Pfizer Inc., NY, NY, 2002a.
781. Product Information: HALDOL(R) Decanoate IM injection, haloperidol IM injection. Janssen Pharmaceutica NV Beerse, Belgium, 2008.
782. Product Information: HALDOL(R) IM injection, haloperidol IM injection. Janssen Pharmaceutica NV, Beerse, Belgium, 2008.
783. Product Information: HALDOL(R) immediate release IM injection, haloperidol immediate release IM injection. Janssen Pharmaceutica NV, Beerse, Belgium, 2008.
784. Product Information: HALDOL(R) injection, haloperidol injection. Ortho-McNeil Pharmaceutical,Inc, Raritan, NJ 2007.
785. Product Information: Haldol Decanoate. McNeil, 1986.
786. Product Information: Haldol(R) Injection, haloperidol injection. Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ, 2001.
787. Product Information: Haldol(R), haloperidol decanoate for injection. Ortho-McNeil Pharmaceutical Corp., Rarita NJ, 2001.
788. Product Information: Haldol(R), haloperidol decanoate for injection. Ortho-McNeil Pharmaceutical Corp., Rarita NJ, 2001a.
789. Product Information: Haldol(R), haloperidol decanoate for injection. Ortho-McNeil Pharmaceutical Corp., Rarita NJ, 2001c.
790. Product Information: Haldol(R), haloperidol decanoate for injection. Ortho-McNeil Pharmaceutical Corp., Rarita NJ, 2001d.
791. Product Information: Haldol(R), haloperidol decanoate for injection. Ortho-McNeil Pharmaceutical Corp., Rarita NJ, 2001e.
792. Product Information: Haldol(R), haloperidol decanoate for injection. Ortho-McNeil Pharmaceutical Corp., Rarita NJ, 2001g.
793. Product Information: Haldol(R), haloperidol decanoate for injection. Ortho-McNeil Pharmaceutical Corp., Rarita NJ, 2001h.
794. Product Information: Haldol(R), haloperidol decanoate for injection. Ortho-McNeil Pharmaceutical Corp., Rarita NJ, 2001i.
795. Product Information: Haldol(R), haloperidol decanoate for injection. Ortho-McNeil Pharmaceutical Corp., Rarita NJ, 2001j.
796. Product Information: Haldol(R), haloperidol decanoate for injection. Ortho-McNeil Pharmaceutical Corp., Rarita NJ, 2001k.
797. Product Information: Haldol(R), haloperidol decanoate for injection. Ortho-McNeil Pharmaceutical Corp., Rarita NJ, 2001l.
798. Product Information: Haldol(R), haloperidol decanoate for injection. Ortho-McNeil Pharmaceutical Corp., Rarita NJ, 2001m.
799. Product Information: Haldol(R), haloperidol decanoate. McNeil Pharmaceutical, Inc., Raritan, NJ, 1998.
800. Product Information: Haldol(R), haloperidol decanoate. McNeil Pharmaceutical, Inc., Raritan, NJ, 1998a.
801. Product Information: Haldol(R), haloperidol decanoate. McNeil Pharmaceutical, Inc., Raritan, NJ, 1998b.
802. Product Information: Haldol(R), haloperidol decanoate. McNeil Pharmaceutical, Inc., Raritan, NJ, 1998c.
803. Product Information: Haldol(R), haloperidol decanoate. McNeil Pharmaceutical, Inc., Raritan, NJ, 1998d.
804. Product Information: Haldol(R), haloperidol decanoate. McNeil Pharmaceutical, Inc., Raritan, NJ, 1998e.
805. Product Information: Haldol(R), haloperidol decanoate. McNeil Pharmaceutical, Inc., Raritan, NJ, 1998f.
806. Product Information: Haldol(R), haloperidol decanoate. McNeil Pharmaceutical, Inc., Raritan, NJ, 1998g.
807. Product Information: Haldol(R), haloperidol decanoate. McNeil Pharmaceutical, Inc., Raritan, NJ, 1998h.
808. Product Information: Haldol(R), haloperidol decanoate. McNeil Pharmaceutical, Inc., Raritan, NJ, 1998i.
809. Product Information: Haldol(R), haloperidol decanoate. McNeil Pharmaceutical, Inc., Raritan, NJ, 1998j.
810. Product Information: Haldol(R), haloperidol decanoate. Ortho McNeil Pharmaceutical, Inc., Raritan, NJ, 2001b.
811. Product Information: Haldol(R), haloperidol decanoate. Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ, 2001f.
812. Product Information: Haldol(R), haloperidol. McNeil Pharmaceutical, Raritan, NJ, 2000.
813. Product Information: Haldol(R), haloperidol. McNeil Pharmaceutical, Raritan, NJ, 2000a.
814. Product Information: Haldol(R), haloperidol. McNeil Pharmaceutical, Raritan, NJ, 2000b.
815. Product Information: Haldol(R), haloperidol. McNeil Pharmaceutical, Spring House, PA, 97.
816. Product Information: Haldol(R), haloperidol. McNeil Pharmaceutical, Spring House, PA, 97a.
817. Product Information: Haldol. McNeil, US, 87.
818. Product Information: Halfan(R), halofantrine hydrochloride. Research Triangle Park, NC, 1998.
819. Product Information: Haloperidol. Kenral, Canada, 89.
820. Product Information: Hismanal(R), astemizole. Janssen Pharmaceutica, Inc., Titusville, NJ, 1996.
821. Product Information: INDERAL(R) LA oral capsules, propranolol hydrochloride oral capsules. Wyeth Pharmaceuticals, Philadelphia, PA, 2007.
822. Product Information: INVEGA(TM) extended-release oral tablets, paliperidone extended-release oral tablets. A Corporation, Mountain View, CA, 2006.

823. Product Information: Inapsine(R), droperidol. Akorn, Inc., Decatur, IL, 2002.
824. Product Information: LITHOBID(R) slow-release oral tablets, lithium carbonate slow-release oral tablets. JDS Pharmaceuticals,LLC, New York, NY, 2005.
825. Product Information: Lariam(R), mefloquine. Roche Laboratories, Nutley, NJ, 1999.
826. Product Information: Lorelco(R), probucol. Marion Merrell Dow, Kansas City, MO, 1991.
827. Product Information: Mellaril(R), thioridazine. Mylan Pharmaceuticals Inc., Morgantown, WV, 2001.
828. Product Information: Nipolept(R), zotepine. Klinge Pharma GmbH, Munich, 1996.
829. Product Information: Nipolept(R), zotepine. Klinge Pharma GmbH, Munich, 1996a.
830. Product Information: Norpace(R), disopyramide. G.D. Searle & Co., Chicago, IL, 1997.
831. Product Information: Orap(R) pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999.
832. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999.
833. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999a.
834. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999b.
835. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999c.
836. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 1999d.
837. Product Information: Orap(R), pimozide. Gate Pharmaceuticals, Sellersville, PA, 2000.
838. Product Information: Orap(R), pimozide. TEVA Pharmaceuticals, Sellersville, PA, 1999e.
839. Product Information: Orlaam(R), levomethadyl. Roxane Laboratories, Inc., Columbus, Ohio, 2001.
840. Product Information: PCE(R), erythromycin particles in tablets. Abbott Laboratories, North Chicago, IL, 1997.
841. Product Information: Pamelor(R), nortriptyline. Mallinkroft Inc., St. Louis, MO, 2001.
842. Product Information: Priftin(R), rifapentine tablets. Aventis Pharmaceuticals, Inc., Kansas City, MO, 2000.
843. Product Information: Propulsid(R), cisapride. Janssen Pharmaceutica Inc., Toronto, Ontario, 2000.
844. Product Information: Propulsid(R), cisapride. Janssen Pharmaceutica Inc., Toronto, Ontario, 2000a.
845. Product Information: Prozac(R), fluoxetine. Eli Lilly and Company, Indianapolis, IN, 2001.
846. Product Information: Quinaglute(R), quinidine gluconate. Berlex Laboratories, Wayne, NJ, 1999.
847. Product Information: Risperdal(R) risperidone. Janssen Pharmaceutica Products, L.P., Titusville, NJ, 2002.
848. Product Information: Risperdal(R) risperidone. Janssen Pharmaceutica Products, L.P., Titusville, NJ, 2002a.
849. Product Information: Risperdal(R) risperidone. Janssen Pharmaceutica, Titusville, NJ, 1999.
850. Product Information: Risperdal(R) risperidone. Janssen Pharmaceutica, Titusville, NJ, 2000.
851. Product Information: Risperdal(R) risperidone. Janssen Pharmaceutica, Titusville, NJ, 2000a.
852. Product Information: Risperdal(R) risperidone. Janssen Pharmaceutica, Titusville, NJ, 2000b.
853. Product Information: Risperdal(R) risperidone. Janssen Pharmaceutica, Titusville, NJ, 2000c.
854. Product Information: SYNERCID(R) intravenous injection, dalfopristin/quinupristin intravenous injection. Monar Pharmaceuticals, Inc, Bristol, TN, 2003.
855. Product Information: Sandostatin(R), octreotide. Novartis Pharmaceuticals, East Hanover, NJ, 1999.
856. Product Information: Serentil(R), mesoridazine. Novartis Pharmaceuticals Corporation, East Hanover, NJ, 200
857. Product Information: Seroquel(R), quetiapine fumarate. AstraZeneca Pharmaceuticals LP, Wilmington, DE, 20
858. Product Information: Serzone(R), nefazodone. Bristol-Myers Squibb Company, Princeton, NJ, 1998.
859. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999.
860. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999a.
861. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999aa.
862. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999ab.
863. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999b.
864. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999c.
865. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999d.
866. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999e.
867. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999f.
868. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999g.
869. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999h.
870. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999i.
871. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999j.
872. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999k.
873. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999l.
874. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999m.
875. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999n.
876. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999o.
877. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999p.
878. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999q.
879. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999r.
880. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999s.
881. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999t.
882. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999u.
883. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999v.
884. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999w.
885. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999x.
886. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999y.
887. Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999z.
888. Product Information: Stalevo(TM), levodopa/carbidopa/entacapone. Novartis Pharmaceuticals Corporation, Ea

Hanover, NJ, 2003.
889. Product Information: Stelazine(R), trifluoperazine hydrochloride. GlaxoSmithKline, Research Triangle Park, NC 2002.
890. Product Information: Syprine(R), trientine hydrochloride. Merck & Co., Inc., West Point, PA, 2001.
891. Product Information: Tambocor(R), flecainide acetate. 3M Pharmaceuticals, Northridge, CA, 1998.
892. Product Information: Thorazine(R), chlorpromazine. Smithkline Beecham Pharmaceuticals, Philadelphia, PA, 2002.
893. Product Information: Trisenox(R), arsenic trioxide injection. Cell Therapeutics, Inc., Seattle, WA, 2001.
894. Product Information: Trisenox(R), arsenic trioxide injection. Cell Therapeutics, Inc., Seattle, WA, 2001a.
895. Product Information: Ultram(R), tramadol hydrochloride. Ortho-McNeil Pharmaceutical, Raritan, NJ, 1998.
896. Product Information: Vascor(R), bepridil. McNeil Pharmaceutical, Spring House, PA, 1997.
897. Product Information: Wellbutrin XL(TM), bupropion hydrochloride extended-release tablets. GlaxoSmithKline, Research Triangle Park, NC, 2003.
898. Product Information: XENAZINE(R) oral tablets, tetrabenazine oral tablets. Prestwick Pharmaceuticals,Inc, Washington, DC, 2008.
899. Product Information: Zagam(R), sparfloxacin. Rhone-Poulenc Rorer Pharmaceuticals Inc, Collegeville, PA, 19
900. Product Information: Zagam(R), sparfloxacin. Rhone-Poulenc Rorer Pharmaceuticals Inc, Collegeville, PA, 1998a.
901. Product Information: Zofran(R), ondansetron. Glaxo Inc, Research Triangle Park, NC, 1999.
902. Product Information: Zomig(R), zolmitriptan tablets. AstraZeneca Pharmaceuticals, Wilmington, DE, 2001.
903. Product Information: Zyban(R), bupropion hydrochloride. Glaxo Wellcome Inc., Research Triangle Park, NC, 2000.
904. Product Information: haloperidol decanoate injection, haloperidol decanoate injection. Bedford Laboratories, Bedford, OH, 2005.
905. Product Information: haloperidol lactate IM injection, haloperidol lactate IM injection. Bedford Laboratories, Bedford, OH, 2005.
906. Product Information: haloperidol lactate injection, haloperidol lactate injection. Sicor Pharmaceuticals Inc., Irvin CA, 2003.
907. Product Information: haloperidol oral solution, haloperidol oral solution. Silarx Pharmaceuticals,Inc, Spring Vall NY, 2001.
908. Product Information: haloperidol oral solution, haloperidol oral solution. Teva Pharmaceuticals USA, Sellersville PA, 2008.
909. Product Information: haloperidol oral tablets, haloperidol oral tablets. Sandoz Inc, Princeton, NJ, 2008.
910. Product Information: haloperidol oral tablets, haloperidol oral tablets. Sandoz,Inc, Princeton, NJ, 2006.
911. Psaras M, Zissis NP, Mouzakis D, et al: Mobilization of refractory chronic schizophrenics with haloperidol. Int Pharmacopsychiatry 1980; 15:180-185.
