DRUGDEX® Evaluations

RISPERIDONE

0.0 Overview

1) Class

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

2) Dosing Information

a) Adult

1) if overlapping of antipsychotics is necessary, in all cases, the period of overlapping should be minimized; if swi antipsychotics and if medically appropriate, initiate risperidone therapy in place of the next scheduled injection (Pr RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005)

2) previous oral antipsychotics should be continued for 3 weeks following the initiation of therapy with risperidone that adequate therapeutic concentrations are maintained until the main release phase of risperidone from the inje RISPERDAL(R) CONSTA(R) long acting injection, 2009)

a) Bipolar I disorder

1) (oral, monotherapy or in combination with lithium or valproate) initial, 2 to 3 mg ORALLY once a day (tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDA

2) (oral, monotherapy or in combination with lithium or valproate) maintenance, dosage adjustments sho mg/day at intervals of at least 24 hours; doses higher than 6 mg/day have not been evaluated in clinical t oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPEF

3) (intramuscular, monotherapy or in combination with lithium or valproate) initiation of therapy, recomm oral risperidone prior to initiation of treatment with the risperidone long-acting IM injection; oral risperidon medication should be given with the initial injection and should be continued for 3 weeks and then discor (R) CONSTA(R) long acting injection, 2009)

4) initial, 25 mg IM every 2 weeks (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

5) (intramuscular, monotherapy or in combination with lithium or valproate) maintenance, dose may be i at intervals of at least 4 weeks; clinical effects of dose adjustment should not be expected earlier than 3 higher dose; MAX 50 mg IM every 2 weeks (Prod Info RISPERDAL(R) CONSTA(R) long acting injection

b) Schizophrenia

1) (oral) initial, 1 mg ORALLY twice daily, with increases in increments of 1 mg twice daily on the secon target dose of 3 mg twice daily on the third day OR 1 mg ORALLY once daily, with increases to 2 mg dai dose of 4 mg once daily on the third day (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, ora tablets, 2005)

2) (oral) maintenance, small, ORAL dose increments/decrements of 1 to 2 mg are recommended at inte Maximal effect is usually seen within a range of 4 to 8 mg/day. Doses above 6 mg/day for twice-daily dos efficacious than lower doses; the safety of doses above 16 mg/day has not been evaluated in clinical tria RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005)

3) (intramuscular) initiation of therapy, recommended to establish tolerability to oral risperidone prior to i risperidone long-acting IM injection; oral risperidone or another antipsychotic medication should be giver should be continued for 3 weeks and then discontinued (Prod Info RISPERDAL(R) CONSTA(R) long act

4) initial, 25 mg IM every 2 weeks (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

5) (intramuscular) maintenance, dose may be increased to 37.5 mg or 50 mg IM at intervals of at least 4 adjustment should not be expected earlier than 3 weeks after the injection of the higher dose; MAX 50 m RISPERDAL(R) CONSTA(R) long acting injection, 2009)

b) Pediatric

1) safety and effectiveness of long-acting risperidone injection has not been established in pediatric patients und RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) safety and effectiveness of oral risperidone in pediatric patients less than 13 years of age with schizophrenia o mania have not been established (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB 2007; Prod Info RISPERDAL(R) oral solution, 2007)

3) safety and effectiveness or oral risperidone in pediatric patients less than 5 years of age with autistic disorder Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod solution, 2007)

a) Autistic disorder - Irritability

1) dosing individualized according to the response and tolerability (Prod Info RISPERDAL(R) oral tablets disintegrating tablets, 2006)

2) (weight less than 20 kg) initial, 0.25 mg ORALLY once a day or half the total daily dose given twice da minimum of 4 days to 0.5 mg/day (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrati

3) (weight less than 20 kg) maintenance, 0.5 mg ORALLY once a day or half the total daily dose given t a minimum of 14 days and may increase doses at 2-week intervals or longer, in increments of 0.25 mg p clinical response; use with caution in children weighing less than 15 kg (Prod Info RISPERDAL(R) oral ta disintegrating tablets, 2006)

4) (weight 20 kg or greater) initial, 0.5 mg ORALLY once a day or half the total daily dose given twice da
minimum of 4 days to 1 mg/day (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating
5) (weight 20 kg or greater) maintenance, 1 mg ORALLY once a day or half the total daily dose given tw
minimum of 14 days; may increase doses at 2-week intervals or longer, in increments of 0.5 mg per day
response (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006)
6) in patients with persistent somnolence, a once-daily dose at bedtime or half the daily dose twice daily
be considered (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006)

b) Bipolar I disorder
1) (10 years and older) initial, 0.5 mg ORALLY once daily as a single dose in the morning or evening; ad
than 24 hours and in increments of 0.5 to 1 mg/day up to a maximum recommended dose of 2.5 mg/day
tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDA

c) Schizophrenia
1) (13 years and older) initial, 0.5 mg ORALLY once daily as a single dose in the morning or evening; ad
than 24 hours and in increments of 0.5 to 1 mg/day up to a recommended dose of 3 mg/day (Prod Info R
Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solut

3) Contraindications
a) hypersensitivity to risperidone or to any product component (Prod Info RISPERDAL(R) CONSTA(R) long acting inje
RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)

4) Serious Adverse Effects
a) Agranulocytosis
b) Death
c) Diabetic ketoacidosis
d) Hypothermia
e) Leukopenia
f) Neuroleptic malignant syndrome
g) Neutropenia
h) Pancreatitis
i) Priapism
j) Purpura
k) Seizure
l) Sudden cardiac death
m) Syncope
n) Tardive dyskinesia
o) Thrombocytopenia
p) Thrombotic thrombocytopenic purpura

5) Clinical Applications
a) FDA Approved Indications
1) Autistic disorder - Irritability
2) Bipolar I disorder
3) 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 In
B) Synonyms
Risperidone
C) Physicochemical Properties
1) Molecular Weight
a) 410.49 (Canada, 1997)
2) pKa
a) pKa1: 8.24 ; pKa2: 3.11 (Prod Info Risperdal, 93)

1.2 Storage and Stability

A) Preparation
1) Intramuscular route

a) Preparation

1) Risperidone long-acting injection must only be suspended in the diluent supplied by the manufacturer and diluent to come to room temperature prior to reconstitution. After injecting the diluent into the vial, sh minimum of 10 seconds. The suspension should appear uniform, thick, and milky in color. The particles v particle should remain. It should be used immediately after suspension and must be used within 6 hours pass before injection, resuspend by shaking vigorously, as settling will occur over time once the product RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) Administration

1) Do NOT inject intravenously. Administer by deep intramuscular injection into the deltoid or gluteal mu arms or two buttocks. Use a 1-inch 21 gauge needle for deltoid injection and a 2-inch 20 gauge needle fo combine different dosage strengths in a single administration (Prod Info RISPERDAL(R) CONSTA(R) lon

2) Oral route

a) Orally Disintegrating Tablets

1) Oral disintegrating tablets are supplied in blister packs and should not be opened until ready for use. do NOT push the tablet through the foil backing because this could damage the tablet. Use dry hands to unit and immediately place the entire tablet on the tongue. The tablet should be consumed immediately o unit. Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or withou tablet (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating table

b) Oral Solution

1) Calibrated dispensing-pipettes are provided with risperidone oral solution. The oral solution is compat juice, and low-fat milk. However, it is not compatible with cola or tea (Prod Info RISPERDAL(R), RISPER solution, orally disintegrating tablets, 2005)

B) Intramuscular route

1) The long-acting injection should be stored in the refrigerator between 36 and 46 degrees Fahrenheit (F) (2 and refrigeration is not available, it may be stored at temperatures not exceeding 77 degrees F (25 degrees C) for no l administration; protect from light (Prod Info Risperdal(R) Consta(TM), 2003h).

C) Oral route

1) Solution

a) Store the oral solution at room temperature 59 to 77 degrees Fahrenheit (15 to 25 degrees Celsius); prote Info Risperdal(R), 2004).

2) Tablet

a) Tablets should be stored at room temperature 59 to 77 degrees Fahrenheit (15 to 25 degrees Celsius); pr (Prod Info Risperdal(R), 2004).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage in Other Disease States

1.3.1 Normal Dosage

Intramuscular route

Intramuscular route/Oral route

Oral route

1.3.1.A Intramuscular route

Bipolar I disorder

Schizophrenia

1.3.1.A.1 Bipolar I disorder

a) For patients who have not previously taken oral risperidone, it is recommended that tolerability be est
prior to initiation of treatment with the long-acting risperidone intramuscular injection (Prod Info RISPERD
injection, 2009).

b) The recommended dose of risperidone long-acting injection is 25 milligrams (mg) intramuscularly eve
responding to a lower dose, the dose may be increased to 37.5 mg or 50 mg at intervals of at least 4 we
dosage adjustment should not be expected earlier than 3 weeks following the first injection of the higher
not exceed 50 mg every 2 weeks. Patients should be maintained on the lowest effective dose and shoul
determine the necessity of continued treatment. Risperidone long-acting injection should be administere
into the deltoid or gluteal muscles, alternating between the two arms or two buttocks; should be administ
professional using the enclosed safety needle and should NOT be administered intravenously (Prod Info
long acting injection, 2009).

c) Oral risperidone or another antipsychotic medication should be administered with the initial injection o
should be continued for 3 weeks (and then discontinued) so that adequate therapeutic plasma concentra
main release phase of risperidone from the injection site (Prod Info RISPERDAL(R) CONSTA(R) long ac

d) Do NOT combine different dosage strengths of risperidone long-acting injection in a single administra
CONSTA(R) long acting injection, 2009).

e) Supplementation with oral risperidone or another antipsychotic should accompany reinitiation of treat
discontinued from risperidone long-acting injection (Prod Info RISPERDAL(R) CONSTA(R) long acting in

1.3.1.A.2 Schizophrenia

a) For patients who have not previously taken oral risperidone, it is recommended that tolerability be est
prior to initiation of treatment with the long-acting risperidone intramuscular injection (Prod Info RISPERD
injection, 2009).

b) The recommended dose of risperidone long-acting injection is 25 milligrams (mg) intramuscularly eve
responding to a lower dose, the dose may be increased to 37.5 mg or 50 mg at intervals of at least 4 we
dosage adjustment should not be expected earlier than 3 weeks following the first injection of the higher
not exceed 50 mg every 2 weeks. Patients should be maintained on the lowest effective dose and shoul
determine the necessity of continued treatment. Risperidone long-acting injection should be administere
into the deltoid or gluteal muscles, alternating between the two arms or two buttocks; should be administ
professional using the enclosed safety needle and should NOT be administered intravenously (Prod Info
long acting injection, 2009).

c) Oral risperidone or another antipsychotic medication should be administered with the initial injection o
should be continued for 3 weeks (and then discontinued) so that adequate therapeutic plasma concentra
main release phase of risperidone from the injection site (Prod Info RISPERDAL(R) CONSTA(R) long ac

d) Do NOT combine different dosage strengths of risperidone long-acting injection in a single administra
CONSTA(R) long acting injection, 2009).

e) Supplementation with oral risperidone or another antipsychotic should accompany reinitiation of treat
discontinued from risperidone long-acting injection (Prod Info RISPERDAL(R) CONSTA(R) long acting in

1.3.1.B Intramuscular route/Oral route

1) Switching Antipsychotics

a) If overlapping of antipsychotics is necessary, in all cases, the period of overlapping should be minimiz
previous antipsychotic treatment may be acceptable for some patients while gradual discontinuation may
switching patients from depot antipsychotics and if medically appropriate, initiate risperidone therapy in p
injection (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating ta

b) Previous oral antipsychotics should be continued for 3 weeks following the initiation of therapy with ris
ensure that adequate therapeutic concentrations are maintained until the main release phase of risperido
begun (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.3.1.C Oral route

Bipolar I disorder

Schizophrenia

1.3.1.C.1 Bipolar I disorder

a) Risperidone is approved for use as monotherapy or in combination with lithium or valproate in the trea
Risperidone should be administered once daily at an initial dose of 2 to 3 milligrams (mg) per day. If nee
be made at intervals of at least 24 hours in increments/decrements of 1 mg/day. In clinical trials, doses r
used; doses higher than 6 mg/day have not been studied (Prod Info RISPERDAL(R) oral tablets, 2007; R
orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) The effectiveness of risperidone for maintenance therapy beyond 3 weeks has not been evaluated. W
treatment in a responding patient is generally desirable for maintenance of the initial response and for pr

there are no data from clinical trials to support the use of risperidone in long-term treatment (Prod Info RI
Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solut

1.3.1.C.2 Schizophrenia

a) Low doses, 1 milligram (mg) twice daily, should be generally used initially to avoid the typical first-dos
adrenoreceptor antagonists. Doses may be increased by 1 mg twice daily until a target dose of 6 mg per
on day 3. Controlled trials have demonstrated that total daily doses of up to 8 mg on a once-daily regime
some patients, slower titration may be indicated. Further increases/decreases in dose, if indicated, shoul
weekly intervals since steady state for the active metabolite would not be attained for one week in the typ
maximal antipsychotic efficacy was seen with doses between 4 and 8 mg/day while effective oral doses
However, doses above 6 mg/day at a twice-daily dosing regimen are not generally recommended as they
extrapyramidal and other adverse effects, with no additional treatment benefit than lower doses (Prod Inf
M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005; Borison et al, 1992b; Anon, 1991a; M

b) If risperidone is discontinued, reinitiate with the initial titration schedule (Prod Info RISPERDAL(R), RI
oral solution, orally disintegrating tablets, 2005).

c) In a controlled, clinical trial, risperidone given at once-daily doses of 2 to 8 milligrams was effective in
had been clinically stable for 4 weeks or longer. However, patients should be periodically re-assessed to
maintenance treatment (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally d

d) The Consensus Study Group on Risperidone Dosing reports their empiric clinical experience has resu
titration strategy for many patients. They target a goal of 2 to 4 milligrams (mg) daily during the first week
response occurs, the dose is increased to 6 to 8 mg/day during the second week of treatment. If there is
the next 2 weeks, then a higher dose may be warranted, usually increases of 2 mg/week up to a maximu
attempted. Any further dosage adjustments, if indicated, should be made at intervals of no less than 1 w

e) In a small study (n=11) rapid oral-loading risperidone was well tolerated within 24 hours. Seven patie
milligrams (mg) twice daily in 16 hours; 3 patients achieved the maintenance dose in 24 hours and 1 pati
three times daily (Feifel et al, 2000).

f) In dose comparison studies chiefly utilizing chronic schizophrenic patients, the most consistently posit
were seen for the 6 milligram (mg) dose group (Marder & Meibach, 1994a; Chouinard et al, 1993b; Mard
in one study (Muller-Spahn, 1992a). In a review of 12 double-blind studies (n=2099), symptom improvem
mg/day (Lemmens et al, 1999). There was no suggestion of increased benefit from larger doses. Anothe
naive patients found a superior outcome in the 2 to 4 mg group versus a 5 to 8 mg dose group (Kopala e

1.3.1.C.3 Bioequivalence

a) Risperdal(R) orally disintegrating tablets are bioequivalent to Risperdal(R) tablets (Prod Info RISPER
tablets, oral solution, orally disintegrating tablets, 2005; van Schaick et al, 2003).

1.3.2 Dosage in Renal Failure

A) Oral

1) The recommended initial dosage in patients with severe renal impairment is 0.5 milligrams twice daily. Do
milligrams twice daily until a dose of 3 milligrams per day (1.5 milligrams twice daily) is reached. Further incre
be limited to 0.5 milligrams twice daily at weekly intervals. Slower titration may be necessary in some patients
RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating tablets, 2005). In Germany, a maximum do
recommended for patients in renal failure and caution is advised for overall use in this patient population until
(Fachinfo Risperdal(R), 1997).

B) Intramuscular

1) Patients with renal impairment should receive titrated doses of oral risperidone prior to initiating treatment
intramuscular injection. For titration, the recommended initial dosage is 0.5 milligram (mg) of oral risperidone
the dosage may be increased to 1 mg twice daily or 2 mg once daily during the second week. If a dose of 2 m
risperidone long-acting injection can be given intramuscularly every 2 weeks. Although the efficacy has not b
12.5 mg of risperidone long-acting injection may be given to patients with renal impairment. Continue oral sup
following the first injection until the main release of risperidone from the injection site has begun. Slower titrat
patients (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.3.3 Dosage in Hepatic Insufficiency

A) Oral

1) The recommended initial dosage in patients with severe hepatic impairment is 0.5 milligrams (mg) twice a
0.5 mg twice daily until a dose of 3 mg per day (1.5 mg twice daily) is reached. Further increases in dose, if ir
mg twice daily at weekly intervals. Slower titration may be necessary in some patients (Prod Info RISPERDAL
tablets, oral solution, orally disintegrating tablets, 2005). In Germany, a maximum dose of 2 mg twice daily is
hepatic insufficiency and caution is advised for overall use in this patient population until further research is a
2000).

B) Intramuscular

1) Patients with hepatic impairment should receive titrated doses of oral risperidone prior to initiating treatme
acting intramuscular (IM) injection. For titration, the recommended initial dosage is 0.5 milligram (mg) of oral
week; then the dosage may be increased to 1 mg twice daily or 2 mg once daily during the second week. If a
mg of risperidone long-acting injection can be given IM every 2 weeks. Although the efficacy has not been co
of risperidone long-acting injection may be given to patients with hepatic impairment. Continue oral suppleme
first injection until the main release of risperidone from the injection site has begun. Slower titration may be n
Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.3.4 Dosage in Geriatric Patients

A) Oral

1) The initial dosage should be 0.5 milligrams (mg) orally twice a day. Doses may be increased by 0.5 mg tw day (1.5 mg twice daily) is reached. Further increases in dose, if indicated, should be limited to 0.5 mg twice titration may be necessary in some patients. If once-daily dosing is desired, initiate and titrate patient on a twi to achieve target dose and switch to once-daily dosing thereafter (Prod Info RISPERDAL(R), RISPERDAL M orally disintegrating tablets, 2005). In Germany, a maximum dose of 2 mg twice daily is recommended for ge advised for overall use in this patient population until further research is available (Fachinfo Risperdal(R), 200

B) Intramuscular

1) The recommended dosage of risperidone long-acting injection for elderly patients is 25 milligrams intramu risperidone or another antipsychotic medication should be administered with the initial injection of long-acting continued for 3 weeks (and then discontinued) so that adequate therapeutic plasma concentrations are maint phase of risperidone from the injection site (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 200

1.3.6 Dosage in Other Disease States

A) Debilitated Patients

1) Debilitated patients may have less ability to eliminate risperidone than normal patients. The initial dosage twice daily. Doses may be increased by 0.5 mg twice daily until a dose of 3 mg per day (1.5 mg twice daily) is dose, if indicated, should be limited to 0.5 mg twice daily at weekly intervals. Slower titration may be necessa dosing is desired, initiate and titrate patient on a twice-daily regimen for 2 to 3 days to achieve target dose an thereafter (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally disintegrating table

B) Hypotension Predisposition

1) Patients with a predisposition to hypotension or for whom hypotension may pose a risk should receive a r dosage should be 0.5 milligrams (mg) twice a day. Doses may be increased by 0.5 mg twice daily until a dos daily) is reached. Further increases in dose, if indicated, should be limited to 0.5 mg twice daily at weekly inte necessary in some patients (Prod Info RISPERDAL(R), RISPERDAL M-TAB(R) tablets, oral solution, orally d

C) Concomitant Medications

1) For patients on CYP2D6 inhibitors (eg, fluoxetine, paroxetine), risperidone long-acting intramuscular injec 12.5 milligrams (mg) or 25 mg. For patients already on 25 mg of long-acting risperidone injection and initiatin continue the 25 mg dose. However, if clinical judgement warrants, the dose of risperidone may be decreased acting intramuscular injection may be discontinued. Although, the efficacy of 12.5 mg has not been confirmed RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) For patients on CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, phenobarbital), the dose of ris intramuscular injection will need to be titrated accordingly, especially during initiation or discontinuation of the CYP3A4 inducers are discontinued, continue with the 25 milligram (mg) dose. However, if clinical judgement may be decreased to 12.5 mg or risperidone long-acting intramuscular injection may be discontinued. Althou not been confirmed in clinical trials (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

D) Poor Tolerability to Psychotropic Medications

1) Although the efficacy has not been confirmed in clinical trials, 12.5 milligrams intramuscularly may be give poor tolerability to psychotropic medications (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 20

1.4 Pediatric Dosage

1.4.1 Normal Dosage

Intramuscular route

Oral route

1.4.1.A Intramuscular route

1) The safety and effectiveness of long-acting risperidone injection has not been established in pediatric pati Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

1.4.1.B Oral route

Autistic disorder - Irritability

Bipolar I disorder

Schizophrenia

1.4.1.B.1 Autistic disorder - Irritability

a) Dosing should be individualized according to the response and tolerability. Doses are administered o dose twice daily. In patients with persistent somnolence, a once-daily dose at bedtime or half the daily d the dose may be considered (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating ta
b) For children weighing less than 20 kilograms (kg), the recommended initial dose is 0.25 milligram (m increased after a minimum of 4 days to 0.5 mg per day. Doses should be maintained for at least 14 days week intervals or longer, in increments of 0.25 mg per day if the patient has not achieved sufficient clinic clinical response has been achieved and maintained, doses may be lowered gradually to obtain the optir safety. Risperidone should be used with caution in children weighing less than 15 kg (Prod Info RISPER orally-disintegrating tablets, 2006).
c) For children weighing 20 kilograms (kg) or greater, the recommended initial dose is 0.5 milligram (mg increased after at least 4 days to 1 mg per day. Doses should be maintained for at least 14 days. They n intervals or longer, in increments of 0.5 mg per day if the patient has not achieved sufficient clinical respo response has been achieved and maintained, doses may be lowered gradually to obtain the optimal bala Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).
d) In clinical trials, a response (based on at least 25% improvement on ABC-I) was achieved in 90% of p risperidone between 0.5 mg and 2.5 mg per day. In one of the pivotal trials, the maximum daily dose of r weighing less than 20 kg, 2.5 mg in patients weighing 20 kg or greater, or 3 mg in patients weighing grea therapeutic effect reached plateau (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrat

1.4.1.B.2 Bipolar I disorder

a) For the short-term treatment of bipolar mania, initiate treatment at 0.5 milligrams (mg) orally once dail either in the morning or evening. Dose adjustments should occur at intervals not less than 24 hours and as indicated and tolerated. The maximum recommended daily dose is 2.5 mg/day. If somnolence occurs into 2 equal doses. Data are unavailable to support use of risperidone beyond 3 weeks for the treatment therapy is required for extended periods, periodically reevaluate the long-term usefulness for the individu (R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RIS

1.4.1.B.3 Schizophrenia

a) In children 13 years of age and older, initiate treatment at 0.5 milligrams (mg) orally once daily, given the morning or evening. Dose adjustments should occur at intervals not less than 24 hours and in increm indicated and tolerated. The maximum recommended daily dose is 3 mg/day. If somnolence occurs, the equal doses. Data are unavailable to support use of risperidone beyond 8 weeks in adolescents with sch is required for extended periods, periodically reevaluate the long-term usefulness for the individual patier reinitiate with the initial titration schedule. When switching schizophrenic patients from depot antipsychot place of the next scheduled injection (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDA tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

4) The safety and effectiveness in children less than 13 years of age with schizophrenia or less than 10 year associated with bipolar I disorder have not been established (Prod Info RISPERDAL(R) oral tablets, 2007; Pr orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
5) The safety and effectiveness in pediatric patients with autistic disorder less than 5 years of age have not b RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006).
6) Risperidone was beneficial in children and adolescents with pervasive developmental disorder. Starting d twice daily and increased in 0.25 mg/day increments every 5 to 7 days have been used (Fisman & Steele, 19 0.75 to 6 mg daily (Perry et al, 1997; Fisman & Steele, 1996).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset
1) Initial Response
a) Psychotic symptoms, oral: 1 to 2 weeks (Vanden Borre et al, 1993; Borison et al, 1992a; Mesotten et al, 1
b) Psychotic symptoms, intramuscular: 3 weeks (Prod Info Risperdal(R) Consta(TM), 2003i).
1) Following a single intramuscular injection of long-acting risperidone, a small initial release of the drug 1% of the dose), followed by a lag time of 3 weeks. The main release of the drug occurs from 3 weeks o weeks, and subsides by 7 weeks following the injection (Prod Info Risperdal(R) Consta(TM), 2003i).
B) Duration
1) Single Dose
a) Psychotic symptoms, intramuscular: 7 weeks (Prod Info Risperdal(R) Consta(TM), 2003i).
1) Following a single intramuscular injection of long-acting risperidone, a small initial release of the drug

1% of the dose), followed by a lag time of 3 weeks. The main release of the drug occurs from 3 weeks o
weeks, and subsides by 7 weeks following the injection (Prod Info Risperdal(R) Consta(TM), 2003i).

2) Multiple Dose

a) Psychotic symptoms, oral: 1 year (Addington et al, 1993; Carman & Wyatt-Knowles, 1993; Bressa et al, 1
(Mertens, 1991).

1) Clinical improvement in positive and negative symptoms has been observed for up to 7 months (Addi
Wyatt-Knowles, 1993; Bressa et al, 1991; De Wilde & Dierick, 1991); (Mertens, 1991).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Oral

a) A therapeutic range has not been established. A dose of 6 mg/day produces a risperidone serum level of
patients (Olesen et al, 1998).

b) Plasma concentrations are dose proportional over the dosing range of 1 to 16 mg daily (Prod Info Risperd
1993a).

B) Time to Peak Concentration

1) Oral, solution: 1 hour (Prod Info Risperdal(R), 2004).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) Oral: 70% (CV=25%) (Prod Info Risperdal(R), 2004)(Nyberg et al, 1993a; Anon, 1991; Vanden Bussche e

a) The relative oral bioavailability from a tablet was 94% (CV=10%) when compared to a solution (Prod
et al, 1993a; Anon, 1991; Vanden Bussche et al, 1988).

B) Effects of Food

1) None (Prod Info Risperdal(R), 2004)(Anon, 1991; Vanden Bussche et al, 1988).

2.3.2 Distribution

A) Distribution Sites

1) Protein Binding

a) Risperidone: approximately 90% (Prod Info Risperdal(R), 2004)(Prod Info Risperdal(R) Consta(TM),

b) 9-hydroxyrisperidone: 77% (Prod Info Risperdal(R), 2004)(Prod Info Risperdal(R) Consta(TM), 2003i)

B) Distribution Kinetics

1) Volume of Distribution

a) 1 to 2 liters/kilogram (Prod Info Risperdal(R), 2004)(Prod Info Risperdal(R) Consta(TM), 2003i).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Liver, extensive (Prod Info Risperdal(R) Consta(TM), 2003i); (Prod Info Risperdal(R), 2004)(Nyberg et al,

a) Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxyla
hydroxyrisperidone by the enzyme, CYP2D6 (debrisoquin hydroxylase) with a second minor pathway of
Risperdal(R) Consta(TM), 2003i); (Prod Info Risperdal(R), 2004)(Nyberg et al, 1993a).

b) Metabolism is sensitive to the debrisoquine hydroxylation type genetic polymorphism (Prod Info Risp
1993a).

B) Metabolites

1) 9-hydroxyrisperidone, active (Prod Info Risperdal(R), 2004)(Nyberg et al, 1993a).

a) Metabolite is approximately equi-effective to the parent compound in terms of receptor binding activity
(Nyberg et al, 1993a).

2.3.4 Excretion

A) Total Body Clearance

1) 3.2 to 13.7 liters/hour (L/hr) (Prod Info Risperdal(R) Consta(TM), 2003i).

a) The clearance of risperidone and risperidone plus 9-hydroxyrisperidone is 13.7 L/h and 5 L/h in exten

3.3 L/h and 3.2 L/h in poor metabolizers, respectively (Prod Info Risperdal(R) Consta(TM), 2003i).

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) oral: 20 to 30 hours (Prod Info Risperdal(R), 2004)(Anon, 1991; Vanden Bussche et al, 1988).

1) The apparent half-life of risperidone was 3 hours in extensive metabolizers and 20 hours in poor Risperdal(R), 2004).

2) ELIMINATION HALF-LIFE

a) intramuscular: 3 to 6 days (Prod Info Risperdal(R) Consta(TM), 2003i).

1) The half-life of intramuscular risperidone is related to the erosion of the microspheres and subse (Prod Info Risperdal(R) Consta(TM), 2003i).

B) Metabolites

1) 9-hydroxyrisperidone, 21 to 30 hours (Prod Info Risperdal(R), 2004).

a) The apparent half-life of 9-hydroxyrisperidone was 21 hours in extensive metabolizers and 30 hours i Risperdal(R), 2004).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Intramuscular (Powder for Suspension, Extended Release)

a) Increased Mortality in Elderly Patients with Dementia Related Psychosis: Elderly patients with dementia-relate antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 1 taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 tir treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients wa rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increa studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clea for the treatment of patients with dementia-related psychosis (Prod Info RISPERDAL(R) CONSTA(R) long acting

2) Oral (Tablet; Tablet, Disintegrating; Solution)

a) Increased Mortality in Elderly Patients with Dementia Related Psychosis - Elderly patients with dementia-relate antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo controlled trials (modal duration of 1 taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 tir treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients wa rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increa studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clea for the treatment of patients with dementia-related psychosis (Prod Info RISPERDAL(R) CONSTA(R) long acting

3.1 Contraindications

A) hypersensitivity to risperidone or to any product component (Prod Info RISPERDAL(R) CONSTA(R) long acting inj RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)

3.2 Precautions

A) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attri (eg, heart failure or sudden death) or infections (eg, pneumonia) (Prod Info RISPERDAL(R) CONSTA(R) long acting ir RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)

B) agranulocytosis; potentially fatal; has been reported; risk factors include history of low WBC, leukopenia and neutr (R) CONSTA(R) long acting injection, 2009)

C) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration, medications); increased risk of orthostatic hypotension (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2 oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)

D) cerebrovascular adverse events (stroke, transient ischemic attack), including fatalities, have been reported in elde

psychosis (unapproved use) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDA
RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)
E) conditions that may contribute to elevated body temperature; may disrupt body temperature regulation (Prod Info F
acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating
F) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia (Prod Info RISPERDA
injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets
G) diseases or conditions that could affect metabolism or hemodynamic responses (Prod Info RISPERDAL(R) CONS
Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)
H) elderly patients; increased risk of tardive dyskinesia, especially among elderly women (Prod Info RISPERDAL(R) C
2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)
I) elderly patients; increased risk of orthostatic hypotension, especially during the initial dose-titration period (oral) (Pr
tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)
J) esophageal dysmotility and aspiration may occur; use cautiously in patients at risk for aspiration pneumonia (Prod
long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegra
K) hepatic impairment, severe; increased risperidone exposure and side effects have been reported; dosage adjustm
RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL
disintegrating tablets, 2008)
L) hyperglycemia has been reported, some may lead to ketoacidosis, hyperosmolar coma, or death (Prod Info RISPE
acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating
M) hyperprolactinemia; may result in galactorrhea, amenorrhea, gynecomastia, impotence, hypogonadism and decre
hyperprolactinemia appears to be higher with risperidone relative to other antipsychotic agents (Prod Info RISPERDAL
injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets
N) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info RISP
acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating
O) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotic drugs; imme
Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPER
disintegrating tablets, 2008)
P) Parkinson's disease or dementia with Lewy bodies; increased sensitivity to antipsychotic medications (Prod Info RI
acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating
Q) priapism has been reported; severe cases may require surgical intervention (Prod Info RISPERDAL(R) CONSTA(R
Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)
R) renal impairment, severe; increase in free fraction of risperidone and side effects have been reported; dosage adju
RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL
disintegrating tablets, 2008)
S) seizure disorder, history, or conditions which lower seizure threshold (Prod Info RISPERDAL(R) CONSTA(R) long
RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)
T) suicide risk; close monitoring of high-risk patients recommended (Prod Info RISPERDAL(R) CONSTA(R) long actir
RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)
U) tardive dyskinesia, potentially irreversible; discontinue treatment if appropriate (Prod Info RISPERDAL(R) CONSTA
Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Cardiac dysrhythmia

Hypertension

Orthostatic hypotension

Palpitations

Peripheral edema

Sudden cardiac death

Summary

Syncope

Tachycardia

3.3.1.A Cardiac dysrhythmia

1) During clinical trials of schizophrenic and bipolar I disorder patients, there was no significant difference in patients receiving risperidone long-acting injection at recommended doses and patients receiving placebo (P CONSTA(R) long acting injection, 2009).

2) The manufacturer reports that intergroup comparisons for pooled, placebo-controlled studies did not revea differences between oral risperidone and placebo in mean changes from baseline in ECG parameters, includ and heart rate. There was a mean increase in heart rate of 1 beat per minute when all risperidone doses wer controlled studies in several indications, as compared with no change for patients who received placebo. In s schizophrenia, higher doses of risperidone (8 to 16 milligrams/day) were associated with a higher mean incre per minute) as compared with placebo (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) QRS prolongation and QTc prolongation, sometimes resulting in death, have been reported in patients tak (Duenas-Laita et al, 1999ak; Ravin & Levenson, 1997p; Gesell & Stephen, 1997h; Lo Vecchio et al, 1996h; E

4) A 40-year-old man experienced symptomatic bradyarrhythmia 1 day following an increase in his risperido (mg)/day to 6 mg/day. The patient developed sinus bradycardia (38 beats per minute) and had several episo seconds. During this time, the QTc interval was 410 milliseconds. Risperidone was discontinued and the sym following 48 hours (Goyal & Goyal, 2003).

5) A 7-year-old boy developed sinus dysrhythmia and a QTc interval of 0.46 seconds after a single dose of ri attention deficit hyperactivity disorder (Gesell & Stephen, 1997h).

6) A 34-year-old woman with no history of cardiac disease developed fatal pulseless electrical activity followi day 3, she developed postural hypotension and was then maintained on 2 milligrams (mg) twice daily. On da and was treated for pulseless electrical activity with a prolonged QRS interval and an abnormal QTc interval Despite resuscitative efforts, the patient expired (Ravin & Levenson, 1997p).

3.3.1.B Hypertension

1) Incidence: 3% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) In a 24-month, double-blind, placebo-controlled trial of adult bipolar I disorder patients, hypertension was receiving risperidone intramuscular (n=154) as monotherapy compared with 1% in placebo (n=149) (Prod Inf long acting injection, 2009).