912. Purkis IE: The action of thiethylperazine (Torecan(R)), a new anti-emetic, compared with perphenazine (Trilafo (R)), trimethobenzamide (Tigan(R)) and a placebo in the suppression of postanaesthetic nausea and vomiting. Can Anaesth Soc J 1965; 12:595-607.
913. Rabins PV, Blacker D, Rovner BW, et al: American Psychiatric Association practice guideline for the treatment patients with Alzheimer's disease and other dementias. Second edition. Am J Psychiatry 2007; 164(12 Suppl): 56.
914. Raft D, Tomey T, & Gregg JM: Behavior modification and haloperidol in chronic facial pain. South Med J 1979; 72:155-159.
915. Ramaekers, JG, Louwerens JW, et al: Psychomotor, cognitive, extrapyramidal, and affective functions of healt volunteers during treatment with an atypical (amisulpride) and a classic (haloperidol) antipsychotic. J Clin Psychopharmacol 1999; 19(3):209-221.
916. Ramirez FC & Graham DY: Treatment of intractable hiccups with baclofen: results of a double-blind randomize controlled, cross-over study. Am J Gastroenterol 1992; 87(12):1789-1791.
917. Rao VAR, Bishop M, & Coppen A: Clinical state, plasma levels of haloperidol and prolactin: a correlation study chronic schizophrenia. Br J Psychiatry 1980; 137:518-521.
918. Rapp W, Hellbom E, Norrman O, et al: A double-blind crossover study comparing haloperidol decanoate and perphenazine enantate. Curr Ther Res 1986; 39:665-670.
919. Raskind MA, Cyrus PA, Ruzicka BB, et al: The effects of Metrifonate on the cognitive, behavioral, and function performance of Alzheimer's Disease in patients. J Clin Psychiatry 1999; 60:318-325.
920. Ravin DS & Levenson JW: Fatal cardiac event following initiation of risperidone therapy. Ann Pharmacother 1997; 31:867-870.
921. Ravin DS & Levenson JW: Fatal cardiac event following initiation of risperidone therapy. Ann Pharmacother 1997a; 31:867-870.
922. Ravin DS & Levenson JW: Fatal cardiac event following initiation of risperidone therapy. Ann Pharmacother 1997b; 31:867-870.
923. Ravin DS & Levenson JW: Fatal cardiac event following initiation of risperidone therapy. Ann Pharmacother 1997c; 31:867-870.
924. Ravin DS & Levenson JW: Fatal cardiac event following initiation of risperidone therapy. Ann Pharmacother 1997d; 31:867-870.
925. Ravin DS & Levenson JW: Fatal cardiac event following initiation of risperidone therapy. Ann Pharmacother 1997e; 31:867-870.
926. Ravin DS & Levenson JW: Fatal cardiac event following initiation of risperidone therapy. Ann Pharmacother

1997f; 31:867-870.
927. Ravin DS & Levenson JW: Fatal cardiac event following initiation of risperidone therapy. Ann Pharmacother 1997g; 31:867-870.
928. Ravin DS & Levenson JW: Fatal cardiac event following initiation of risperidone therapy. Ann Pharmacother 1997h; 31:867-870.
929. Ray WA, Chung CP, Murray KT, et al: Atypical antipsychotic drugs and the risk of sudden cardiac death. N Eng Med 2009; 360(3):225-235.
930. Ray WA, Griffin MR, Schaffner W, et al: Psychotropic drug use and the risk of hip fracture. N Engl J Med 1987 316:363-369.
931. Reilly PP: RI Med J 1977; 60:455-456. RI Med J 1977; 60:455-456.
932. Reinke M & Wiesert KN: High incidence of haloperidol deconate injection site reactions (letter). J Clin Psychiat 1992; 53:415-416.
933. Remington G, Sloman L, Konstantareas M, et al: Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. J Clin Psychopharmacol 2001; 21:440-444.
934. Resnick M & Burton BT: Droperidol vs haloperidol in the initial management of acutely agitated patients. J Clin Psychiatry 1984; 45:298-299.
935. Reviewers responses to monograph revision.. ., 10/3/91.
936. Reyntjens AJM, Heykants JJP, Wocstenborghs RJH, et al: Pharmacokinetics of haloperidol decanoate. Int Pharmacopsychiatry 1982; 17:238-246.
937. Rice E: Prolonged parkinsonian reaction after haloperidol in a patient with monoclonal IgM. Br J Psychiatry 19 130:103.
938. Rifkin A, Doddi S, Karajgi B, et al: Dosage of haloperidol for mania. Br J Psychiatry 1994; 165:113-116.
939. Rifkin A, Doddi S, Karajgi B, et al: Dosage of haloperidol for schizophrenia. Arch Gen Psychiatr 1991; 48:166-170.
940. Rifkin A, Karajgi B, Doddi S, et al: Dose and blood levels of haloperidol in treatment of mania. Psychopharmac Bull 1990; 26:144-146.
941. Riker RR, Fraser GL, & Cox PM: Continuous infusion of haloperidol controls agitation in critically ill patients. C Care Med 1994; 22:433-440.
942. Riker RR, Fraser GL, & Cox PM: Continuous infusion of haloperidol controls agitation in critically ill patients. C Care Med 1994a; 22:433-440.
943. Rita Moretti, MD, Universita degli Studi di Trieste
944. Robbins EL & Nagel JD: Haloperidol parenterally for treatment of vomiting and nausea from gastrointestinal disorders in a group of geriatric patients: double-blind placebo-controlled study. J Am Geriat Soc 1975; 23:38-4
945. Rochon PA, Stukel TA, Sykora K, et al: Atypical antipsychotics and parkinsonism. Arch Intern Med 2005; 165:1882-1888.
946. Ropert R, Payan C, & Allard S: Sultopride versus haloperidol dans le traitement des etats psychotiques aigus (French). Ann Psychiatr 1989; 4:92-98.
947. Rosenheck R, Chang S, Choe Y, et al: Medication continuation and compliance; a comparison of patients trea with clozapine and haloperidol. J Clin Psychiatry 2000; 61:382-386.
948. Rosenheck R, Cramer J, Xu W, et al: A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. N Engl J Med 1997; 337(12):809-815.
949. Ross MS & Moldofsky H: A comparison of pimozide and haloperidol in the treatment of Gilles de la Tourette's syndrome. Am J Psychiatry 1978; 135:585-587.
950. Rounsaville BJ, Kosten T, & Kleber H: Success and failure at outpatient opioid detoxification: evaluating the process of clonidine and methadone-assisted withdrawal. J Nerv Mental Dis 1985; 173:103-110.
951. Rubin RT & Forster B: Haloperidol stimulation of prolactin secretion: How many blood samples are needed to define hormone response?. Comm Psychopharmacol 1980; 4:41-47.