3.3.1.C Orthostatic hypotension

1) Incidence: intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPER

injection, 2009)
2) Orthostatic hypotension was reported in less than 2% of schizophrenic patients and in less than 4% of bip premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schi (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) Orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope (0.2% of p receiving oral risperidone, and 0.8% of patients receiving intramuscular risperidone in multiple-dose studies) clinical trial revealed a positive dose-related trend for orthostatic dizziness. A dose reduction should be consi risperidone cautiously in patients with known cardiovascular or cerebrovascular disease and conditions which hypotension (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrat RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.1.D Palpitations
1) Incidence: oral, adults, 2% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I dis RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Palpitations were reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorde trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) In two 3-week, double-blind, placebo-controlled studies of adjuvant oral risperidone therapy in adults, palp patients receiving risperidone (n=127) compared to 0% for placebo (n=126) (Prod Info RISPERDAL(R) oral ta RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
4) During premarketing (n=2607) evaluation of oral risperidone, palpitations were reported. Data from a large of risperidone (1, 4, 8, 12, and 16 mg/day) revealed a positive dose-related trend (p less than 0.05) for palpita oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL

3.3.1.E Peripheral edema
1) Incidence: adults, up to 3%; children, less than 5% (Prod Info RISPERDAL(R) CONSTA(R) long acting inj RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod solution, 2007)
2) In a 12-week placebo-controlled trial of adult schizophrenic patients , peripheral edema was reported in 2% 25 mg (n=99) and 50 mg (n=103) of risperidone intramuscular therapy, respectively, compared with 1% in pla RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During premarketing risperidone studies of various design types, peripheral edema was reported in less th oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral ta RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
4) In a study of 110 elderly Chinese patients (age 65 or greater), 16% experienced peripheral edema. Leg-pi complaint leading to discontinuation of treatment (Hwang et al, 2001).
5) A 27-year-old woman developed pitting edema in the legs and moderate periorbital and facial edema duri (4 milligrams per day (mg/day)) treatment for schizophrenia. She experienced a 5 kilogram (kg) weight gain d received diphenhydramine during the first 3 weeks for the management of mild dystonia and restlessness; thi after week 3. Resolution of edema occurred within 1 week when the dose of risperidone was reduced to 3 mg was reported during an 8-month follow-up period (Tamam et al, 2002).
6) A 35-year-old male experienced edema with a 15 pound weight gain after 2 1/2 weeks of risperidone thera included divalproex sodium and clorazepate. Diuretic therapy with hydrochlorothiazide 25 milligrams (mg)/day resolved the edema within 1 week. The authors note that although edema is associated with divalproex, it did was added. They suggest that both of these medications when used together may be more likely to cause ed mechanism (Baldassano & Ghaemi, 1996).

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 drug antipsychotic drugs, there was an increased risk of sudden cardiac death in adult participants 30 to 74 years who were using risperidone compared to those who were not using antipsychotic drugs (incidence-rate ratio, (CI), 2.26 to 3.76; p less than 0.001). In participants being treated with atypical antidepressants (clozapine, ol risperidone), the incidence-rate ratio for sudden cardiac death increased from 1.59 (95% CI, 1.03 to 2.46) for (95% CI, 2.25 to 3.65) for those using high doses (p=0.01) (Ray et al, 2009).

3.3.1.G Summary
1) AV block, myocardial infarction, palpitations, hypertension, hypotension, pulmonary embolism, T-wave inv prolonged QRS interval, abnormal QTc interval, tachycardia, bradyarrhythmia, and edema have all been repo administration. Stroke and transient ischemic attack have been reported in the elderly (mean age 85 years ol CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.1.H Syncope
1) Incidence: adults, up to 2%(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting inject
2) Syncope was reported in 0.2% (6/2607) of patients receiving oral risperidone in Phase 2 and 3 clinical tria tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R)

3) During a 12-week clinical trial, syncope was observed in 2% of patients receiving risperidone 25 mg long-
patients receiving risperidone 50 mg long-acting injection (n=103), compared with 0% of patients receiving pl
studies, syncope occurred in 0.8% (12/1499) of patients receiving long-acting injections (Prod Info RISPERD
injection, 2009).

3.3.1.I Tachycardia

1) Incidence: oral, adults, up to 5%; children, up to 7% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod In
disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less
than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Tachycardia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorde
trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and
RISPERDAL(R) CONSTA(R) long acting injection, 2009), and in up to 5% of adult patients receiving oral ther
patients receiving oral therapy. Tachycardia was responsible for 0.3% and 0.5% of discontinuation of therapy
patients receiving 2 to 8 mg/day (n=366) and in 8 to 16 mg/day or greater (n=198), respectively, compared w
Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; F
solution, 2007).

3) A compensatory increased heart rate (7 to 8 beats/minute) may develop at therapeutic doses of risperidor

3.3.2 Dermatologic Effects

Acne

Discoloration of skin

Dry skin

Injection site reaction

Peeling of skin

Rash

Summary

3.3.2.A Acne

1) Incidence: adults, 1% to 2% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TA
2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) During risperidone clinical trials, acne was reported in 2% of adult patients receiving intramuscular therapy
patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TA
2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting inject

3.3.2.B Discoloration of skin

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007;
TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) During risperidone clinical trials, skin discoloration was reported in less than 1% of adult patients receiving
of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDA
tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.2.C Dry skin

1) Incidence: intramuscular, adults, up to 2% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2

2) In a 12-week placebo-controlled trial of adult schizophrenic patients, dry skin was reported in 2% and 0%
(n=99) and 50 mg (n=103) of risperidone intramuscular therapy, respectively, compared with 0% in placebo (
CONSTA(R) long acting injection, 2009).

3.3.2.D Injection site reaction

1) Incidence: intramuscular, 1% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) During the 10th week of a 12-week clinical trial, injection site reaction (including redness, swelling, or indu
patients receiving risperidone 25 mg or 50 mg long-acting injection (n=202). Between the first and last injectio
mean injection pain intensity scores (0=no pain to 100=unbearable pain) in the placebo group (16.7 to 12.6) a
injection groups (25 mg: 12 to 9; 50 mg: 18.2 to 11.8). In a separate study in which long-acting risperidone inj
muscle every 2 weeks over 8 weeks period, only mild injection site events were observed in patients receivin
hours after the injection (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.2.E Peeling of skin

1) A 37-year-old male with DSM-IV bipolar I disorder experienced rash and desquamation following oral risp
presented to an inpatient clinic as euphoric and irritable with rapid speech, sleep and appetite disturbances. T
consisted of several manic episodes since the age of 23. Treatment with oral risperidone solution 2 mg at bed
lithium (900 mg/day), diazepam (15 mg/day), zolpidem (10 mg at bedtime), and procyclidine hydrochloride (5
and rash under the patient's eyes were seen on day 3 of treatment. Risperidone and lithium were both increa
mg/day, respectively, on day 4, due to persisting manic symptoms. By day 5, the rash had spread over the en
desquamation developing over areas of his face. Risperidone was discontinued on day 6 and switched to que
was increased to 600 mg/day to manage the patient's manic symptoms. Lithium dosing was maintained. Two
discontinuation, the patient's skin lesions had completely cleared (Chae & Kang, 2008).

3.3.2.F Rash

1) Incidence: oral, adults, 2% to 4%; children, up to 11% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod
orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni
disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Rash was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder patie
various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar
(R) CONSTA(R) long acting injection, 2009).

3) During risperidone clinical trials, rash was reported in 2% to 4% of adult patients receiving oral therapy, ar
patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TA
2007; Prod Info RISPERDAL(R) oral solution, 2007).

4) A 37-year-old male with DSM-IV bipolar I disorder experienced rash and desquamation following oral risp
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mg/day, respectively, on day 4, due to persisting manic symptoms. By day 5, the rash had spread over the en
desquamation developing over areas of his face. Risperidone was discontinued on day 6 and switched to que
was increased to 600 mg/day to manage the patient's manic symptoms. Lithium dosing was maintained. Two
discontinuation, the patient's skin lesions had completely cleared (Chae & Kang, 2008).

3.3.2.G Summary

1) Rash, dry skin, seborrhea, skin discoloration, injection site reaction, photosensitivity, skin exfoliation, pruri
sweating, skin ulceration, and dermatitis were reported with risperidone therapy (Prod Info RISPERDAL(R) or
RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Proc
(R) long acting injection, 2009).

3.3.3 Endocrine/Metabolic Effects

Body temperature above normal

Diabetes mellitus

Diabetic ketoacidosis

Excessive thirst

Hyperglycemia

Hyperprolactinemia

Hypothermia

Metabolic syndrome

Weight gain

Weight loss

3.3.3.A Body temperature above normal

1) Hyperthermia has been associated with the use of antipsychotic agents, including oral risperidone (Prod I
2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral sol

RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.3.B Diabetes mellitus

See Drug Consult reference: ATYPICAL ANTIPSYCHOTIC AGENTS - EFFECT ON GLUCOSE AND RISK C

3.3.3.C Diabetic ketoacidosis

1) Incidence: rare (Lu & Yan, 2009)

2) Diabetic ketoacidosis in patients with impaired glucose metabolism has been reported during the risperidc Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) A 27-year-old schizophrenic male was hospitalized with fever and severe diabetic ketoacidosis (DKA) resu of risperidone treatment. The patient had no history of diabetes. On admission his serum glucose was 1297 r metabolic acidosis were positive, and his glycosylated hemoglobin was 13%. Risperidone was immediately d insulin treatment and fluid replacement, the patient died within 12 hours due to the rapid progression of DKA. risperidone-induced hyperglycemia resulting in fatal diabetic ketoacidosis (Lu & Yan, 2009).

3.3.3.D Excessive thirst

1) Incidence: adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Proc orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) During the double-blind, placebo-controlled trials for oral risperidone, less than 1% of adults and less than experiencing thirst (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disi Info RISPERDAL(R) oral solution, 2007).

3) Risperidone was suspected of causing polydipsia in a 28-year-old male receiving the drug for treatment of type). His schizophrenia had been refractory to various oral and injectable antipsychotics and electroconvulsi risperidone 8 mg/day (which improved his psychotic symptoms). Within 2 weeks, he started drinking water ex variable period of a few minutes to 8 hours. His polydipsia episodes initially occurred intermittently at 10- to 1 became more frequent (ie, every 3 to 4 days, sometimes twice daily), especially after his risperidone was incı to polydipsia, the patient experienced polyuria and, occasionally, nausea, vomiting, marked lassitude, slurring an episode. Staring and unresponsiveness would sometimes precede an episode. Later risperidone was dec decrease in frequency of polydipsia episodes occurred. Then risperidone was withdrawn. Polydipsia disappe period. The patient was started on clozapine, and had no return of polydipsia. The authors noted that during t excessive amounts of water, he never developed hyponatremia or water intoxication. Diabetes mellitus or ins inappropriate secretion of antidiuretic hormone (SIADH), had been ruled out, and he was taking no other mec et al, 2002).

3.3.3.E Hyperglycemia

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizop disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Hyperglycemia, including cases associated with ketoacidosis, hyperosmolar coma, or death, has been rep atypical antipsychotics, including risperidone. Hyperglycemia has resolved in some cases after discontinuatio cases, continuation of antidiabetic treatment was required after drug discontinuation (Prod Info RISPERDAL(RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Proc (R) long acting injection, 2009).

3) Hyperglycemia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar diso trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia anc RISPERDAL(R) CONSTA(R) long acting injection, 2009). Hyperglycemia was reported in less than 1% of adı and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.3.F Hyperprolactinemia

1) Summary

a) Hyperprolactinemia was reported in less than 2% of schizophrenic patients and in less than 4% of bip premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) Antipsychotic-induced hyperprolactinemia was reported in 65.6%, 45.1%, and 42.4% of women of ch postmenopausal women, and men, respectively, in an open-label, clinical trial of patients treated with firs risperidone at average doses of 4.2 to 5.2 mg/day. Compared to baseline, prolactin levels were significar following use of first-generation antipsychotics (ie, chlorpromazine, droperidol, flupenthixol, fluphenazine perazine, perphenazine, pimozide, trifluoperazine, and zuclopenthixol) or risperidone in several clinical tr schizophrenia. Younger patients and women of childbearing potential have a greater risk for hyperprolac higher doses of these antipsychotics. Hyperprolactinemia may potentially result in menstrual disturbance bone mineral density (ie, osteopenia and osteoporosis), and breast and pituitary tumors (Bostwick et al,

c) Elevated prolactin levels associated with risperidone use appear to be dose-dependent and greater ir elevations are higher with risperidone use compared to elevations associated with other antipsychotic ag oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPEF

d) Adverse events associated with hyperprolactinemia include inhibited reproductive function, galactorrh and impotence. Hypogonadism associated with chronic hyperprolactinemia may lead to reduced bone de (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table

(R) oral solution, 2007).

2) Incidence: oral, adults, less than 1%; children, 49% to 87% (Prod Info RISPERDAL(R) oral tablets, 2007; orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

3) Adult

a) Hyperprolactinemia was reported in less than 2% of schizophrenic patients and in less than 4% of bip premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Hyperprolactinemia was re receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB or Prod Info RISPERDAL(R) oral solution, 2007).

b) Risperidone is associated with increased prolactin which persists with chronic therapy (Prod Info RIS acting injection, 2009; Hellings et al, 2005; Kleinberg et al, 1999; Caracci & Ananthamoorthy, 1999). Mal hypothyroidism may be particularly sensitive to a neuroleptic-induced elevation of prolactin levels and clo within the first 3 months of initiating risperidone therapy (Mabini et al, 2000).

c) Prolactin concentrations increased and remained elevated for at least 26 weeks in males and females experiencing a significantly greater increase. During a double-blind, placebo-controlled trial, serum prola during the acute and maintenance phases in a subset of 10 children and adolescents and 11 adults with developmental disorders. For children and adolescents (mean age of 12.5 years), the mean acute and m were 0.92 milligrams/day (mg/day) (range, 0.25 to 1.36 mg/day) and 1.25 mg per day (0.25 to 2 mg/day) age of 35.3 years), the mean acute and maintenance doses of risperidone were 2 mg/day and 1.36 mg/d respectively. Normal prolactin concentrations were 1.6 to 18.8 nanograms/mL for males and 1.4 to 24.2 n children and adolescents, the mean baseline serum prolactin of 13.2 +/- 8.6 nanograms/milliliter (ng/mL) nanograms/mL (p=0.01) in the acute phase and 37.9 +/- 10.4 nanograms/mL (p=0.02) in the maintenanc weeks from baseline. In adults, the mean baseline serum prolactin of 11.6 +/- 7.4 nanograms/mL increas nanograms/mL (p=0.001) in the acute phase and 67.8 +/- 62.9 nanograms/mL (p=0.02) in the maintenar weeks from baseline. With similar mean baseline prolactin levels in adult females and males (11.7 nanog nanograms/mL; p=0.86), the prolactin elevation was 2.2 greater in adult females compared with adult ma versus 57.8 nanograms/mL; p=0.01) and 3.7 times greater in the maintenance phase (98.5 nanograms/m (Hellings et al, 2005).

d) In a small study of 20 women, risperidone produced prolactin levels twice as high as in women receiv (Caracci & Ananthamoorthy, 1999). Another author reviewed the results of 4 clinical trials and found sign levels with risperidone versus haloperidol. In women, risperidone increased prolactin levels significantly l receiving haloperidol 10 milligrams/day (mg/day) (p less than 0.001). Women receiving haloperidol 20 m to women receiving risperidone. In men, risperidone 4 to 6 mg/day produced significantly higher prolactin mg/day (p=0.01) but not 20 mg/day. With doses of risperidone 6 mg/day and greater, prolactin levels wer haloperidol doses (p less than 0.01). Elevated prolactin levels are associated with amenorrhea, galactorr osteoporosis. Amenorrhea or galactorrhea has been reported in 10% of female patients receiving risperi

4) Pediatric

a) In double-blind clinical trials lasting 8 weeks in children and adolescents (5 to 17 years) with autistic d other than autistic disorder, bipolar mania, or schizophrenia, elevated prolactin levels were reported in 4 compared to 2% of patients receiving placebo (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RI disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) In placebo-controlled clinical trials in adolescents (13 to 17 years) with schizophrenia and children an with bipolar disorder, elevated prolactin levels were reported in 82% to 87% of patients receiving risperid placebo (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegra RISPERDAL(R) oral solution, 2007).

c) Prolactin concentrations increased and remained elevated for at least 26 weeks in males and females experiencing a significantly greater increase. During a double-blind, placebo-controlled trial, serum prola during the acute and maintenance phases in a subset of 10 children and adolescents and 11 adults with developmental disorders. For children and adolescents (mean age of 12.5 years), the mean acute and m were 0.92 milligrams/day (mg/day) (range, 0.25 to 1.36 mg/day) and 1.25 mg per day (0.25 to 2 mg/day) age of 35.3 years), the mean acute and maintenance doses of risperidone were 2 mg/day and 1.36 mg/d respectively. Normal prolactin concentrations were 1.6 to 18.8 nanograms/mL for males and 1.4 to 24.2 n children and adolescents, the mean baseline serum prolactin of 13.2 +/- 8.6 nanograms/milliliter (ng/mL) nanograms/mL (p=0.01) in the acute phase and 37.9 +/- 10.4 nanograms/mL (p=0.02) in the maintenanc weeks from baseline. In adults, the mean baseline serum prolactin of 11.6 +/- 7.4 nanograms/mL increas nanograms/mL (p=0.001) in the acute phase and 67.8 +/- 62.9 nanograms/mL (p=0.02) in the maintenar weeks from baseline. With similar mean baseline prolactin levels in adult females and males (11.7 nanog nanograms/mL; p=0.86), the prolactin elevation was 2.2 greater in adult females compared with adult ma versus 57.8 nanograms/mL; p=0.01) and 3.7 times greater in the maintenance phase (98.5 nanograms/m (Hellings et al, 2005).