952. Ruther E, Eben E, Klein H et al: Comparative double-blind study of amisulpride and haloperidol in the treatmer of acute episodes of positive schizophrenia. In Amisulpride. Borenstein P et al Eds. Expansion Scientifique Francaise - Paris. :63-72, 1989.
953. Ryken TC & Merrell AN: Haloperidol-induced neuroleptic malignant syndrome in a 67-year-old woman with parkinsonism. West J Med 1989; 151:326-328.
954. Saha AR, Petrie JL, & Ali MW: Safety and efficacy profile of aripiprazole, a novel antipsychotic. Schizophr Res 1999; 36(1-3):295.
955. Saleh JW & Lebwohl P: Metoclopramide-induced gastric emptying in patients with anorexia nervosa. Am J Gastroenterol 1980; 74:127-132.
956. Salem MR, Baraka A, Rattenborg CC, et al: Treatment of hiccups by pharyngeal stimulation in anesthetized ar conscious subjects.. JAMA 1967; 202(1):126-130.
957. Salem MR: An effective method for the treatment of hiccups during anesthesia. Anesthesiology 1967; 28(2):46 464.
958. Salem RS & Muniz CE: Treatment of propoxyphene dependence with thioridazine. J Clin Psychiatry 1980; 41:179.
959. Sallee FR, Nesbitt L, Jackson C, et al: Relative efficacy of haloperidol and pimozide in children and adolescent with Tourette's disorder. Am J Psychiatry 1997; 154:1057-1062.
960. Sallee FR, Nesbitt L, Jackson C, et al: Relative efficacy of haloperidol and pimozide in children and adolescent with Tourette's disorder. Am J Psychiatry 1997a; 154(8):1057-1062.
961. Salmon MA & Wilson J: Drugs for alternating hemiplegic migraine. Lancet 1984; 2:980.
962. Sanders KM, Murray GB, & Cassem NH: High-dose intravenoushaloperidol for agitated delirium in a cardiac

patient on intra-aortic balloon pump (letter). J Clin Psychopharmacol 1991; 11:146-147.
963. Sandyk R & Hurwitz MD: Toxic irreversible encephalopathy induced by lithium carbonate and haloperidol. S Af Med J 1983; 65:875-876.
964. Sanger TM, Lieberman JA, Tohen M, et al: Olanzapine versus haloperidol treatment in first-episode psychosis. Am J Psychiatry 1999; 156:79-87.
965. Sato R, Uematsu T, Sato R, et al: Human scalp hair as evidence of individual dosage history of haloperidol: prospective study. Ther Drug Monit 1989; 11:686-691.
966. Schelosky L, Raffauf C, Jendroska K, et al: Kava and dopamine antagonism. J Neurol Neurosurg Psych 1995; (5):639-640.
967. Schelosky L, Raffauf C, Jendroska K, et al: Kava and dopamine antagonism. J Neurol Neurosurg Psych 1995a 58(5):639-640.
968. Schmidt L, Schuessler G, Kappes C, et al: Vergleich einer hoeher dosierten Haloperidol-Therapie mit einer Perazin-Standard-Therapie bei akut-schizophrenen Patienten. Nervenarzt 1982; 53:530-536.
969. Schneeweiss S & Avorn J: Antipsychotic agents and sudden cardiac death — How should we manage the risk N Engl J Med 2009; 360(3):294-296.
970. Schneeweiss S, Setoguchi S, Brookhart A, et al: Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ 2007; 176(5):627-632.
971. Schottland JR: Ofloxacin in the Lambert-Eaton myasthenic syndrome. Neurology 1999; 52:435.
972. Schulz-Du Bois C, Schulz-Du Bois AC, Bewig B, et al: Major increase of quetiapine steady-state plasma concentration following co-administration of clarithromycin: confirmation of the pharmacokinetic interaction potential of quetiapine. Pharmacopsychiatry 2008; 41(6):258-259.
973. Segal J, Berk M, & Brook S: Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. Clin Neuropharmacol 1998; 21:176-180.
974. Seneff MG & Mathews RA: Use of haloperidol infusions to control delirium in critically ill adults. Ann Pharmacother 1995; 29:690-693.
975. Serban G & Siegel S: Response of borderline and schizotypal patients to small doses of thiothixene and haloperidol. Am J Psychiatry 1984; 141:1455-1458.
976. Serra-Mestres J, Shapleske J, & Tym E: Treatment of palilalia with trazodone (letter). Am J Psychiatry 1996; 153:580-581.
977. Serrano AC: Haloperidol - its use in children. J Clin Psychiatry 1981; 42:154-155.
978. Sewell DD, Jeste DV, McAdams LA, et al: Neuroleptic treatment of HIV-associated psychosis. Neuropsychopharmacology 1994; 10:223-229.
979. Shader RI & DiMascio A (Eds): Psychotropic Drug Side Effects, Williams and Wilkins Company, Maryland, 197
980. Shapiro AK & Shapiro E: The treatment and etiology of tics and Tourette syndrome. Compr Psychiatry 1981a; 22:193-205.
981. Shapiro AK, Shapiro E, & Eisenkraft GJ: Treatment of Tourette disorder with penfluridol. Compr Psychiatry 198 24:327-331.
982. Shapiro E & Shapiro AK: Tic disorders. JAMA 1981; 245:1583-1585.
983. Shapiro E, Shapiro AK, Fulop G, et al: Controlled study of haloperidol, pimozide and placebo for the treatment Gilles de la Tourette's syndrome. Arch Gen Psychiatry 1989a; 46(8):722-730.
984. Shapiro E, Shapiro AK, Fulop G, et al: Controlled study of haloperidol, pimozide, and placebo for the treatment Gilles de la Tourette's syndrome. Arch Gen Psychiatry 1989; 46:722-730.
985. Sharma ND, Rosman HS, Padhi D, et al: Torsades de pointes associated with intravenous haloperidol in critica ill patients. Am J Cardiol 1998; 81:238-240.
986. Sharma ND, Rosman HS, Padhi D, et al: Torsades de pointes associated with intravenous haloperidol in critica ill patients. Am J Cardiol 1998b; 81:238-240.
987. Sharma ND, Rosman HS, Padhi D, et al: Torsades de pointes associated with intravenous haloperidol in critica ill patients. Am J Cardiol 1998c; 81:238-240.
988. Sharma ND, Rosman HS, Padhi D, et al: Torsades de pointes associated with intravenous haloperidol in critica ill patients. Am J Cardiol 1998d; 81:238-240.
989. Sharma ND, Rosman HS, Padhi D, et al: Torsades de pointes associated with intravenous haloperidol in critica ill patients. Am J Cardiol 1998e; 81:238-240.