5) Management

a) Appropriate drug selection, monitoring and management are all important when prescribing antipsych inducing hyperprolactinemia. Prior to treatment with an antipsychotic, question patients regarding change Female patients should be assessed for menstrual abnormalities and male patients, for erectile or ejacul that any of these symptoms are present, consider obtaining baseline prolactin levels. Patients should be sexual dysfunction with antipsychotic use. Several weeks after an antipsychotic is initiated, obtain a prola cases where the patient experiences troublesome adverse effects related to elevated prolactin levels and

is not an option, treatment with a dopamine agonist (eg, bromocriptine or cabergoline) should be conside

3.3.3.G Hypothermia

1) Hypothermia has been associated with the use of antipsychotic agents, including oral risperidone (Prod In 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral sol RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) A 37-year-old woman with psychosis in association with Prader-Willi syndrome suffered hypothermia with risperidone therapy. Her rectal temperature was 30 degrees Celsius. She had experienced 2 previous episod month after starting risperidone treatment. Withdrawal of risperidone resulted in normalization of temperature with olanzapine therapy. Hypothyroidism was excluded. The authors hypothesized that hypothermia may res the serotonin 5-HT(2) receptor (Phan et al, 1998).

3.3.3.H Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.I Weight gain

1) Summary

a) In adult clinical trials, up to 18% of patients receiving oral risperidone reported weight gains of at leas 9% reported for placebo. (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) Weight gain was reported in up to 14% of adolescent and pediatric patients (5 to 16 years) receiving (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007).

c) During clinical trial of schizophrenic patients, weight gain was reported in 5% and 4% of patients rece acting injection and risperidone 50 mg long-acting injection, respectively. In 2 clinical trials of adult bipola was reported in 5% to 7% of patients receiving long-acting risperidone injection (Prod Info RISPERDAL(injection, 2009).

d) An adverse event analysis from a large study comparing five fixed doses of oral risperidone (1, 4, 8, 1 demonstrated a dose-related effect for reports of weight gain (p less than 0.05) (Prod Info RISPERDAL(R RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) Incidence: oral, adults, up to 18%; children, up to 14%(Prod Info RISPERDAL(R) oral tablets, 2007; Prod orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni 5% to 7% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

3) Adult

a) Statistically significant weight gains of at least 7% of body weight were reported in 18% of patients re 9% reported for placebo in a pooled analysis of 6- to 8-week placebo-controlled trials of adults with schiz (R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RIS

b) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, weight gain was repor risperidone 25 mg long-acting injection (n=99) and 4% of patients receiving risperidone 50 mg long-actin with 2% of patients receiving placebo (n=98). In a 24-month, double-blind, placebo-controlled trial of adu weight gain was reported in 5% of patients receiving long-acting risperidone injection (n=154) as monoth placebo (n=149). In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, weigh patients receiving long-acting risperidone injection (n=72) compared with 0% in placebo (n=67)(Prod Info long acting injection, 2009).

c) An adverse event analysis from a large study comparing five fixed doses of oral risperidone (1, 4, 8, 1 demonstrated a dose-related effect for reports of weight gain (p less than 0.05) (Prod Info RISPERDAL(R RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

d) Mean weight gain in patients treated with atypical neuroleptics included zotepine 4.3 kilograms (kg), and risperidone 1.5 kg, according to a retrospective chart review. The weight gain was significantly more neuroleptics compared with patients receiving classic neuroleptics, such as haloperidol, flupenthixol, or p risk of weight gain was seen in patients who were young and had not been previously treated with neuro Mussigbrodt, 1999).

e) A controlled study of risperidone treatment in children, adolescents, and adults with mental retardatio weight gain in the group treated with risperidone over a year period (children aged 8 to 12 (n=5) gained a (n=6) a mean of 8.4 kg; adults aged 21 to 51 (n=8) a mean of 5.4 kg (Hellings et al, 2001).

4) Pediatric

a) In two pooled 8-week, double-blind, placebo-controlled trials of adolescent and pediatric patients (5 to associated with autistic disorder, increases in weight were reported in 5% of patients receiving oral rispe for placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally Prod Info RISPERDAL(R) oral solution, 2007).

b) Treatment-emergent weight gain (mean increases of 9 kg) was reported in 14% of adolescents (n=10 extension study of oral risperidone. Most increases were observed within the first months of the study (P tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDA

c) A controlled study of risperidone treatment in children, adolescents, and adults with mental retardatio weight gain in the group treated with risperidone over a year period (children aged 8 to 12 (n=5) gained a (n=6) a mean of 8.4 kg; adults aged 21 to 51 (n=8) a mean of 5.4 kg (Hellings et al, 2001).

d) Risperidone-treated adolescents had significantly higher weight gains and increases in body mass in treated with conventional neuroleptic agents (p=0.0141 and p=0.0011, respectively). Adolescent inpatien

center being treated with risperidone (n=18), conventional antipsychotics (n=23), or no antipsychotic me
and BMI followed for 6 months. In the risperidone group mean changes were a gain of 8.64 kilograms (k
(2)), for conventional antipsychotics changes were a gain of 3.03 kg and 0.31 kg/m(2), and for the no an
loss of 1.04 kg and 1.01 kg/m(2). The average daily dose of risperidone was 2.83 milligrams (mg) and ga
(Kelly et al, 1998).

3.3.3.J Weight loss

1) Incidence: adults, 1% to 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) During a 12-week, placebo-controlled trial of intramuscular risperidone, weight decreases were reported i
risperidone 25 mg (n=99), and 1% receiving risperidone 50 mg (n=103), compared to 1% receiving placebo (
CONSTA(R) long acting injection, 2009).

3.3.4 Gastrointestinal Effects

Abdominal pain

Constipation

Decrease in appetite

Diarrhea

Excessive salivation

Increased appetite

Indigestion

Nausea

Pancreatitis

Summary

Toothache

Vomiting

Xerostomia

3.3.4.A Abdominal pain

1) Incidence: oral, adults, 2% to 4%; children, 15% to 18% (Prod Info RISPERDAL(R) M-TAB orally disintegr
RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2007); ir
than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) Abdominal pain was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar
premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for
disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) During risperidone clinical trials, abdominal pain was reported in 2% to 4% of adult patients receiving
RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; I
solution, 2007).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, abdominal p
treated with risperidone 0.5 to 2.5 mg daily (n=50), 15% in patients treated with 3 to 6 mg daily (n=61), c
(n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrati
RISPERDAL(R) oral solution, 2007).

3.3.4.B Constipation

1) Incidence: oral, adults, 5% to 9%; children, 21% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info R
disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 5%
CONSTA(R) long acting injection, 2009)

2) Adult

a) In a 12-week placebo-controlled trial of adult schizophrenic patients, constipation was reported in 5% mg (n=99) and 50 mg (n=103) of long-acting risperidone intramuscular therapy, respectively, compared Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) During risperidone clinical trials, constipation was reported in 8% to 9% of adult patients receiving ora (R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RIS

3) Pediatric

a) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of constipation was 21% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), com (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007).

3.3.4.C Decrease in appetite

1) Incidence: adult, bipolar disorder, 6% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, decreased appetite was r receiving long-acting risperidone injection (n=72) compared with 1% in placebo (n=67) (Prod Info RISPERDA injection, 2009).

3.3.4.D Diarrhea

1) Incidence: oral, adults, up to 6%; children, 7% to 8% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod In disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) Diarrhea was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disord trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia RISPERDAL(R) CONSTA(R) long acting injection, 2009). Diarrhea was reported up to 6% of adult patien Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20 oral solution, 2007).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, diarrhea occ with risperidone 0.5 to 2.5 mg daily (n=50), 7% in patients treated with 3 to 6 mg daily (n=61), compared Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20 oral solution, 2007).

3.3.4.E Excessive salivation

1) Incidence: oral, adults, 1% to 4%; children, up to 22% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, salivary hypersecretio receiving risperidone 25 mg long-acting injection (n=99) and 1% of patients receiving risperidone 50 mg compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long act risperidone clinical trials, increased salivation was reported in 1% to 4% of adult patients receiving oral th oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPER

3) Pediatric

a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, increased s patients treated with risperidone 1 to 3 mg daily (n=55), 10% treated with 4 to 6 mg daily (n=51), compar (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007).

b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of increased salivation was 22% in patients treated with oral risperidone 0.5 to 4 mg daily (n=7 (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrati RISPERDAL(R) oral solution, 2007).

3.3.4.F Increased appetite

1) Incidence: oral, children, 4 to 49% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, bipolar I disorder, 4% (Prod Info long acting injection, 2009)

2) Adult

a) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, increased appetite w receiving long-acting risperidone injection (n=72) compared with 0% in placebo (n=67) (Prod Info RISPE acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB ora Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, increased a treated with risperidone 0.5 to 2.5 mg daily (n=50), 7% in patients treated with 3 to 6 mg daily (n=61), co (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrati RISPERDAL(R) oral solution, 2007).

b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of increased appetite was 49% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76 (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrati RISPERDAL(R) oral solution, 2007).

3.3.4.G Indigestion

1) Incidence: oral, adults, 4% to 10%; children, 5% to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; Pro orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni CONSTA(R) long acting injection, 2009)

2) In a 12-week placebo-controlled trial of adult schizophrenic patients, dyspepsia was reported in 6% and 6 (n=99) and 50 mg (n=103) of long-acting risperidone intramuscular therapy, respectively, compared with 0% RISPERDAL(R) CONSTA(R) long acting injection, 2009). During risperidone clinical trials, dyspepsia was rep patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TA 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, dyspepsia o treated with risperidone 0.5 to 2.5 mg daily (n=50), 5% in patients treated with 3 to 6 mg daily (n=61), co (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrati RISPERDAL(R) oral solution, 2007).

3.3.4.H Nausea

1) Incidence: oral, adults, 4% to 9%; children, 8% to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) In a 12-week placebo-controlled trial of adult schizophrenic patients, nausea was reported in 3% and (n=99) and 50 mg (n=103) of long-acting risperidone intramuscular therapy, respectively, compared with RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) During risperidone clinical trials, nausea was reported in 4% to 9% of adult patients receiving oral the for 1.4% of discontinuation of therapy in schizophrenic adult trials in patients receiving oral therapy with with 0% in patients receiving risperidone 8 to 16 mg/day (n=198), or in placebo (n=225) (Prod Info RISPE Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solut

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, nausea occ with risperidone 0.5 to 2.5 mg daily (n=50), 13% in patients treated with 3 to 6 mg daily (n=61), compare (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007).

3.3.4.I Pancreatitis

1) During postmarketing risperidone use, pancreatitis has been reported (Prod Info RISPERDAL(R) oral tabl (R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPE acting injection, 2009).

2) In one study of reported cases (n=192) of antipsychotic-induced pancreatitis, 16% of the cases were asso at a mean daily dose of 4 milligrams. In most patients, time to onset of pancreatitis was within 6 months after al, 2003c).

3) A 32-year-old, male, chronic, paranoid schizophrenic, patient developed cholestatic hepatitis and pancrea risperidone 2 milligrams (mg) daily. He had a sudden onset of nausea, anorexia, vomiting, abdominal pain, ja colored stools. He had no history of abdominal trauma, alcohol, or drug abuse and tests for autoimmune dise A, B, and C were all negative. Initial laboratory results were: amylase, 1,617 international units/L; AST, 179 ir international units/L; GGT, 448 international units/L; AP, 367 international units/L; TB, 2.8 mg/dL; CB, 1.9 mg risperidone, the patient improved clinically and his laboratory results were: amylase, 113 international units/L ALT, 118 international units/L; GGT, 292 international units/L; AP, 284 international units/L; TB, 0.7 internatio units/L (Cordeiro & Ikis, 2001).

4) A 32-year-old male was diagnosed with pancreatitis after he complained of diffuse abdominal pain, nause after starting risperidone therapy. His initial amylase level was 1087 international units (international units)/lite slight glycemic elevation, but no other changes in liver function tests. His risperidone was tapered off over 2 v 147 international units/L (Berent et al, 1997).

3.3.4.J Summary

1) Hypersalivation, pancreatitis, constipation, diarrhea, nausea, dyspepsia, vomiting, abdominal pain, toothac dysphagia, melena, flatulence, fecal incontinence, rectal hemorrhage, gingivitis, and gastroesophageal reflux risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally dis Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.4.K Toothache

1) Incidence: intramuscular, 1% to 3% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) In a 12-week placebo-controlled trial of adult schizophrenic patients, toothache was reported in 1% and 3 (n=99) and 50 mg (n=103) of risperidone intramuscular therapy, respectively, compared with 0% in placebo (

CONSTA(R) long acting injection, 2009).

3.3.4.L Vomiting

1) Incidence: oral, children, 10% to 12% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipo (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) Vomiting was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disord trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, vomiting occ with risperidone 0.5 to 2.5 mg daily (n=50), 10% in patients treated with 3 to 6 mg daily (n=61), compared (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007).

3.3.4.M Xerostomia

1) Incidence: oral, adults, up to 4%; children, up to 13% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod I disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 0% CONSTA(R) long acting injection, 2009)

2) Adult

a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, dry mouth was reporte risperidone 25 mg long-acting injection (n=99) and 7% of patients receiving risperidone 50 mg long-actin with 1% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injectio clinical trials, dry mouth was reported up to 4% of adult patients receiving oral therapy (Prod Info RISPEI Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2

3) Pediatric

a) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of dry mouth was 13% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compa (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007).

3.3.5 Hematologic Effects

Agranulocytosis

Anemia

Leukopenia

Neutropenia

Purpura

Thrombocytopenia

Thrombotic thrombocytopenic purpura

3.3.5.A Agranulocytosis

1) Agranulocytosis, including fatal cases, has been reported during postmarketing use of risperidone (Prod I long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, orally disintegrating tablets, 2008)

2) A case report described agranulocytosis in a 40-year-old woman after 2 weeks of risperidone treatment. S agranulocytosis with other antipsychotic therapies: chlorpromazine with carbamazepine (WBC count, 2500/m haloperidol (WBC count, 2200/mm(3); neutrophil rate, 52%), and zuclopenthixol (WBC count, 2700/mm(3); n risperidone 4 mg/day, her WBC count was 2400/mm(3) and her neutrophil count was 32% (Finkel et al, 1998

3.3.5.B Anemia

1) Incidence: oral, adults, up to 1% (Prod Info RISPERDAL(R) oral tablets, solution, orally disintegrating tabl schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long ac

2) Anemia was reported in less than 1% of adult patients treated with oral risperidone 2 to 8 mg per day (n=3 risperidone greater than 8 to 16 mg/day (n=198), and 0% of those treated with placebo in three double-blind, weeks duration including adult patients being treated for schizophrenia (Prod Info RISPERDAL(R) oral tablets tablets, 2008).

3) Anemia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder pat of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipo RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.5.C Leukopenia

1) Leukopenia has been reported during postmarketing use of risperidone. The potential risk factors include induced leukopenia and neutropenia. These patients should have frequent monitoring of CBC during the first Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) A case report described leukopenia in a 32-year-old man following treatment with risperidone and aripipra history of paranoid schizophrenia, had been initiated on risperidone 2 mg/day a few years earlier. Although h results of his annual physical exam were normal, laboratory assessment showed a WBC and absolute neutro and 1.27 x 10(9), respectively. Risperidone-induced leukopenia was suspected and the patient agreed to red mg/day. A few weeks later, a lab workup showed WBC count and ANC at 2.7 x 10(9) and 1.22 x 10(9), respe risperidone was discontinued and the patient was initiated on aripiprazole 10 mg daily. He was evaluated eve adverse effects. Six months later, his WBC count and ANC were 2.4 x 10(9) and 0.85 x 10(9), respectively, a Two weeks later, he experienced paranoid delusions, irritable mood, and auditory hallucinations for which he admission, his WBC count and ANC were 6.4 x 10(9) and 1.29 x 10(9), respectively. He was discharged afte 10 mg/day. At a follow-up appointment, his WBC count and ANC were again low (2.9 x 10(9) and 1.29 x 10(9 discontinue aripiprazole and treat the patient with paliperidone 6 mg and lithium 300 mg. Subsequent to the n count and ANC increased to 3.3 x 10(9) and 1.42 x 10(9). A full hematologic workup was pending at the time Rubin, 2008).

3) A 63-year-old man developed leukopenia and neutropenia 1 week after beginning risperidone 2 mg twice reaction was confirmed upon rechallenge. He had experienced a similar reaction with clozapine (Dernovsek &

4) A case of leukopenia, possibly related to risperidone, was reported following 7 days of therapy (2 to 6 mg/ count decreased from 5100/mm(3) to 3500/mm(3) over 7 days, and the neutrophil count decreased from 343 9, the neutrophil count had further decreased to 980/mm(3). The patient also had influenza during this same confounded the circumstances (Meylan et al, 1995).

3.3.5.D Neutropenia

1) Neutropenia has been reported during postmarketing use of risperidone. The potential risk factors include induced leukopenia and neutropenia. These patients should be evaluated for signs of infection, and frequent few months of treatment is recommended. Patients with severe neutropenia (absolute neutrophil count less t discontinue risperidone and have their WBC followed at discontinuation of treatment until recovery (Prod Info long acting injection, 2009).

3.3.5.E Purpura

1) Incidence: adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, solution, o

2) During premarketing risperidone studies of various design types, purpura was reported in less than 1% of therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablet tablets, 2008).

3) During premarketing trials of approximately 1300 patients receiving oral risperidone, a 28-year-old female thrombotic thrombocytopenic purpura, which included fever, jaundice and bruising. The patient recovered foll RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.5.F Thrombocytopenia

1) Thrombocytopenia has been reported during postmarketing use of risperidone (Prod Info RISPERDAL(R) injection, 2009; Prod Info RISPERDAL(R) oral tablets, solution, orally disintegrating tablets, 2008).