990. Sharma ND, Rosman HS, Padhi D, et al: Torsades de pointes associated with intravenous haloperidol in critica ill patients. Am J Cardiol 1998f; 81:238-240.
991. Sharma ND, Rosman HS, Padhi ID, et al: Torsades de Pointes associated with intravenous haloperidol in critically ill patients. Am J Cardiol 1998a; 81(2):238-240.
992. Sheikh R: Haloperidol and benztropine interaction presenting as acute intestinal pseudo-obstruction. Am J Gastroenterol 2001; 96(3):934-935.
993. Shelton PS & Brooks VG: Estrogen for dementia-related aggression in elderly men. Ann Pharmacother 1999; 33:808-812.
994. Shen WW: Cytochrome P450 monooxygenases and interactions of psychotropic drugs: a five-year update. Int Psychiatry Med 1995; 25:277-290.
995. Sheppard JD & Schaid DJ: Oral haloperidol lowers human intraocular pressure. J Ocular Pharmacol 1986; 2:2 224.
996. Shi L, Namjoshi MA, Zhang F, et al: Olanzapine versus haloperidol in the treatment of acute mania: clinical outcomes, health-related quality of life and work status. Int Clin Psychopharmacol 2002; 17(5):227-237.
997. Shields KG, Ballinger CM, & Hathaway BN: Anti-emetic effectiveness of haloperidol in human volunteers challenged with apomorphine. Anesth Analg 1971; 50:1017-1024.

998. Shields WD & Bray PF: A danger of haloperidol therapy in children. J Pediatr 1976; 88:301-303.
999. Shostak M, Perel JM, Stiller RL, et al: Plasma haloperidol and clinical response: a role for reduced haloperidol antipsychotic activity?. J Clin Psychopharmacol 1987; 7:394-400.
1000. Sieb JP: Fluoroquinolone antibiotics block neuromuscular transmission. Neurology 1998; 50(3):804-807.
1001. Silverstone T, Cookson J, Ball R, et al: The relationship of dopamine receptor blockade to clinical response in schizophrenic patients treated with pimozide or haloperidol. J Psychiatr Res 1984; 18:255-268.
1002. Silvey L, Carpenter JT Jr, Wheeler RH, et al: A randomized comparison of haloperidol plus dexamethasone versus prochlorperazine plus dexamethasone in preventing nausea and vomiting in patients receiving chemotherapy for breast cancer. J Clin Oncol 1988; 6:1397-1400.
1003. Simpson GM & Lindenmayer J-P: Extrapyramidal symptoms in patients treated with risperidone. J Clin Psychopharm 1997; 17:194-201.
1004. Simpson MA: Delayed drug-induced dystonias (letter). Br Med J 1973; 4:174.
1005. Singer HS, Gammon K, & Quaskey S: Haloperidol, fluphenazine, and clonidine in Tourette syndrome: Controversies in treatment. Pediatr Neurosci 1986; 12:71-74.
1006. Singh MM & Kay SR: Therapeutic antagonism between anticholinergic antiparkinsonism agents and neurolepti in schizophrenia. Implications for a neuropharmacological model. Neuropsychobiology 1979; 5:74-86.
1007. Singh MM & Kay SR: Therapeutic antagonism between anticholinergic antiparkinsonism agents and neurolepti in schizophrenia. Implications for a neuropharmacological model. Neuropsychobiology 1979a; 5:74-86.
1008. Singh MM & Kay SR: Therapeutic antagonism between anticholinergic antiparkinsonism agents and neurolepti in schizophrenia: implications for a neuropharmacological model. Neuropsychobiology 1979b; 5:74-86.
1009. Singh MM & Smith JM: Reversal of some therapeutic effects of an antipsychotic agent by an antiparkinsonism drug. J Nerv Ment Dis 1973; 157:50.
1010. Slaughter RL & Edwards DJ: Recent advances: the cytochrome P450 enzymes. Ann Pharmacother 1995; 29:619-624.
1011. Snyder SH: Dopamine receptors, neuroleptics and schizophrenia. Am J Psychiatry 1981; 138:460-464.
1012. Snyder SH: Receptors, neurotransmitters and drug responses. N Engl J Med 1979; 300:465-472.
1013. Soloff PH, Cornelius J, George A, et al: Efficacy of phenelzine and haloperidol in borderline personality disorde Arch Gen Psychiatry 1993; 50:377-385.
1014. Soloff PH, George A, Nathan RS, et al: Amitriptyline and haloperidol in unstable and schizotypal borderline disorders. Psychopharmacol Bull 1986; 22:177-182.
1015. Solomon DA & Nasinnyk KK: Compatibility of haloperidol lactate and heparin sodium. Am J Hosp Pharm 1982 39:843-844.
1016. Souadjian JV & Cain JC: Intractable hiccup: etiologic factors in 220 cases. Postgrad Med 1968; 43:72-77.
1017. Sourgens H, Winterhoff H, Gumbinger HG, et al: Antihormonal effects of plant extracts on hypophyseal hormoi in the rat. Acta Endocrinol 1980; 234(Suppl):49.
1018. Sourgens H, Winterhoff H, Gumbinger HG, et al: Antihormonal effects of plant extracts on hypophyseal hormoi in the rat. Acta Endocrinol 1980a; 234(Suppl):49.
1019. Sourgens H, Winterhoff H, Gumbinger HG, et al: Antihormonal effects of plant extracts. TSH- and prolactin-suppressing properties of Lithospermum officinale and other plants. Planta Medica 1982; 45(2):78-86.
1020. Sourgens H, Winterhoff H, Gumbinger HG, et al: Antihormonal effects of plant extracts. TSH- and prolactin-suppressing properties of Lithospermum officinale and other plants. Planta Medica 1982a; 45(2):78-86.
1021. Speller JC, Barnes TRE, Curson DA, et al: One-year, low-dose neuroleptic study of in-patients with chronic schizophrenia characterised by persistent negative symptoms. Br J Psychiatry 1997; 71:564-568.
1022. Spies CD, Otter HE, Huske B, et al: Alcohol withdrawal severity is decreased by symptom-orientated adjusted bolus therapy in the ICU. Intensive Care Med 2003; 29(12):2230-2238.
1023. Spillane PK, Fisher DA, & Currie BJ: Neurological manifestations of kava intoxication. Med J Australia 1997; 1((3):172-173.
1024. Spillane PK, Fisher DA, & Currie BJ: Neurological manifestations of kava intoxication. Med J Australia 1997a; ((3):172-173.
1025. Spitzer M, Sajjad R, & Benjamin F: Pattern of development of hyperprolactinemia after initiation of haloperidol therapy. Obstet Gynecol 1998; 91:693-695.