2) A case report described thrombocytopenia in a 48-year-old man following risperidone use. The patient, wh hematological disorders, presented to the emergency room with sudden right hemiplegia, aphasia, and disori hypertension but was not receiving medication for it. According to a brain CT scan, there was hemorrhaging i Upon admission, his platelet count was 160,000/microliter and he was treated fairly conservatively. On day 3, brain edema and underwent emergency surgery. His postoperative regimen included carbamazepine 600 mg nizatidine 300 mg/day to prevent gastric ulcer, and nifedipine 40 mg/day for hypertension. At 2 days post-ope agitation, emotional lability, and sensory aphasia and would not remain on bedrest. A diagnosis of postoperat the patient was initiated on risperidone 1 mg twice daily resulting in an improvement in symptoms. Two week 38,000/microliter. Because thrombocytopenia was suspected and his delirium had improved, risperidone was risperidone discontinuation, platelet count increased to 112,000/microliter. He continued to receive carbamaz discharge, but nizatidine was discontinued 3 days after risperidone was discontinued. Upon discharge on pos count was 158,000/microliter with WBC and RBC counts within normal limits. Two months later, his platelet c (Semba & Okui, 2009).

3.3.5.G Thrombotic thrombocytopenic purpura

1) In a large open-marketing trial of approximately 1300 patients receiving oral risperidone therapy, a 28-yea thrombotic thrombocytopenic purpura (TTP), which included fever, jaundice and bruising. The patient recover The relationship of the TTP to risperidone is not known (Prod Info RISPERDAL(R) CONSTA(R) long acting in

3.3.6 Hepatic Effects

gamma-Glutamyltransferase deficiency

Increased liver function test

3.3.6.A gamma-Glutamyltransferase deficiency

1) Reductions in plasma gamma-glutamyl transferase have been reported with risperidone therapy (Anon, 19

3.3.6.B Increased liver function test

1) Incidence: oral, adults, up to 1%; children, up to 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod In disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Increased hepatic enzymes were reported in less than 2% of schizophrenic patients and in less than 4% o premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schi (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) During risperidone clinical trials, increased hepatic enzymes were reported in up to 1% of adult patients re than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info R disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

4) A 32-year-old male patient with chronic paranoid schizophrenia developed cholestatic hepatitis and pancr risperidone 2 milligrams (mg) daily. He had a sudden onset of nausea, anorexia, vomiting, abdominal pain, ja colored stools. He had no history of abdominal trauma, alcohol, or drug abuse, and tests for autoimmune dise A, B, and C were all negative. Initial laboratory results were: amylase, 1,617 international units/L; AST, 179 ir international units/L; GGT, 448 international units/L; AP, 367 international units/L; TB, 2.8 mg/dL; and CB, 1.9 discontinuing risperidone, the patient improved clinically and his laboratory results were: amylase, 113 interna international units/L; ALT, 118 international units/L; GGT, 292 international units/L; AP, 284 international units and CB, 0.5 international units/L (Cordeiro & Ikis, 2001).

5) Two patients developed moderate increases of liver function tests within the first 1 or 2 weeks of risperido normalized spontaneously with only a slight decrease of 1 milligram in one patient and an unchanged dose ir to check liver function tests in the early phase of risperidone treatment (Whitworth et al, 1999).

6) An 81-year-old man with paranoid delusions, Parkinson's disease, dementia, and depression developed h of risperidone 0.5 milligrams (mg). Other medications included aspirin, diltiazem, sublingual nitroglycerin, levo liver functions tests had been normal before beginning risperidone. After 2 doses, he was noted to be jaundic aminotransferase (AST) 434 units/liter (L), alanine aminotransferase (ALT) 101 units/L, total bilirubin 3.6 milli alkaline phosphatase 244 units/L. Ultrasound showed mild splenomegaly and small gallstones. Two weeks a risperidone, liver function tests were normal (Phillips et al, 1998).

3.3.8 Musculoskeletal Effects

Abnormal gait

Arthralgia

Decreased bone mineral density

Myalgia

Pain, in Extremity

Summary

3.3.8.A Abnormal gait

1) Incidence: intramuscular, bipolar disorder, 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injectio

2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, gait abnormality was repo long-acting risperidone injection (n=72) compared with 0% in placebo (n=67) (Prod Info RISPERDAL(R) CON 2009).

3.3.8.B Arthralgia

1) Incidence: oral, schizophrenia, 2% to 3% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPER disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, bipolar I disorder, 4 CONSTA(R) long acting injection, 2009)

2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, arthralgia was reported ir acting risperidone injection (n=72) compared with 3% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA

3) During risperidone clinical trials, arthralgia was reported in 2% to 3% of adult schizophrenic patients recei

RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod solution, 2007).

3.3.8.C Decreased bone mineral density

1) In a small study, decreased bone mineral density was observed in female, premenopausal schizophrenia (n=12; 3 to 6 milligrams (mg)/day for at least 24 months), but not in those receiving olanzapine (n=14; 15 to 2 Age-adjusted bone speed of sound was significantly lower in women treated with risperidone as compared w when determined at the radius and phalanx (p less than 0.05), but not the tibia. This effect is most likely due t hyperprolactinemia (Becker et al, 2003).

3.3.8.D Myalgia

1) Incidence: oral, adults, 0% to 2% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipo (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Myalgia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder pa of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipo RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) During risperidone clinical trials, myalgia was reported in 0% to 2% of adult patients receiving oral therapy tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R)

3.3.8.E Pain, in Extremity

1) Incidence: intramuscular, schizophrenia, 2% to 6% (Prod Info RISPERDAL(R) CONSTA(R) long acting inj

2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, pain in extremity was repo risperidone 25 mg long-acting injection (n=99) and 2% of patients receiving risperidone 50 mg long-acting inj 1% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.8.F Summary

1) Arthralgia, myalgia, arthrosis, synostosis, skeletal pain, abnormal gait, and decreases in bone mineral den risperidone therapy (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDA RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9 Neurologic Effects

Akathisia

Cerebrovascular accident

Chorea

Confusion

Disturbance of attention

Dizziness

Dystonia

EEG abnormality

Extrapyramidal disease

Headache

Insomnia

Paresthesia

Parkinsonism

Reduced sensation of skin

Seizure

Somnolence

Stuttering

Summary

Tardive dyskinesia

Transient ischemic attack

Tremor

3.3.9.A Akathisia

1) Incidence: oral, adults, 5% to 9%; children, up to 10% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod
orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni
RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) In a 12-week placebo-controlled trial of adult schizophrenic patients, akathisia, including restlessness
patients receiving 25 mg (n=99) and 50 mg (n=103) of risperidone intramuscular therapy, respectively, c
(n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). During premarketing risperid
types, akathisia, which includes akathisia and hyperkinesia, was reported in 5% to 9% of adult patients r
RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; P
solution, 2007).

b) A 69-year-old woman suffered protracted akathisia after risperidone withdrawal. The akathisia and pa
with haloperidol therapy, but due to lack of efficacy she was switched to risperidone 1.5 milligrams (mg) t
persisted for 4 months and risperidone was discontinued. Her restlessness became worse during the firs
lorazepam. Five weeks later, propranolol therapy resulted in a gradual resolution of the akathisia (Roseb

3) Pediatric

a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, akathisia oc
with risperidone 1 to 3 mg daily (n=55), 10% treated with 4 to 6 mg daily (n=51), compared with 6% in pla
RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; P
solution, 2007).

b) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, akathisia oc
with risperidone 0.5 to 2.5 mg daily (n=50), 7% in patients treated with 3 to 6 mg daily (n=61), compared
Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20
oral solution, 2007).

3.3.9.B Cerebrovascular accident

1) Incidence: adults, less than 1%, children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Proc
orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) In premarketing oral risperidone clinical trials, cerebrovascular disorder was reported in less than 1% of ac
pediatric patients receiving risperidone therapy. During postmarketing period, cerebrovascular accidents have
of long-acting risperidone injection (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M
2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting inject

3) Cerebrovascular adverse events (stroke, transient ischemic attack) occurred at a significantly higher rate i
85 years of age) who received risperidone compared to those given placebo. Individuals in these 4 placebo-c
97 years of age and were being treated for dementia-related psychosis (Prod Info RISPERDAL(R) oral tablet
(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9.C Chorea

1) In a case report, chorea and tardive dyskinesia were reported in a 13 1/2 year-old female receiving risperi
initiation of risperidone and dose decrease, chorea-like movements were evident. Risperidone was discontinu
were decreased and at month 16, the movement disorder was resolved (Carroll et al, 1999).

3.3.9.D Confusion

1) Incidence: children, 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB or
Prod Info RISPERDAL(R) oral solution, 2007)

2) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associated w
incidence of confusion was 5% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared wi
Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; P
solution, 2007).

3.3.9.E Disturbance of attention

1) Incidence: adults, 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, disturbance in attention w receiving long-acting risperidone intramuscular (n=72) compared with 0% in placebo (n=67) (Prod Info RISPE acting injection, 2009).

3.3.9.F Dizziness

1) Incidence: oral, adults, 4% to 11%; children, 7% to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; Pro orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni 3% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) During a 12-week clinical trial in schizophrenic patients, dizziness was observed in 7% of patients rec acting injection (n=99) and 11% of patients receiving risperidone 50 mg long-acting injection (n=103), co receiving placebo (n=98). In a 24-month, double-blind, placebo-controlled trial of adult bipolar I disorder p in 3% of patients receiving risperidone intramuscular (n=154) as monotherapy compared with 1% in plac RISPERDAL(R) CONSTA(R) long acting injection, 2009). Dizziness was responsible for 1.4% and 1% of schizophrenic adult trials in patients receiving oral therapy with 2 to 8 mg/day (n=366) and in 8 to 16 mg/ respectively, compared with 0% in placebo (n=225).

b) During premarketing risperidone studies of various design types, dizziness was reported in 4% to 10% therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrat RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, dizziness oc with risperidone 1 to 3 mg daily (n=55), 14% treated with 4 to 6 mg daily (n=51), compared with 2% in pla responsible for 2% of discontinuation of therapy in schizophrenic trials including pediatric patients treated Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20 oral solution, 2007).

b) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, dizziness oc with risperidone 0.5 to 2.5 mg daily (n=50), 13% in patients treated with 3 to 6 mg daily (n=61), compared (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007).

c) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of dizziness was 9% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compare (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007).

3.3.9.G Dystonia

1) Incidence: oral, adults, less than 5% to 11%; children, 8% to 18% (Prod Info RISPERDAL(R) oral tablets, M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schiz disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Dystonia, which includes spasm of the neck muscles, sometimes progressing to tightness of the throat, sw and/or protrusion of the tongue, was reported in less than 2% of schizophrenic patients and in less than 4% o premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schi (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Dystonia was reported in 5% to 11% of a therapy, and in 8% to 18% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9.H EEG abnormality

1) In a case report, fifteen days after initiation of risperidone 2 milligrams (mg) per day, a 55-year-old man de symptoms, with EEG (electroencephalogram) revealing bifrontal slow-wave abnormalities (De Leon et al, 199

3.3.9.I Extrapyramidal disease

1) Summary

a) Extrapyramidal symptoms were reported in 7% to 31% of adult patients receiving oral risperidone the risperidone, extrapyramidal symptoms were found to be dose-related (Prod Info RISPERDAL(R) oral tab RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007) extrapyramidal symptoms in patients treated with 25 mg long-acting risperidone injection was comparabl higher in patients receiving 50 mg long-acting risperidone injection (Prod Info RISPERDAL(R) CONSTA(

2) Incidence: adults, 7% to 31% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-T 2007; Prod Info RISPERDAL(R) oral solution, 2007)

3) Adult

a) In a 12-week, double-blind, placebo-controlled trial comparing 3 doses of long-acting risperidone (25 placebo in patients with schizophrenia, the overall incidence of extrapyramidal symptoms in patients trea risperidone injection was comparable to that of placebo but was higher in patients receiving 50 mg long-a Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) In two 8-week, fixed-dose trials of adult schizophrenia patients, extrapyramidal symptoms increased i risperidone dose increased 7% to 31% in 1 mg to 16 mg treatment groups (Prod Info RISPERDAL(R) ora RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

c) A 43-year-old male treated with risperidone 6 milligrams per day presented with episodic blepharospa occurred spontaneously or were brought on by stress requiring him to discontinue driving. The more he t tightly they closed (Ananth et al, 2000).

d) In a review of risperidone studies, factors associated with the development of extrapyramidal sympto increase in severity with higher doses, especially above 8 milligrams (mg)/day (p less than 0.001). Also, extrapyramidal symptom rating scale (ESRS) was associated with a reduction in the severity of EPS (p l noted that worse scores on the ESRS scale correspond with an increased time since diagnosis, especial 1999).

e) A 79-year-old woman treated with risperidone 1 milligram (mg) twice daily for behavior problems asso severe extrapyramidal symptoms when donepezil 10 mg daily was added to her regimen. Risperidone w decreased to 5 mg. There was a complete resolution of symptoms. The authors hypothesize that extrapy to an excess in central acetylcholine while dopamine receptors were blocked (Magnuson et al, 1998).

f) Data from a multicenter comparative study of risperidone, placebo, and haloperidol revealed that rispe extrapyramidal symptoms. Mean changes in Extrapyramidal Symptom Rating Scale (ESRS) scores from significantly lower in each risperidone group than the haloperidol group (P less than 0.001). At 6 milligrar change score was not significantly different from that of the placebo group (Simpson & Lindenmayer, 19

g) A 26-year-old man developed extrapyramidal symptoms the day after starting risperidone 4 milligram breathing which his physician characterized as possible laryngospasm. This resolved after the medicatio later, the patient requested that the risperidone be restarted. Risperidone 2 mg was restarted and after 2 and very distressing tongue movements. The risperidone was decreased to 1 mg and these symptoms s 1997).

h) A 55-year-old man with a left acoustic neurinoma (a manifestation of his neurofibromatosis) develope reaction to risperidone. Over a period of 10 years, he had experienced a gradual deterioration with perio ideation. He was started on risperidone 2 milligrams daily. Fifteen days later, he experienced multiple sy cogwheeling, and slowness. Risperidone was discontinued and he returned to baseline (De Leon et al, 1

i) Acute dystonia with an oculogyric crisis occurred in a 33-year-old male with paranoid schizophrenia d treatment after a period of noncompliance. Following a 2-month period of noncompliance, he restarted ri milligrams (mg) twice daily by the third day of treatment; the next day he experienced intermittent retroc both eyes for 2 hours. The only other medication at the time of this dystonic reaction was clonazepam 3 with benztropine 2 mg IM (intramuscular) and all signs resolved; a second dose was given when he com which resolved 30 minutes after treatment. He continued risperidone, clonazepam, and benztropine 1 m which he discontinued the benztropine. At a 1-month follow-up, there was no further indication of dystoni reaction occurred in a 34-year-old schizophrenic male who was titrated in 3 days up to risperidone 3 milli noncompliant period in which he used crack cocaine. He experienced rigid extremities, mild torticollis, to laryngospasm and was cyanotic. He was treated with diphenhydramine 50 milligrams intravenously with symptoms within 10 minutes. Risperidone dose was decreased to 1 mg twice daily and titrated more slo (Brody, 1996).

j) Acute dystonia occurred in a 17-year-old male with new onset schizophrenia who had been administe twice daily. After 3 doses, he experienced throat restriction, thickening of the tongue, increased salivatio minutes, mild cogwheel rigidity, and stiffness. Risperidone was reduced to 2 mg at bedtime and benztrop Benztropine 2 mg IM was given. Risperidone 2 mg at bedtime and benztropine 2 mg twice daily were giv he showed increased mental and autonomic instability; risperidone was reduced to 2 mg at bedtime, ben and two doses of lorazepam 1 mg were given. All medications were then discontinued and all symptoms Manchanda, 1996).

4) Pediatric

a) A 12-year-old boy, with attention-deficit hyperactivity disorder and psychotic symptoms, developed ex treatment with risperidone and several other drugs. On the day before a laser treatment to remove a birth risperidone 1 milligram (mg) twice daily in addition to sertraline 25 mg per day and methylphenidate 10 m premedications for the procedure included morphine, ketorolac, and tropisetron. Eight hours after the pro of breath, stiffness, difficulty talking and moving, had slurred speech, and was unable to close his mouth. shoulders, neck, and head and progressed to jerking movements of his jaw and arms. He was treated wi for these acute dystonic reactions and his symptoms gradually improved. His risperidone dose was decr ketorolac and tropisetron were eliminated from the premedication regimen (due to potential synergism fo reactions). There was no recurrence of dystonic symptoms during the remaining five laser procedures (T

b) A 7-year-old boy developed hypertonicity of the extremities, confusion, lethargy, and limited tongue m risperidone 1 milligram (mg) for attention deficit hyperactivity disorder. Two doses of diphenhydramine di child recovered the following day (Gesell & Stephen, 1997h).

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.J Headache

1) Incidence: intramuscular, 15% to 21% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, headache was reported in risperidone 25 mg long-acting injection (n=99) and 21% of patients receiving risperidone 50 mg long-acting ir 12% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

3.3.9.K Insomnia

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizop

disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Insomnia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder p of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipo RISPERDAL(R) CONSTA(R) long acting injection, 2009). Insomnia was reported in less than 1% of adult pat in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Proc orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.9.L Paresthesia

1) Incidence: intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPER injection, 2009)
2) Paresthesia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorde trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia anc RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) Six patients (aged 37 to 65 years old) developed burning paresthesias while on risperidone therapy. The l feet, lower body, back, face, arms, throat, and chest. The burning resolved with continued therapy in two cas discontinued in the other 4 cases (Heimberg & Yearian, 1996).

3.3.9.M Parkinsonism

1) Incidence: oral, adults, 0.6% to 20%; children, 2% to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; P orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni 15% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) During risperidone clinical trials, parkinsonism, which includes extrapyramidal disorder, musculoskeletal s bradykinesia, was reported in 8% to 15% of adult patients receiving intramuscular therapy for schizophrenia. muscle rigidity, hypokinesia, cogwheel rigidity, and bradykinesia, was reported in 15% of patients receiving in disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Adult patients receiving oral the in 2% to 16% of pediatric patients receiving oral therapy. Parkinsonism was responsible for 0.4% of discontin adult trials in patients receiving oral therapy with 1 to 6 mg/day (n=448) compared with 0% in placebo (n=424 tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R)
3) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar risk fo parkinsonism as does typical antipsychotic therapy. In a population-based, retrospective cohort study, adults evidence of dementia were followed for up to 1 year for the development of parkinsonism symptoms associat antipsychotic use. As compared with older adults receiving atypical antipsychotic therapy (ie, olanzapine, risp parkinsonism was 30% more likely to occur in those taking typical antipsychotics (ie, chlorpromazine, haloper HR, 1.3; 95% CI, 1.04 to 1.58), and 60% less likely to occur in patients who did not receive either therapy (HF Older adults using higher potency typical antipsychotics had almost a 50% greater risk of experiencing parkin patients prescribed atypical antipsychotics (all were considered lower potency) (HR, 1.44; 95% CI, 1.13 to 1.8 receiving lower potency typical antipsychotics, the risk of developing parkinsonism was no different from that antipsychotics (HR, 0.75; 95% CI. 0.48 to 1.15). In addition, a positive dose-related relationship was observe incident parkinsonism and the use of atypical antipsychotics. The risk for developing parkinsonism was more using a high-dose atypical antipsychotic agent as compared with those prescribed a low-dose atypical antips 1.42 to 3.02). Furthermore, patients taking a typical antipsychotic were found to have a similar risk for the dev patients receiving high-dose atypical antipsychotic therapy (p=ns). The authors conclude that atypical antipsy typical antipsychotics when dose and potency are considered (Rochon et al, 2005).

3.3.9.N Reduced sensation of skin

1) Incidence: intramuscular, schizophrenia, 2% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection,
2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, hypoesthesia was reported risperidone 25 mg long-acting injection (n=99) and 0% of patients receiving risperidone 50 mg long-acting inj 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.9.O Seizure

1) Incidence: 0.3% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally dis Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) During premarketing trials, seizures occurred in 0.3% of patients receiving oral risperidone (9/2607) (Prod 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral sol patients receiving intramuscular risperidone (5/1499) (Prod Info RISPERDAL(R) CONSTA(R) long acting inje with oral therapy were associated with hyponatremia. Risperidone should be used cautiously in patients with RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod solution, 2007; Diaz, 1996).
3) A 64-year-old woman experienced a seizure 2 days after beginning risperidone therapy. She received two 2 mg doses before having a 1-minute generalized tonic-clonic seizure with a 5-minute postictal confusion per risperidone therapy, she also received trimethoprim-sulfamethoxazole for a urinary tract infection and astemiz risperidone was restarted at 0.5 mg/day and increased to 0.5 mg twice daily with control of her psychotic sym (Lane et al, 1998).

3.3.9.P Somnolence

1) Incidence: oral, adults, 5% to 14%; children, 12% to 67% (Prod Info RISPERDAL(R) oral tablets, 2007; Pr orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni

7% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) During risperidone clinical trials of various design types, somnolence was reported in 5% to 6% of adu intramuscular therapy for schizophrenia and 7% in patients with bipolar disorder (Prod Info RISPERDAL(injection, 2009), and in 5% to 14% of adult patients receiving oral therapy. Somnolence was responsible discontinuation of therapy in schizophrenic adult trials in patients receiving oral therapy with 2 to 8 mg/da or greater (n=198), respectively, compared with 0% in placebo (n=225) (Prod Info RISPERDAL(R) oral ta RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

3) Pediatric

a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, somnolence treated with risperidone 1 to 3 mg daily (n=55), 12% treated with 4 to 6 mg daily (n=51), compared with 4 Somnolence was responsible for 2% of discontinuation of therapy in schizophrenic trials including pediat risperidone (n=106) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orall Prod Info RISPERDAL(R) oral solution, 2007).

b) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, somnolence treated with risperidone 0.5 to 2.5 mg daily (n=50), 56% in patients treated with 3 to 6 mg daily (n=61), c (n=58). Somnolence was responsible for 5% of discontinuation of therapy in bipolar mania trials including risperidone (n=111) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orall Prod Info RISPERDAL(R) oral solution, 2007).

c) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of somnolence was 67% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), com (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrati RISPERDAL(R) oral solution, 2007).

3.3.9.Q Stuttering

1) A 32-year-old Korean patient with a prior history of stuttering demonstrated a recurrence of stuttering with day 5 of hospitalization. The dosage was increased to 8 milligrams daily on day 25 and the stuttering was mo auditory hallucinations and idea of reference, the dosage was maintained. On day 48, the stuttering was less

3.3.9.R Summary

1) Stutter, chorea, EEG (electroencephalogram) abnormalities, extrapyramidal symptoms, catatonia, tardive seizures, somnolence, dizziness, insomnia, headache, amnesia, vertigo, stupor, confusion, impaired concent paralysis, torticollis, coma, migraine, withdrawal syndrome, sleep-related eating disorder, and yawning have l administration (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegr RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.9.S Tardive dyskinesia

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizop disorder, up to 6% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Tardive dyskinsia was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar di premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schi (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) During premarketing risperidone studies of various design types, tardive dyskinesia was reported in less t receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

4) In a 52-week, double-blind, placebo-controlled trial in patients with bipolar disorder, dyskinesia was report long-acting risperidone injection (n=72) compared with 3% receiving placebo (n=67) (Prod Info RISPERDAL(injection, 2009).

5) A potentially irreversible tardive dyskinesia may develop in patients receiving antipsychotic drugs; this ma treatment and the cumulative dose. Less commonly, the syndrome can develop after brief treatment periods mask the underlying process by suppressing the signs and symptoms of the syndrome. The prevalence of th highest among the elderly, especially elderly women; however, it is impossible to rely upon prevalence to esti develop the syndrome. The syndrome may remit partially or completely upon discontinuation of the antipsych RISPERDAL(R) CONSTA(R) long acting injection, 2009; Prod Info RISPERDAL(R) oral tablets, oral solution, 2006; Carroll et al, 1999; Saran, 1998; Sakkas et al, 1998; Campbell, 1999; Gwinn & Caviness, 1997; Meco e

6) The use of long-acting risperidone in schizophrenic patients has been associated with a low incidence of e well as improvement in existing dyskinesia. In an open label trial (n=725), patients with stable schizophrenia received long-acting risperidone in 25 mg, 50 mg, or 75 mg intramuscular doses every 2 weeks for up to 50 v via the Extrapyramidal Symptom Rating Scale (ESRS) at months 1, 2, 3, 6, 9, and 12; tardive dyskinesia was "mild" scores or 1 or more "moderate" scores on the ESRS dyskinesia 7-item subscale over at least a 4-week whom ESRS data were available, 530 (80.1%) had no dyskinesia and 132 (19.2%) has existing dyskinesia at tardive dyskinesia was observed in 0.94% (5/530) of patients without dyskinesia at baseline. This represents when adjusted for study drug exposure or when assessed by Kaplan-Meier survival analysis (95% confidence incidence of tardive dyskinesia was similar among all doses, with no observation of a dose-dependent effect. existing at baseline, mean ESRS scores were significantly improved from baseline to endpoint (6.9 vs 4.6, re (Gharabawi et al, 2005).

7) Case Reports

a) Tardive dyskinesia (TD) has been reported in a 24-year-old male following risperidone treatment for T
15, the patient developed repetitive twisting movements of his head and neck. Nine years following the o
diagnosed with TS. He experienced motor and phonic tics, along with obsessional thoughts. Sertraline (5
mg/day) was initiated. No follow-up was available. The patient returned for treatment with identical sympt
and fluoxetine (40 mg/day) were initiated and maintained. His tics were mild, but the patient developed o
movements of the lower jaw after 4 months of treatment. Treatment with risperidone was discontinued a
was initiated. The patient experienced a significant improvement in dyskinetic symptoms within about 45
significantly worsened causing severe distress (Thomas et al, 2009).

b) Tardive dyskinesia (TD) has been reported in a 44-year-old female following risperidone treatment fo
The patient suffered for 4 years with delusions, hallucinations, alogia, and had minimal contact with reali
episode, she was hospitalized and risperidone 4 mg/day was initiated. Symptoms improved, but without
discharge, the patient maintained her risperidone dose without issue for approximately 4 years. Her rispe
mg/day following a worsening of positive psychotic symptoms. Within 2 weeks, she experienced partial r
significant reduction of aggression, hostility and auditory hallucinations. However, the patient reported ab
lips, mouth, tongue, and lower extremities 4 months following the increased risperidone dose. With no fa
disorders and testing results were normal, the patient was diagnosed with neuroleptic-induced TD. Rispe
aripiprazole 15 mg/day, and was gradually discontinued. Her severity of TD started to subside within 2 w
aripiprazole with no reoccurrence of TD or other involuntary movements or psychotic symptoms (Caykoy

c) In a substudy (n=21) of a randomized double-blind, placebo-controlled trial, a 51-year-old female dev
manifested by involuntary tongue movements during maintenance. For the substudy, the mean risperido
first 10 weeks (acute) and 1.36 mg per day (maintenance). During the acute phase, prolactin level was 2
maintenance after 41 weeks from initial risperidone dose, prolactin was 199.6 nanograms/mL. Prolactin r
nanograms/mL after 5.1 years (Hellings et al, 2005).

d) In case reports, risperidone has caused tardive dyskinesias with doses as low as 1 milligrams (mg) d
course of therapy as short as 8 months (Sakkas et al, 1998). In patients with a history of tardive dyskines
their dyskinesia or made it reappear within 1 week of therapy (Sherr & Thaker, 1998). Several more case
risperidone have been reported in the literature (Campbell, 1999).

e) A 69-year-old man with a long history of bipolar disorder developed involuntary oral-buccal-lingual dy
treated with risperidone. A few months after being treated with valproic acid, lorazepam, bupropion, trihe
milligrams (mg) twice daily, he developed involuntary mouth movements, tremor, slowness, and difficulty
risperidone and trihexyphenidyl were discontinued. Three weeks later the movements and parkinsonism
was no rigidity present but the dyskinesia persisted. The patient was then lost to follow-up. The authors b
and parkinsonism was induced by risperidone and that the bupropion may have contributed. However, si
after discontinuation of risperidone, they believe that the risperidone was mostly responsible for these ex
Caviness, 1997).

3.3.9.T Transient ischemic attack

1) Cerebrovascular adverse events (eg, stroke, transient ischemic attack) occurred at a significantly higher ra
age 85 years of age) who received oral risperidone compared to those given placebo. Individuals in these 4 p
from 73 to 97 years of age and were being treated for dementia-related psychosis, which is not an approved
RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod
solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.9.U Tremor

1) Incidence: oral, adults, up to 5% to 6%; children, 10% to 12% (Prod Info RISPERDAL(R) oral tablets, 200
TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizop
disorder, 24% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, tremor was reported i
risperidone 25 mg long-acting injection (n=99) and 3% of patients receiving risperidone 50 mg long-actin
with 0% of patients receiving placebo (n=98). In a 52-week, double-blind, placebo-controlled trial of bipol
reported in 24% of patients receiving long-acting risperidone intramuscular (n=72) compared with 16% ir
RISPERDAL(R) CONSTA(R) long acting injection, 2009). Adult patients receiving oral therapy reported t
(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table
(R) oral solution, 2007).

3) Pediatric

a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, tremor occu
with risperidone 1 to 3 mg daily (n=55), 10% treated with 4 to 6 mg daily (n=51), compared with 6% in pla
RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; R
solution, 2007).

b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa
incidence of tremor was 12% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared
Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20
oral solution, 2007).

3.3.10 Ophthalmic Effects

3.3.10.A Abnormal vision

1) Incidence: oral, adults, 1% to 3%; children, 4% to 7% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod I disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 2% CONSTA(R) long acting injection, 2009)
2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, blurred vision was reporte risperidone 25 mg long-acting injection (n=99) and 3% of patients receiving risperidone 50 mg long-acting inj 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, abnormal vision was reported in 1% to 3% of adult patients receiving oral pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.12 Psychiatric Effects

Agitation

Anxiety

Catatonia

Delirium

Fatigue

Mania

Nocturnal sleep-related eating disorder

Obsessive-compulsive disorder

Summary

3.3.12.A Agitation

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizop disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Agitation was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder pa of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipo RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, agitation was reported in less than 1% of adult patients receiving oral the pediatric patients receiving oral therapy. Agitation was responsible for 1.1% and 1% of discontinuation of ther in patients receiving oral therapy with 2 to 8 mg/day (n=366) and in 8 to 16 mg/day or greater (n=198), respec placebo (n=225) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disinte RISPERDAL(R) oral solution, 2007).
4) Agitation and aggressive reaction occurred in 1% or more (and were at least as frequent among) risperidc mg/day or less) than among placebo-treated patients (Diaz, 1996).

3.3.12.B Anxiety

1) Incidence: oral, adults, 2% to 16%; children, up to 16% (Prod Info RISPERDAL(R) oral tablets, 2007; Proc orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Adult
a) Anxiety was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorde trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia RISPERDAL(R) CONSTA(R) long acting injection, 2009).
b) During risperidone clinical trials, anxiety was reported in 2% to 16% of adult patients receiving oral th M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
3) Pediatric
a) In a 6-week double-blind, placebo-controlled trial in pediatric patients with schizophrenia, anxiety occ with risperidone 1 to 3 mg daily (n=55), 6% treated with 4 to 6 mg daily (n=51), compared with 0% in pla responsible for 1% of discontinuation of therapy in schizophrenic trials including pediatric patients treate Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20 oral solution, 2007).
b) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, anxiety occu

with risperidone 0.5 to 2.5 mg daily (n=50), 8% in patients treated with 3 to 6 mg daily (n=61), compared
Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20
oral solution, 2007).

c) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa
incidence of anxiety was 16% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compare
(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table
(R) oral solution, 2007).

3.3.12.C Catatonia

1) A 61-year-old schizophrenic woman developed catatonia after beginning risperidone 2 milligrams (mg) da
frontal lobotomy 36 years previously. She had been receiving fluphenazine decanoate 25 mg intramuscularly
her last dose, she began risperidone which was increased to 5 mg. Catatonic symptoms worsened and she v
placed on clozapine. Her catatonia subsided within 5 days (Bahro et al, 1999).

3.3.12.D Delirium

1) Three cases of possible risperidone-induced delirium were reported in patients aged 71, 83, and 83 years
being treated for major depression with psychotic features. In each case, the mania abated after risperidone
acknowledge that the delirium may have been multifactorial in etiology, however, risperidone use appeared t
Springer et al, 1998).

2) An 85-year-old woman with schizophreniform disorder was treated with risperidone 1 milligrams (mg) dail
twice daily after 4 days with resultant delirium. The woman was restless, disoriented, and hallucinating. Rispe
recovered after 18 hours (Tavcar & Dernovsek, 1998).

3.3.12.E Fatigue

1) Incidence: oral, adults, 1% to 3%; children, 18% to 42% .(Prod Info RISPERDAL(R) oral tablets, 2007; Pr
orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni
RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adults

a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, fatigue, which include
patients receiving risperidone 25 mg long-acting injection (n=99) and 9% of patients receiving risperidon
(n=103), compared with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R)

b) During risperidone clinical trials, fatigue was reported in 1% to 3% of adult patients receiving oral ther
oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPER

3) Pediatrics

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, fatigue occu
with risperidone 0.5 to 2.5 mg daily (n=50), 30% in patients treated with 3 to 6 mg daily (n=61), compare
(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table
(R) oral solution, 2007).

b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa
incidence of fatigue was 42% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compare
(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table
(R) oral solution, 2007).

3.3.12.F Mania

1) Mania has been reported during postmarketing use of risperidone (Prod Info RISPERDAL(R) oral tablets,
M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDA
injection, 2009).

2) A review of the literature identified 16 cases of mania related to risperidone therapy. Patients were treated
schizoaffective, bipolar type, mixed (n=2); schizoaffective, bipolar type, depressed (n=4); schizophrenia (n=5
(n=2); recurrent depression, psychotic (n=1); and bipolar type I, manic (n=2). The onset of development of ma
40 days. Five of 16 patients were receiving no other medications and in 6 cases it wasn't determined if there
Two patients received valproate, 1 lithium, and 1 haloperidol concomitantly, which makes causality difficult to
was continued and manic symptoms resolved without treatment. On 7 occasions, risperidone was discontinu
instances, risperidone was either continued with antimanic medications or reduced in dosage, or both. Remis
occurred within 2 to 14 days, although there was one case where it took 60 days for manic symptoms to reso

3) Four cases of mania developing after beginning risperidone therapy were presented. Two patients were tr
risperidone 5 and 6 milligrams (mg) while 1 patient was treated for schizoaffective disorder with risperidone 2
of the most predominant symptoms. In 1 patient, only risperidone discontinuation was needed to resolve the
patient, carbamazepine, benzodiazepines, and neuroleptics were required for control. In the schizoaffective p
(Zolezzi & Badr, 1999).

4) Mania occurred in a 50-year-old male with chronic schizophrenia and mild mental retardation. He had bee
risperidone was started and titrated to 9 milligrams/day (mg/day) within 12 days. Forty days later he exhibited
was reduced to 6 mg/day and clonazepam 2 mg was initiated. A week later the patient was hospitalized and,
treated with lithium, valproic acid, and haloperidol until the mania resolved (Diaz, 1996).