1026. Spring GK: Neurotoxicity with the combined use of lithium and thioridazine. J Clin Psychiatry 1979; 40:135-13
1027. Sridhar KS & Donnelly E: Combination antiemetics for cisplatin chemotherapy. Cancer 1988; 61:1508-1517.
1028. Stacher G, Abatzi-Wenzel T-A, Wiesnagrotzki S, et al: Gastric emptying, body weight, and symptoms in primar anorexia nervosa: long-term effects of cisapride. Br J Psychiatry 1993; 162:398-402.
1029. Stalnikowicz R, Fich A, & Troudart T: Amitriptyline for intractable hiccups. N Engl J Med 1986; 315:64-65.
1030. Stein GS: Lithium in a case of severe anorexia nervosa. Br J Psychiatry 1982; 140:526-528.
1031. Stein MH: Tardive dyskinesia in a patient taking haloperidol and fluoxetine (letter). Am J Psychiatry 1991; 148:683.
1032. Stein MH: Tardive dyskinesia in a patient taking haloperidol and fluoxetine (letter). Am J Psychiatry 1991a; 148:683.
1033. Steinhart MJ: The use of haloperidol in geriatric patients with organic mental disorder. Curr Ther Res 1983; 33:132-143.
1034. Stevenson RN, Blanshard C, & Patterson DLH: Ventricular fibrillation due to lithium withdrawal - an interaction with chlorpromazine?. Postgrad Med J 1989; 65:936-938.
1035. Stewart RB, Karas B, & Springer PK: Haloperidol excretion in human milk. Am J Psychiatry 1980; 137(7):849-5
1036. Stramba-Badiale M, Nador F, Porta N, et al: QT interval prolongation and risk of life-threatening arrhythmias during toxoplasmosis prophylaxis with spiramycin in neonates. Am Heart J 1997; 133:108-111.

1037. Stroup TS, Lieberman JA, McEvoy JP, et al: Results of phase 3 of the CATIE schizophrenia trial. Schizophr Re 2008; Epub:1.
1038. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 03/2003k.
1039. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 03/2003l.
1040. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003.
1041. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003a.
1042. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003b.
1043. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003c.
1044. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003d.
1045. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003e.
1046. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003g.
1047. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003h.
1048. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003i.
1049. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003j.
1050. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003m.
1051. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003n.
1052. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003o.
1053. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2004.
1054. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2004a.
1055. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2004b.
1056. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2004c.
1057. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2004d.
1058. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2004e.
1059. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2004f.
1060. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic versi MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2004g.
1061. Sweetman S (Ed): Martindale: The Complete Drug Reference. London: Pharmaceutical Press. London: Pharmaceutical Press. Electronic version, MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003f.
1062. Swett C: Drug-induced dystonia. Am J Psychiatry 1975; 132:532.
1063. Takeda M, Nishinuma K, Yamashita S, et al: Serum haloperidol levels of schizophrenics receiving treatment fo tuberculosis. Clin Neuropharmacol 1986; 9:386-397.
1064. Tariot PN: Treatment of agitation in dementia. J Clin Psychiatry 1999; 60(suppl):11-20.
1065. Tate JL: Extrapyramidal symptoms in a patient taking haloperidol and fluoxetine (letter). Am J Psychiatry 1989 146:399-400.
1066. Tate JL: Extrapyramidal symptoms in a patient taking haloperidol and fluoxetine (letter). Am J Psychiatry 1989 146:399-400.
1067. Taverna P, Ghisoni T, & Pogg E: Controlled study of the antipsychotic effect of sulpiride. Psychol Med 1972; 4:811-818.
1068. Tedeschi G: Influence of age and disease state on the plasma protein binding of haloperidol (Abstr). Br J Clin Pharmacol 1981; 4:430P.
1069. Tennant FS: Propoxyphene napsylate for heroin addiction. JAMA 1973; 1012, 1973.
1070. Tennant FS: Propoxyphene napsylate treatment of heroin and methadone dependence: one year's experience Psychedelic Drugs 1974; 6:201.
1071. Thomas CJ: Brain damage with lithium/haloperidol (letter). Br J Psychiatry 1979; 134:552.
1072. Thomas H Jr, Schwartz E, & Petrilli R: Droperidol versus haloperidol for chemical restraint of agitated and

combative patients. Ann Emerg Med 1992; 21:407-413.
1073. Thornton WE: Dementia induced by methyldopa with haloperidol. N Engl J Med 1976; 294:1222.
1074. Thornton WE: Dementia induced by methyldopa with haloperidol. N Engl J Med 1976a; 294:1222.
1075. Thornton WE: Dementia induced by methyldopa with haloperidol. N Engl J Med 1976b; 294:1222.
1076. Tollefson GD, Beasley CM Jr, Tran PV, et al: Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychia 1997; 154:457-465.
1077. Tollefson GD, Sanger TM, Lu Y, et al: Depressive signs and symptoms in schizophrenia. Arch Gen Psych 199 55:250-258.
1078. Tornatore FL, Lee D, & Sramek JJ: Psychotic exacerbation with haloperidol. Drug Intell Clin Pharm 1981; 15:2 213.
1079. Tornetta FJ: Double-blind evaluation of haloperidol for antiemetic activity. Anesth Analg 1972; 51:964-967.
1080. Town IG: Haloperidol: neuroleptic malignant syndrome. N Z Med J 1982; 95:199.
1081. Tran PV, Dellva MA, Tollefson GD, et al: Extrapyramidal symptoms and tolerability of olanzapine versus haloperidol in the acute treatment of schizophrenia. J Clin Psychiatry 1997; 58:205-211.
1082. Trissel LA & Bready BB: Turbidimetric assessment of the compatibility of taxol with selected other drugs during simulated Y-site injection. Am J Hosp Pharm 1992; 49:1716-1719.
1083. Trissel LA & Martinez JF: Compatibility of allopurinol sodium with selected drugs during simulated Y-site administration. Am J Hosp Pharm 1994a; 51:1792-1799.
1084. Trissel LA & Martinez JF: Compatibility of amifostine with selected drugs during simulated Y-site administration Am J Health Syst Pharm 1995a; 52:2208-2212.
1085. Trissel LA & Martinez JF: Compatibility of aztreonam with selected drugs during simulated Y-site administration Am J Health Syst Pharm 1995; 52:1086-1090.
1086. Trissel LA & Martinez JF: Compatibility of filgrastim with selected drugs during simulated Y-site administration. Am J Hosp Pharm 1994; 51:1907-1913.
1087. Trissel LA & Martinez JF: Compatibility of piperacillin sodium plus tazobactam with selected drugs during simulated Y-site injection. Am J Hosp Pharm 1994b; 51:672-678.
1088. Trissel LA & Martinez JF: Visual, turbidimetric, and particle-content assessment of compatibility of vinorelbine tartrate with selected drugs during simulated Y-site injection. Am J Hosp Pharm 1994c; 51:495-499.