5) Three cases of mania developing within days of starting risperidone therapy were reported. The patient's
schizoaffective disorder, one with schizophrenia, and one with bipolar I disorder. Risperidone was discontinu
decreased in the last 2 patients with resolution of symptoms (Schnierow & Graeber, 1996).

3.3.12.G Nocturnal sleep-related eating disorder

1) Risperidone-induced sleep-related eating disorder was observed in a 68-year-old man following the admir treatment of vascular dementia. The patient's psychotic symptoms resolved after his daily dose of risperidone (mg) to 2 mg; however, he began experiencing sleep disturbances almost nightly, including episodes during v quantities of food while asleep. These episodes persisted for 2 months and then quickly resolved when the d (Lu & Shen, 2004).

3.3.12.H Obsessive-compulsive disorder

1) A schizophrenic man developed obsessive imagery after being treated with risperidone 4 milligrams/day (also receiving valproate, trihexyphenidyl, and zuclopenthixol. He repeatedly saw the image of a person's face This disappeared after the dosage of risperidone was decreased to 3 mg/day (Mahendran, 1999).

2) A 26-year-old woman with schizophrenia developed obsessive-compulsive symptoms after 2 weeks of risp receiving risperidone 4 milligrams (mg) daily when she experienced excessive thoughts about playing mahjor mg without success. Clomipramine 25 mg was added and the ruminations disappeared. The clomipramine w weeks and she was maintained on risperidone 1 mg daily (Mahendran, 1998).

3.3.12.I Summary

1) Nervousness, depression, psychosis, apathy, delusion, euphoria, emotional lability, and delirium have bee risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally dis Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.13 Renal Effects

Hemorrhagic cystitis

Urinary incontinence

3.3.13.A Hemorrhagic cystitis

1) An 11-year-old boy with significant behavioral problems developed hemorrhagic cystitis 1 week after begi medications included fluoxetine, valproic acid, benztropine, haloperidol, clonidine, trazodone, and nasal desm acute onset of dysuria and increased frequency with gross hematuria. There were no signs of viral illness and Ultrasonography showed a thickened bladder wall and mild hydronephrosis. Symptoms were not relieved wit sulfamethoxazole. Risperidone was withdrawn and symptoms resolved within a week. At a 1-month follow-up and ultrasonography showed a normal thin-walled bladder (Hudson & Cain, 1998).

3.3.13.B Urinary incontinence

1) Incidence: oral, adults, 2%; children, up to 22% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RI disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) Urinary incontinence was reported in less than 2% of schizophrenic patients and in less than 4% of bi premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) During risperidone clinical trials, urinary incontinence was reported in 2% of adult patients receiving o RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; F solution, 2007).

c) There was a temporal correlation with risperidone therapy and urinary incontinence in 2 case reports. incontinence with risperidone 4 milligrams daily. Upon discontinuation of risperidone, urinary incontinenc

3) Pediatric

a) In a 3-week double-blind, placebo-controlled trial in pediatric patients with bipolar mania, urinary inco patients treated with risperidone 0.5 to 2.5 mg daily (n=50), 5% in patients treated with 3 to 6 mg daily (n placebo (n=58) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally dis Info RISPERDAL(R) oral solution, 2007).

b) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of urinary incontinence was 22% in patients treated with oral risperidone 0.5 to 4 mg daily (n=7 placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally dis Info RISPERDAL(R) oral solution, 2007).

3.3.14 Reproductive Effects

Abnormal ejaculation

Absence of ejaculation

Amenorrhea

Erectile dysfunction

Priapism

Summary

3.3.14.A Abnormal ejaculation

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizop disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Ejaculation disorder was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schi (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) During risperidone clinical trials, ejaculation disorder was reported in less than 1% of adult patients receivi 5% of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPE disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

4) A large study comparing 5 fixed-doses of oral risperidone revealed a positive dose-related trend (p less th dysfunction among patients receiving oral risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; F orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

5) Two cases of probable retrograde ejaculation were attributed to risperidone treatment. A 36-year-old Afric old Caucasian man, being treated with risperidone 6 milligrams (mg) and 3 mg per day, respectively, were pc was later determined that their poor compliance was due to concern over an absence of semen with ejaculati

6) The absence of ejaculation was reported in 2 male patients treated with risperidone. In one patient, ejacul spontaneously after 4 weeks of risperidone treatment. In the other patient, absence of ejaculation was still pr of risperidone (Raga, 1999).

7) A 38-year-old man experienced ejaculatory dysfunction and dysuria one week after starting risperidone. H genitourinary problems. On day 12 of treatment, risperidone was discontinued with symptoms resolving 2 day rechallenge with risperidone and symptoms recurred in 2 days. (Madhusoodanan & Brenner, 1996).

3.3.14.B Absence of ejaculation

1) Incidence: adults, 0.1% to 1% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M- 2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) During risperidone clinical trials, ejaculation failure was reported in up to 1% of adult patients receiving ora (R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPER

3.3.14.C Amenorrhea

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, bipolar (RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, amenorrhea was reporte acting risperidone injection (n=72) compared with 1% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA During risperidone clinical trials, amenorrhea was reported in less than 1% of adult patients receiving oral the pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Five psychiatric patients developed amenorrhea with elevated serum prolactin levels on risperidone 1 to 8 menstruation resumed upon discontinuation; menstruation resumed in case 5 after tapering risperidone (Kim

3.3.14.D Erectile dysfunction

1) Incidence: intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPER injection, 2009)

2) Erectile dysfunction was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar premarketing trials of various design types in patients receiving long-acting intramuscular risperidone for schi (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) A large study comparing 5 fixed-doses of oral risperidone revealed a positive dose-related trend (p less th among patients receiving oral risperidone therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RIS disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.14.E Priapism

1) Incidence: adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Proc orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

2) During risperidone clinical trials, priapism was reported in less than 1% of adult patients receiving oral the pediatric patients receiving oral therapy. Also, there have been reports of priapism with the use of risperidone postmarketing period (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally d

Info RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) An African American male developed priapism on two occasions after receiving risperidone and again afte
treatment of schizophrenia. Following risperidone treatment (4 milligrams (mg) twice daily), the man develope
which resolved upon irrigation of the corpora with phenylephrine 200 micrograms. Following discontinuation c
developed another unwanted erection after an increase in his ziprasidone dose from 20 mg twice daily to 40 r
lasted 2 hours and resolved upon urination. He experienced several more unwanted erections until the zipras
priapism quickly resolved (Reeves & Mack, 2002).
4) A 47-year-old African American man developed priapism after taking risperidone 2 milligrams twice daily f
prolonged painful erections multiple times in the past few weeks. Physical and laboratory examinations revea
the erect penis. Penile irrigation with normal saline and phenylephrine injection caused detumescence. Rispe
other antipsychotic treatment was started. One month later, he reported spontaneous, partial rigid erection (A
5) A 26-year-old Hispanic man had a 5-day episode of persistent erection, dysuria, and urinary incontinence.
been receiving for one year, included risperidone, 3 milligrams (mg)/day and divalproex sodium 1500 mg/day
mood and psychotic symptoms. His erection persisted despite two corpora cavernosa irrigations with phenyle
venous blood gas analysis was consistent with a diagnosis of low-flow priapism. A cavernosal glandular shun
cavernosum/corpus spongiosum shunt were performed. As there have not been any previously reported insta
divalproex use, the authors assumed that risperidone was the likely cause of the condition (Bourgeois and Mu

3.3.14.F Summary

1) Amenorrhea, dysmenorrhea, erectile dysfunction, priapism, and ejaculation failure have been reported in p
therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating t
RISPERDAL(R) oral solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.15 Respiratory Effects

Cough

Dyspnea

Pharyngitis

Pulmonary embolism

Rhinitis

Sinusitis

Summary

Upper respiratory infection

3.3.15.A Cough

1) Incidence: oral, adults, 3%; children, 24% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERI
disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 2%
(Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, cough was reported in 4%
25 mg long-acting injection (n=99) and 2% of patients receiving risperidone 50 mg long-acting injection (n=10
receiving placebo (n=98). In a 52-week, double-blind, placebo-controlled trial of bipolar I disorder patients, co
patients receiving long-acting risperidone injection (n=72) compared with 1% in placebo (n=67) (Prod Info RIS
acting injection, 2009).
3) During risperidone clinical trials, coughing was reported in 3% of adult patients receiving oral therapy, and
receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally d
Info RISPERDAL(R) oral solution, 2007).

3.3.15.B Dyspnea

1) Incidence: oral, adults, 2%; children, 2% to 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RIS
disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less
than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Dyspnea was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder pa
of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipo
RISPERDAL(R) CONSTA(R) long acting injection, 2009).
3) During risperidone clinical trials, dyspnea was reported in 2% of adult patients receiving oral therapy, and
receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally d

Info RISPERDAL(R) oral solution, 2007).

3.3.15.C Pharyngitis

1) Incidence: oral, adults, 5% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less than 2%; bipolar I dis RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Pharyngitis was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder trials of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) During clinical trials, pharyngitis was reported in 5% of adult patients receiving risperidone oral therapy co (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2 oral solution, 2007).

3.3.15.D Pulmonary embolism

1) A case report described 3 episodes of pulmonary embolism in a 25-year-old man after treatment with olan early-onset schizoaffective disorder. His physical health was generally good and there was no personal or fa overweight nor had his weight or physical activity level changed under neuroleptic medication. Smoking a pa only known cardiovascular risk factor. His antipsychotic therapy included olanzapine 20 mg/day, paroxetine 2 2000 mg/day for his psychotic symptoms. After 12 weeks of treatment, the patient presented with a complain the left front part of his thorax. Over the next few hours, he became short of breath and experienced an episo revealed bilateral pulmonary embolism. Ultrasound of the lower extremities showed no signs of DVT. His coa demonstrate any abnormalities. Olanzapine was discontinued and oral warfarin treatment with a target INR o initiated and maintained for 6 months. Twelve weeks after olanzapine was discontinued, he was initiated on r recurrence of psychotic symptoms. After 3 weeks of risperidone treatment, the patient presented with chest p hemoptysis. Multiple peripheral pulmonary emboli were observed on a chest spiral CT scan. Concomitant DV out. Nonadherence to warfarin treatment (evidenced by low INR) appeared to be the cause of this second ep Therefore, warfarin was reinitiated under close supervision to confirm adherence. Sixteen weeks later, the pa and dyspnea. Spiral chest CT scan and Doppler ultrasound of the lower limbs indicated bilateral pulmonary e lower limbs. Because antipsychotic agents appeared to be the causal factor of the pulmonary emboli, the pat anticoagulant therapy and amisulpride 400 mg/day which resulted in improvement in his condition. Paroxetin mg/day therapy was continued after being maintained throughout the 3 episodes of pulmonary embolism (Bo

3.3.15.E Rhinitis

1) Incidence: oral, adults, 2% to 11%; children, 13% to 36% (Prod Info RISPERDAL(R) oral tablets, 2007; Pr orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophreni disorder, less than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Rhinitis was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder pat various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipolar (R) CONSTA(R) long acting injection, 2009).

3) During risperidone clinical trials, rhinitis was reported in 2% to 11% of adult patients receiving oral therapy patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TA 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3.3.15.F Sinusitis

1) Incidence: intramuscular, schizophrenia, less than 2%; bipolar I disorder, less than 4% (Prod Info RISPER injection, 2009)

2) Sinusitis was reported in less than 2% of schizophrenic patients and in less than 4% of bipolar disorder pa of various design types in patients receiving long-acting intramuscular risperidone for schizophrenia and bipo RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3.3.15.G Summary

1) Rhinitis, coughing, sinusitis, pharyngitis, dyspnea, stridor, pneumonia, and aspiration have been reported Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; F solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). A case report described t embolism in a 25-year-old man following oral risperidone therapy. The patient experienced improvement afte and anticoagulation therapy was initiated (Borras et al, 2008).

3.3.15.H Upper respiratory infection

1) Incidence: oral, adults, 2% to 3%; children, 34% (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info R disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, 0% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) Adult

a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, upper respiratory tract patients receiving risperidone 25 mg long-acting injection (n=99) and 0% of patients receiving risperidon (n=103), compared with 1% of patients receiving placebo (n=98). In a 52-week, double-blind, placebo-co patients, upper respiratory tract infection was reported in 6% of patients receiving long-acting risperidone 3% in placebo (n=67) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Upper respira in 2% to 3% of adult patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod In

disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

3) Pediatric

a) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa incidence of upper respiratory tract infection was 34% in patients treated with oral risperidone 0.5 to 4 m 15% in placebo (n=80) (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB c Prod Info RISPERDAL(R) oral solution, 2007).

3.3.16 Other

Angioedema

Death

Drug withdrawal

Extrapyramidal disease

Fever

Neuroleptic malignant syndrome

Opioid withdrawal

Pain, General

3.3.16.A Angioedema

1) Angioedema has been reported during postmarketing use of risperidone (Prod Info RISPERDAL(R) oral ta RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Proc (R) long acting injection, 2009).

2) A 63-year-old woman, who had been hospitalized for 36 years with paranoid schizophrenia, developed pe occasions when risperidone was added to her continuing therapy. In all instances, the edema disappeared w discontinuation of risperidone. The first time, risperidone 2 milligrams (mg) daily, titrated to 6 mg/day over 2 w regimen of fluphenazine, biperiden, and bromazepam. Periorbital edema occurred after 1 month and faded 1 risperidone, with all other medications maintained. A year later, risperidone 6 mg/day was again introduced, a promethazine, biperiden, clonazepam, and nitrazepam; after 45 days moderate periorbital and orbital edema promethazine did not alter the edema. Discontinuation of risperidone resulted in disappearance of the edema risperidone was reintroduced at 3 mg/day. After 3 weeks, angioedema occurred, affecting the lips, face, neck difficult. She was given intensive anti-allergenic therapy and risperidone was discontinued. The edema dimini completely in 4 days (Plesnicar et al, 2001).

3.3.16.B Death

1) Sudden death has been reported in postmarketing use of oral risperidone (Prod Info RISPERDAL(R) oral RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

2) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antip even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisor matched pairs were identified and the dementia cohort was stratified based on place of residence (community In order to adjust for difference in baseline health status, propensity score matching was used. The primary o cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medica There was a statistically significant increase in the risk for death at 30 days associated with new use of atypic compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confide absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist associated with conventional antipsychotics was even greater than the risk identified with atypical antipsycho for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the lor difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Son study include unknown or unmeasured confounders may influence the results and cause of death could not b

3) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater ris use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypica analysis excluded patients with cancer and included only new users of antipsychotic medications. The primar all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1

atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-v
for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional ve
1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were com
mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.
difference associated with olanzapine. The increased mortality risk for conventional versus atypical drug thera
higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40
1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score
estimation confirmed the results of the study (Schneeweiss et al, 2007).
4) The findings of one meta-analysis suggest that there may be a small increased risk of death associated w
antipsychotic agents for the treatment of dementia in elderly patients. The study analysis (n=5110), including
placebo-controlled, parallel group trials of antipsychotic use (ie, aripiprazole (n=3), olanzapine (n=5), quetiapi
elderly patients (weighted mean age, 81.2 years) with dementia, found that death occurred more often in pati
antipsychotic therapy as compared with placebo (118 (3.5%) vs 40 (2.3%), respectively). The overall odds ra
analysis, for death in elderly patients receiving atypical antipsychotics as compared with placebo was 1.54 (9
to 2.23; p=0.02), and the risk difference was 0.01 (95% CI, 0.004 to 0.02; p=0.01). Overall, the relative risk as
antipsychotic use was 1.65 (95% CI, 1.19 to 2.29; p=0.003); however this increased risk was only identified w
analysis; meta-analyses of individual drugs did not show a statistically significant increased risk. A similar dro
antipsychotic- and placebo-treated patients (32.2% vs 31.4%, respectively), with no significant difference in d
(Schneider et al, 2005).
5) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as l
agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,14
agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher ad
associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all time pc
therapy (within 180 days: relative risk (RR), 1.37; 95% confidence interval (CI), 1.27 to 1.49; less than 40 day
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 addit
observed in patients with dementia (RR, 1.29; 95% CI, 1.15 to 1.45), without dementia (RR, 1.45; 95% CI, 1.3
(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
antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and
higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Addit
investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriat
intervention can be provided (Wang et al, 2005).

3.3.16.C Drug withdrawal

1) A 38-year-old man with long-standing schizophrenia unresponsive to conventional therapy received an un
which resulted in mania when the drug was withdrawn. He had been increased to risperidone 2 milligrams (m
tachycardia, tremor, and akathisia. After a taper, his hallucinations and delusions reoccurred but with manic s
Risperidone 1 mg twice daily was reinitiated with resolution of his psychotic symptoms and his mania (Lane &

3.3.16.D Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.E Fever

1) Incidence: oral, adults, 1% to 2%; children, 20% .(Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info R
disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizophrenia, less
than 4% (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009)
2) Adult
a) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, pyrexia was reported
risperidone 25 mg long-acting injection (n=99) and 1% of patients receiving risperidone 50 mg long-actin
with 0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injectio
b) During risperidone clinical trials, fever was reported in 1% to 2% of adult patients receiving oral thera
tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDA
3) Pediatric
a) In two 8-week double-blind, placebo-controlled trials in pediatric patients treated for irritability associa
incidence of fever was 20% in patients treated with oral risperidone 0.5 to 4 mg daily (n=76), compared v
Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20
oral solution, 2007).