1089. Trissel LA, Bready BB, Kwan JW, et al: Visual compatibility of sargramostim with selected antineoplastic agent anti-infectives, or other drugs during simulated Y-site injection. Am J Hosp Pharm 1992; 49:402-406.
1090. Trissel LA, Chandler SW, & Folstad JT: Visual compatibility of amsacrine with selected drugs during simulated site injection. Am J Hosp Pharm 1990; 47:2525-2528.
1091. Trissel LA, Gilbert DL, & Martinez JF: Compatibility of propofol injectable emulsion with selected drugs during simulated Y-site administration. Am J Health-Syst Pharm 1997; 54:1287-1292.
1092. Trissel LA, Gilbert DL, Martinez JF, et al: Compatibility of parenteral nutrition solutions with selected drugs duri simulated Y-site administration. Am J Health-Syst Pharm 1997a; 54:1295-1300.
1093. Trissel LA, Parks NPT, & Santiago NM: Visual compatibility of fludarabine phosphate with antineoplastic drugs anti-infectives, and other selected drugs during simulated Y-site injection. Am J Hosp Pharm 1991a; 48:2186-2189.
1094. Trissel LA, Saenz CA, Ogundele OB, et al: Compatibility of fenoldopam mesylate with other drugs during simulated Y-site administration. Am J Health-Syst Pharm 2003; 60:80-85.
1095. Trissel LA, Tramonte SM, & Grilley BJ: Visual compatibility of ondansetron hydrochloride with selected drugs during simulated Y-site injection. Am J Hosp Pharm 1991b; 48:988-992.
1096. Trissel LA: Handbook on Injectable Drugs, 6th. American Society of Hospital Pharmacists, Bethesda, MD, 199
1097. Troung DD, Bressman S, Shale H, et al: Clonazepam, haloperidol, and clonidine in tic disorders. South Med J 1988; 81:1103-1105.
1098. Troung DD, Bressman S, Shale H, et al: Clonazepam, haloperidol, and clonidine in tic disorders. South Med J 1988a; 81:1103-1105.
1099. Tuason VB: A comparison of parenteral loxapine and haloperidol in hostile and aggressive acutely schizophrer patients. J Clin Psychiatry 1986; 47:126-129.
1100. Tzianetas I, Habal F, & Keystone JS: Short report: severe hiccups secondary to doxycycline-induced esophagi during treatment of malaria. Am J Trop Med Hyg 1996; 54(2):203-204.
1101. U.S. Food and Drug Administration: Conventional Antipsychotics - Healthcare Professional Sheet text version. U.S. Food and Drug Administration. Rockville, MD. 2009. Available from URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.h As accessed 2009-06-23.
1102. US Food and Drug Administration: Information for Healthcare Professionals Haloperidol (marketed as Haldol, Haldol Decanoate and Haldol Lactate). US Food and Drug Administration. Rockville, MD. 2007. Available from URL: http://www.fda.gov/cder/drug/InfoSheets/HCP/haloperidol.htm.
1103. Uematsu T, Sato R, Suzuki K, et al: Human scalp hair as evidence of individual dosage history of haloperidol: method and retrospective study. Eur J Clin Pharmacol 1989; 37:239-244.
1104. Uematsu T, Yamada K, Matsuno H, et al: The measurement of haloperidol and reduced haloperidol in neonata hair as an index of placental transfer of maternal halopridol. Ther Drug Monit 1991; 13:183-187.
1105. Ueno S, Takahashi M, Kajiyama K, et al: Parkinson's disease and myasthenia gravis: adverse effect of trihexyphenidyl on neuromuscular transmission. Neurology 1987; 37:823-833.
1106. Ulrich S, Wurthmann C, Brosz M, et al: The relationship between serum concentration and therapeutic effect o haloperidol in patients with acute schizophrenia. Clin Pharmacokinet 1998; 34(3):227-263.

1107. Umeki S: Intravenous etoposide therapy and intractable hiccups. Chest 1991; 100(3):887.
1108. Van Putten T, Marder SR, & Mintz J: A controlled dose comparison of haloperidol in newly admitted schizophrenic patients. Arch Gen Psychiatry 1990; 47:754-758.
1109. Van Putten T, May PRA, & Marder SR: Akathisia with haloperidol and thiothixene. Arch Gen Psychiatry 1984b 41:1036-1039.
1110. Van Putten T, May PRA, & Marder SR: Akathisia with haloperidol and thiothixene. Psychopharmacol Bull 1984 20:114-117.
1111. Verma SD, Davidoff DA, & Kambhampati KK: Management of the agitated elderly patient in the nursing home: the role of the atypical antipsychotics. J Clin Psychiatry 1998; 59(suppl 19):50-55.
1112. Vigersky RA & Loriaux DL: The effect of cyproheptadine in anorexia nervosa: A double blind trial. In: Vigersky (Ed). Anorexia Nervosa, Raven Press, New York, NY; pp 349-356, 1977.
1113. Vincent FM, Zimmerman JE, & Van Haren J: Neuroleptic malignant syndrome complicating closed head injury. Neurosurgery 1986; 18:190-193.
1114. Volavka J, Coooper TB, Czobor P, et al: High-dose treatment with haloperidol: the effect of dose reduction. J C Psychopharmacol 2000; 20(2):252-256.
1115. Walinder J & Carlsson A: Potentiation of neuroleptics by catecholamine inhibitors. Br Med J 1973; 1:551-552.
1116. Wang PS, Schneeweiss S, Avorn J, et al: Risk of death in elderly users of conventional vs. atypical antipsycho medications. N Engl J Med 2005; 353:2335-2341.
1117. Washton AM, Resnick RB, & Rawson RA: Clonidine for outpatient opiate detoxification (letter). Lancet 1980; 1:1078-1079.
1118. Wassmann S, Nickenig G, & Bohm M: Long QT syndrome and torsade de pointes in a patient receiving fluconazole. Ann Intern Med 1999; 131:797.
1119. Weegink CJ, Chamuleau RAFM, Reesink HW, et al: Development of myasthenia gravis during treatment of chronic hepatitis C with interferon-alpha and ribavirin. J Gastroenterol 2001; 36:723-724.
1120. Westlake RJ & Rastegar A: Hyperpyrexia from drug combinations. JAMA 1973; 225:1250.
1121. Whalley LJ, Blain PG, & Prime JK: Haloperidol secreted in breast milk. Br Med J 1981; 282(6278):1746-1747.
1122. White JA & Schnaultz NL: Successful treatment of anorexia nervosa with imipramine. Dis Nerv Syst 1977; 38:567-568.
1123. White K, Busk J, Eaton E, et al: Dysphoric response to neuroleptics as a predictor of treatment outcome with schizophrenics. Int Pharmacopsychiatry 1981; 16:34-38.
1124. Williamson BW & MacIntyre IM: Management of intractable hiccup. Br Med J 1977; 2(6085):501-3.
1125. Wilt JL, Minnema AM, Johnson RF, et al: Torsade de pointes associated with the use of intravenous haloperid Ann Intern Med 1993; 119:391-394.
1126. Wilt JL, Minnema AM, Johnson RF, et al: Torsade de pointes associated with the use of intravenous haloperid Ann Intern Med 1993a; 119:391-394.
1127. Wilt JL, Minnema AM, Johnson RF, et al: Torsade de pointes associated with the use of intravenous haloperid Ann Intern Med 1993b; 119:391-394.
1128. Wilt JL, Minnema AM, Johnson RF, et al: Torsade de pointes associated with the use of intravenous haloperid Ann Intern Med 1993c; 119:391-394.
1129. Wilt JL, Minnema AM, Johnson RF, et al: Torsade de pointes associated with the use of intravenous haloperid Ann Intern Med 1993d; 119:391-394.
1130. Wilt JL, Minnema AM, Johnson RF, et al: Torsade de pointes associated with the use of intravenous haloperid Ann Intern Med 1993e; 119:391-394.
1131. Wilt JL, Minnema AM, Johnson RF, et al: Torsade de pointes associated with the use of intravenous haloperid Ann Intern Med 1993f; 119:391-394.
1132. Wilt JL, Minnema AM, Johnson RF, et al: Torsade de pointes associated with the use of intravenous haloperid Ann Intern Med 1993g; 119:391-394.
1133. Wilt JL, Minnema AM, Johnson RF, et al: Torsade de pointes associated with the use of intravenous haloperid Ann Intern Med 1993h; 119:391-394.
1134. Wilt JL, Minnema AM, Johnson RF, et al: Torsade de pointes associated with the use of intravenous haloperid Ann Intern Med 1993i; 119:391-394.
1135. Wilt JL, Minnema AM, Johnson RF, et al: Torsade de pointes associated with the use of intravenous haloperid Ann Intern Med 1993j; 119:391-394.
1136. Winter M, Lehmann E, & Scholz OB: Effects of high and low dosage of haloperidol on the brain in relation to schizophrenic thought disorder. Neuropsychobiology 1984; 12:115-121.
1137. Wistedt B, Koskinen T, Thelander S, et al: Zuclopenthixol decanoate and haloperidol decanoate in chronic schizophrenia: a double-blind multicentre study. Acta Psychiatr Scand 1991; 84:14-16.
1138. Wittbrodt ET: Drugs and myasthenia gravis. Arch Intern Med 1997; 157:399-407.
1139. Wolfersdorf M, Koenig F, & Straub R: Pharmacotherapy of delusional depression: experience with combinatior of antidepressants with the neuroleptics zotepine and haloperidol. Pharmacopsychiatry 1994; 29:189-193.
1140. Wood AJJ: Control of chemotherapy-induced emesis. N Engl J Med 1993; 329:1790-1796.
1141. Wyant M, Diamond BI, O'Neal E, et al: The use of midazolam in acutely agitated psychiatric patients. Psychopharmacol Bull 1990; 26:126-129.
1142. Wyant M, Diamond BI, O'Neal E, et al: The use of midazolam in acutely agitated psychiatric patients. Psychopharmacol Bull 1990a; 26:126-129.
1143. Yamagami S: A crossover study of clocapramine and haloperidol in chronic schizophrenia. J Int Med Res 1985 13:301-310.
1144. Yamazumi S & Muira S: Haloperidol concentrations in saliva and serum: determination by the radioimmunoass

method. Int Pharmacopsychiatry 1981; 16:174-183.
1145. Yamreudeewong W, DeBisschop M, Martin LG, et al: Potentially significant drug interactions of class III antiarrhythmic drugs. Drug Safety 2003; 26(6):421-438.
1146. Yamreudeewong W, DeBisschop M, Martin LG, et al: Potentially significant drug interactions of class III antiarrhythmic drugs. Drug Safety 2003a; 26(6):421-438.
1147. Yoshida K, Smith B, Craggs M, et al: Neuroleptic drugs in breast-milk: a study of pharmacokinetics and of possible adverse effects in breast-fed infants. Psychol Med 1998; 28:81-91.
1148. Yoshikawa H, Watanabe T, Abe T, et al: Haloperidol-induced rhabdomyolysis without neuroleptic malignant syndrome in a handicapped child. Brain Dev 2000; 22:256-258.
1149. Yosselson S & Kaplan A: Neurotoxic reaction of haloperidol in a thyrotoxic patient. N Engl J Med 1975; 293:20
1150. Young D, Midha KK, Fossler MJ, et al: Effect of quinidine on the interconversion kinetics between haloperidol a reduced haloperidol in humans: implications for the involvement of cytochrome P450IID6. Eur J Clin Pharmacc 1993; 44:433-438.
1151. Young JB, Vandermolen LA, & Pratt CM: Torsade de pointes: an unusual mainfestation of chloral hydrate poisoning. Am Heart J 1986; 112:181-184.
1152. Young LY & Koda-Kimble MA (Eds): Applied Therapeutics The Clinical Use of Drugs, 4th. Applied Therapeutic Inc, Vancouver, WA, 1988.
1153. Zall H, Therman PG, & Myers JM: Lithium carbonate: a clinical study. Am J Psychiatry 1968; 125:549-555.
1154. Zhang XY, Zhou DF, Cao LY, et al: Risperidone verus haloperidol in the treatment of acute exacerbations of chronic inpatients with schizophrenia: a randomized double-blind study. Int Clin Psychopharmacol 2001; 16 (6):325-330.
1155. de Oliveira IR, Miranda-Scippa AMA, de Sena EP, et al: Risperidone versus haloperidol in the treatment of schizophrenia: a meta-analysis comparing their efficacy and safety. J Clin Pharm Ther 1996; 21:349-358.
1156. de Oliveira IR, de Sena EP, Pereira ELA, et al: Haloperidol blood levels and clinical outcome: a meta-analysis studies relevant to testing the therapeutic window hypothesis. J Clin Pharm Ther 1996a; 21:229-236.
1157. den Boer JA & Westenberg HGM: Atypical neuroleptics in acute schizophrenia: a double-blind comparative stu of remoxipride and haloperidol. Psychopharmacol Bull 1990; 26:99-107.
1158. den Boer JA, Ravelli DP, Huisman J, et al: A double-blind comparative study of remoxipride and haloperidol in acute schizophrenia. Acta Psychiatr Scand 1990; 82(suppl 358):108-110.
1159. van Sweden B: Neuroleptic neurotoxicity; electro-clinical aspects. Acta Neurol Scand 1984; 69:137-146.

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