3.3.16.F Neuroleptic malignant syndrome

1) Incidence: adults, less than 1%; children, less than 5%(Prod Info RISPERDAL(R) oral tablets, 2007; Prod
orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)
2) Neuroleptic malignant syndrome has been reported in patients receiving long-acting risperidone injection
CONSTA(R) long acting injection, 2009)
3) During premarketing risperidone studies of various design types, neuroleptic malignant syndrome was rep
patients receiving oral therapy, and in less than 5% of pediatric patients receiving oral therapy (Prod Info RIS
Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2
4) Neuroleptic malignant syndrome (NMS), with hyperpyrexia, muscle rigidity, autonomic instability, altered n
levels, myoglobinuria, and acute renal failure cannot be excluded as a side effect of risperidone therapy. If ne
does occur, all antipsychotic medications and other drugs not essential to concurrent therapy should be disco

and medical monitoring should be initiated, and treatment of any concomitant serious medical problems shou
reintroduction of antipsychotics after a patient has experienced NMS should be taken; recurrences have beer
RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod
solution, 2007; Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

5) Adult

a) A 27-year-old male developed neuromuscular malignant syndrome 21 months after being treated with
daily (Lee et al, 2000).

b) A 47-year-old man developed neuroleptic malignant syndrome after the administration of risperidone
(diazepam) withdrawal period. Symptoms abated over the next 9 days after discontinuation of risperidon
bromocriptine, and diazepam (Bobolakis, 2000).

c) A 73-year-old woman developed neuroleptic malignant syndrome while on monotherapy with risperid
daily for multiinfarct dementia. Symptoms resolved after discontinuation (Gleason & Conigliaro, 1997).

d) Two cases of neuroleptic malignant syndrome (NMS) were reported in which each patient developed
beginning risperidone 6 milligrams/day (mg/day). The drug was discontinued and both patients were trea
symptoms resolved in 7 and 10 days, respectively. One of these patients was restarted on risperidone 1
returned within 24 to 36 hours. The drug was again discontinued and the symptoms resolved within 72 h
1996). Five previously reported cases of risperidone-associated NMS had histories of extrapyramidal sid
various antipsychotic drugs; two of the patients had experienced a previous episode of NMS (Meterissiar

6) Pediatric

a) Neuroleptic malignant syndrome (NMS) has been reported in a 13-year-old male following risperidone
(JS). The patient was admitted for agitation, fever, diaphoresis, and extremity spasms, including his neck
risperidone 0.5 mg/day and clonazepam 0.1 mg/kg/day for subsequent dystonia. Due to fever, rigidity, ar
elevated CPK levels (1200 units/L), he was diagnosed with risperidone-associated NMS. Risperidone wa
intravenous hydration, biperidene lactate, cold compresses, and paracetamol treatment. His agitation, sv
CPK (390 units/L) improved, and he was discharged normalized biochemical results on the fourth day (V

3.3.16.G Opioid withdrawal

1) Two patients receiving stable doses of opioids experienced withdrawal symptoms 3 days after beginning r
over 2 days following discontinuation of risperidone (Wines & Weiss, 1999d).

3.3.16.H Pain, General

1) Incidence: oral, adults, less than 1%; children, less than 5% (Prod Info RISPERDAL(R) oral tablets, 2007;
TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007); intramuscular, schizop
RISPERDAL(R) CONSTA(R) long acting injection, 2009)

2) During a 12-week, double-blind, placebo-control trial of schizophrenic patients, generalized pain was repo
risperidone 25 mg long-acting injection (n=99) and 1% of patients receiving risperidone 50 mg long-acting inj
0% of patients receiving placebo (n=98) (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

3) During risperidone clinical trials, generalized pain was reported in less than 1% of adult patients receiving
of pediatric patients receiving oral therapy (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDA
tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

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 RISPERDAL(R) oral tablets,
(R) orally disintegrating tablets, 2008) (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other)
studies in women or studies in women and animals are not available. Drugs should be given only if the poten
risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: B3(Australian Drug Evaluation Committee, 1999)

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing ag
frequency of malformation or other direct or indirect harmful effects on the human fetus having been observe
evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in hu

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) Risperidone should be used during pregnancy only after consideration is given to the potential benefit to t
to the fetus. It is recommended that patients notify their physician if they become pregnant or intend to becom
treatment (Prod Info RISPERDAL(R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tab

5) Literature Reports

a) A prospective, observational study of 54 women (mean age, 30.7 years) recruited from the Emory Womer
exposed to antipsychotic medication during pregnant showed permeability of the placental barrier. Outcomes
and umbilical cord blood samples taken at delivery and through data collected from maternal reports and me
showed a significant difference between antipsychotic medications, olanzapine 72.1% (95% CI, 46.8%-97.5%
haloperidol 65.5% (95% CI, 40.3%-90.7%), risperidone 49.2% (95% CI, 13.6%-84.8%), and quetiapine 24.1%
showing the lowest placental passage. In the risperidone group, there were no reports of preterm labor or infa
care admission. Of the 6 infants with maternal risperidone exposure, one infant weighed less than 2500 g (Ne

b) A review of pooled data from the Benefit Risk Management Worldwide Safety database found no increase
abortions, structural malformations, or fetal teratogenic risk from in utero exposure to risperidone. The volunta

197 retrospective) of drug exposure during pregnancy identified 713 pregnancies in women with psychiatric il during pregnancy. Of the 68 prospective pregnancies reported with known outcome, organ malformations (3. (16.9%) were documented (non-medically induced abortions excluded). Third-trimester exposure to risperido withdrawal, or possible withdrawal-emergent syndrome (WES) in 13 retrospectively reported cases. The stud neurodevelopmental outcomes in the neonate and developing child. In addition, many of the reports were co medications, several of which are known teratogens (Coppola et al, 2007).

c) A case report described two successive, normal pregnancies in a 23-year-old woman receiving risperidon unplanned yet uneventful pregnancy 6 months after starting risperidone 3 mg/day for treatment of schizophre at 39 weeks gestation and delivered a healthy baby girl weighing 3.2 kg. There were no postnatal complicatic risperidone dose was decreased to 2 mg/day due to mental stability. Nine months later, she became pregnar the 2 mg/day dose of risperidone without prenatal complications. Following spontaneous labor at 39 weeks, s weighing 3 kg. Both of the infants were breastfed for 6 months. The children did not show any signs of neuro behavioral problems at 36 and 18 months of age, respectively (Mendhekar & Lohia, 2008).

d) A case report described a normal pregnancy and healthy baby born to a middle-aged woman with schizo risperidone prior to and throughout her pregnancy. Successfully maintained for 7 years on risperidone, her do from 3 mg/day to 1 mg/day at 6 months' gestation, then to 0.5 mg/day a few days prior to delivery. The baby remained healthy over the first 3 months of life (Rodriguez-Salgado, 2008).

e) One case report of agenesis of the corpus callosum in an infant exposed in utero to risperidone has been risperidone has not been established. In postmarketing surveillance, following use of risperidone in the last tr extrapyramidal symptoms have been observed in the neonate (Prod Info RISPERDAL(R) oral tablets, solutio orally disintegrating tablets, 2008).

B) Breastfeeding

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

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

2) Clinical Management

a) In animal and human lactation studies, risperidone and its active 9-hydroxy metabolite are excreted into b (R) oral tablets, solution, RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008). It is estimated that a 0.84% of the maternal dose as risperidone and an additional 3.46% from 9-hydroxyrisperidone (as risperidon amount is not likely to result in sedation or extrapyramidal side effects in a full-term or older infant, the possib effects, such as neuroleptic malignant syndrome, should not be overlooked (Hill et al, 2000). Because risperi women should not breastfeed during treatment with risperidone (Prod Info RISPERDAL(R) oral tablets, soluti orally disintegrating tablets, 2008).

3) Literature Reports

a) One case report described a 21-year-old woman who was treated postpartum with risperidone. She was a infant. After a gradual increase in maternal dose to 6 mg/day, she agreed to provide serial samples (over 24 so that risperidone and 9-hydroxyrisperidone could be measured. The milk to plasma ratios calculated from t risperidone and the active metabolite, respectively (Hill et al, 2000).

4) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.42 (Hill et al, 2000)

b) Active Metabolites

1) 9-hydroxyrisperidone (Prod Info Risperdal(R), 1999)

a) Milk to Maternal Plasma Ratio

1) 0.24 (Hill et al, 2000)

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Acecainide

Ajmaline

Amiodarone

Amisulpride

Amitriptyline

Amoxapine

Aprindine

Arsenic Trioxide

Astemizole

Azimilide

Bepridil

Bretylium

Bupropion

Carbamazepine

Chloral Hydrate

Chloroquine

Chlorpromazine

Cimetidine

Cisapride

Clarithromycin

Clozapine

Darunavir

Dehydroepiandrosterone

Desipramine

Dibenzepin

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Encainide

Enflurane

Erythromycin

Flecainide

Fluconazole

Fluoxetine

Foscarnet

Gemifloxacin

Ginkgo Biloba

Halofantrine

Haloperidol

Halothane

Hydroquinidine

Ibutilide

Imipramine

Isoflurane

Isradipine

Itraconazole

Lamotrigine

Levodopa

Levomethadyl

Levorphanol

Lidoflazine

Linezolid

Lithium

Lorcainide

Mefloquine

Mesoridazine

Methadone

Midodrine

Nortriptyline

Octreotide

Paroxetine

Pentamidine

Phenobarbital

Phenylalanine

Phenytoin

Pimozide

Pirmenol

Prajmaline

Probucol

Procainamide

Prochlorperazine

Propafenone

Protriptyline

Quetiapine

Ranitidine

Rifampin

Ritonavir

Ropinirole

Sematilide

Sertindole

Simvastatin

Sotalol

Spiramycin

Sulfamethoxazole

Sultopride

Tedisamil

Telithromycin

Terfenadine

Tetrabenazine

Thioridazine

Topiramate

Tramadol

Trifluoperazine

Trimethoprim

Trimipramine

Valproic Acid

Vasopressin

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 risperidone is not recommended due to the risk of additive e concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of acecainide and risperidone is not recommended d life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring i
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 fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as acecainide and risperidor 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, halop quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets 1999z; O'Brien et al, 1999q; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001ab; Du et al, 2001v; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetma antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent a with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinag
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
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), iloperic 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 ther 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study de in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol tre under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/ peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on com and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors is more likely responsible for the plasma level changes than an elimination 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 risperidone is not recommended due to the risk of additive concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of amiodarone and risperidone is not recommended life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring i
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 fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as amiodarone and risperidc the 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: Coadministration of amisulpride with other drugs that potentiallly prolong the QTc interval, such approached with caution (Prod Info Solian(R), 1999n; Prod Info Risperdal(R), 2002b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as amisu 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 rispe Laita et al, 1999r; Ravin & Levenson, 1997f; Gesell & Stephen, 1997b; Lo Vecchio et al, 1996b; Brown e

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 haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stuc coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis 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 haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stuc coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis 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 risperidone with other drugs that potentially prolong the QTc interval, such approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is a Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of aprindine and risperidone is not recommended du threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
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 ventricular ta and torsades de pointes and should not be administered with other drugs that may prolong the QT interval (P Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), al, 1999i), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-La (Agelink et al, 2001m), quetiapine (Owens, 2001r), sultopride (Lande et al, 1992o), ziprasidone (Prod Info GE 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 recomme
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 pointe block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treate evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc in Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then re end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more 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 I haloperidol (O'Brien et al, 1999h), quetiapine (Owens, 2001p), risperidone (Duenas-Laita et al, 1999q; Prod I 2002a), sertindole (Agelink et al, 2001l), sultopride (Lande et al, 1992n), and zotepine (Sweetman, 2003). Ev interaction studies have been done, the coadministration of astemizole and other drugs known to prolong the 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 interva 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 doses (I et al, 1993c). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidc delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac haloperidol. Four patients developed the dysrhythmia after administration of 170 to 580 mg over 1 to 4 da bacterial meningitis (1), status asthmaticus (2) or respiratory insufficiency (1). All 4 patients recovered wi

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 risperidone is not recommended due to the risk of additive effe concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of azimilide and risperidone is not recommended due threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
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 fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as azimilide and risperidone QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.K 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 which lengthen the QT interval (Prod Info Geodon(TM), 2002a; Agelink et al, 2001c; Owens, 2001e; Prod Info Haldol(R), 1998a). In U.S. clinical trials, bepridil increased QT and QTc intervals which was associated with t approximately 1% of patients. Other drugs that increase the QT interval may exaggerate the prolongation of t bepridil (Prod Info Vascor(R), 1997). Pimozide is contraindicated in patients taking other drugs which may pro Orap(R), 1999d).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT inte contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patient arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pro interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999
b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe Laita et al, 1999e; Ravin & Levenson, 1997a).

3.5.1.L Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of bretylium and risperidone is not recommended due to the risk of additive effe concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of bretylium and risperidone is not recommended du threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
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 fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as bretylium and risperidone QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.M Bupropion

1) Interaction Effect: increased plasma levels of risperidone
2) Summary: It is recommended that risperidone, an antipsychotic metabolized by the cytochrome P450 2D6 lower end of the dose range when administered concomitantly with bupropion (Prod Info Wellbutrin XL(TM), 2
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of bupropion and risperidone should be approached with caution a lower end of the dose range of risperidone. If bupropion is added to the treatment regimen of a patient alread decreasing the dose of risperidone.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated risperidone metabolism

3.5.1.N Carbamazepine

1) Interaction Effect: increased risperidone clearance
2) Summary: The manufacturer reports that carbamazepine may increase risperidone clearance with chronic be closely monitored. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before th carbamazepine therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hy subjects received risperidone titrated to 6 mg/day orally for 3 weeks, followed by coadministration of carbama Plasma concentrations of risperidone and 9-hydroxyrisperidone were decreased by 50%. The plasma concer unaffected (Prod Info Risperdal(R) Consta(TM), 2003a). One published case report describes a patient who h less than expected during carbamazepine therapy, along with decreased risperidone efficacy. The risperidon when carbamazepine was discontinued (de Leon & Bork, 1997a). Carbamazepine is an inducer of cytochrom while risperidone is primarily metabolized by CYP2D6. Whether carbamazepine is also inducing CYP2D6 or partly metabolized by CYP3A is uncertain (Lane & Chang, 1998; de Leon & Bork, 1998). The marked decrea by carbamazepine may result in decreased therapeutic efficacy. When risperidone is used in combination wit risperidone may be required to achieve or maintain a desired antipsychotic effect (Spina et al, 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of carbamazepine

therapy; higher risperidone doses may be needed. Patients may be placed on a lower dose of risperidone be
discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations of risp
hydroxyrisperidone.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of risperidone by carbamazepi
8) Literature Reports
a) Carbamazepine was reported to induce the metabolism of risperidone in a 22-year-old male with chro
low risperidone levels and lack of effectiveness. The patient was started on carbamazepine 600 mg daily
plasma concentration of 9-hydroxyrisperidone was less than half the expected concentration when the d
8 mg daily. After achieving a therapeutic plasma concentration of 9-hydroxyrisperidone (19 mcg/L), the d
tapered and stopped. Plasma levels of 9-hydroxyrisperidone increased to 49 mcg/L, necessitating a decr
(de Leon & Bork, 1997).
b) Plasma concentrations of risperidone and 9-OH risperidone decreased when carbamazepine was ad
discontinued. One study evaluated the pharmacokinetic interactions between risperidone and carbamaze
DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder participated in the study
risperidone alone or in combination with carbamazepine for at least four weeks. Steady-state plasma cor
hydroxyrisperidone (9-OH risperidone) were compared in patients treated with risperidone alone and pat
carbamazepine. The plasma concentrations of both 9-OH risperidone and the sum of risperidone and 9-(
differed significantly among groups. In five patients evaluated with and without comedication, the plasma
and 9-OH risperidone decreased when carbamazepine was added or increased when it was discontinue
in patients receiving risperidone alone, the concentration of the active moiety (risperidone plus its active
was reduced by approximately 70% when carbamazepine was given concomitantly (Spina et al, 2000).
c) The concomitant use of carbamazepine and risperidone leads to a marked decrease in the steady-sta
risperidone and 9-hydroxyrisperidone through stimulation of an inducible cytochrome as well as the influe
2D6 genotype. A 50-year-old male with chronic schizophrenia and deficient CYP2D6 activity was given c
risperidone therapy. Carbamazepine 800 mg/day for 5 days was added to his medication regimens as a
carbamazepine treatment, the patient exhibited psychotic symptoms including hallucinations, paranoid d
mild excitement. Plasma concentrations of risperidone and its active metabolite 9-hydroxyrisperidone, ha
ng/mL, respectively. Carbamazepine concentration was 8.2 mcg/mL. The risperidone dose was increase
was discontinued, and lorazepam 5 mg/day was added. Psychotic symptoms improved over the followin
risperidone and 9-hydroxyrisperidone increased to 40 and 57 ng/mL, respectively. A resultant decrease i
risperidone and 9-hydroxyrisperidone suggest that the CYP2D6 genotype may influence susceptibility to
with risperidone and carbamazepine (Spina et al, 2001).
d) Eleven schizophrenic patients in a drug interaction study received oral risperidone titrated to 6 mg/da
concurrent administration of carbamazepine for an additional 3 weeks. The plasma concentrations of risp
pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. At the initiatio
carbamazepine, patients should be closely monitored during the first 4-8 weeks, since the dose of risperi
dose increase or additional risperidone may need to be considered. If carbamazepine is discontinued, th
be re-evaluated and, if necessary, decreased. A lower dose of risperidone may be required between 2 to
discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations o
hydroxyrisperidone (Prod Info Risperdal(R) Consta(TM), 2003).

3.5.1.O Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Chloral hydrate has been shown to prolong the QTc interval at the recommended therapeutic d
though no formal drug interaction studies have been done, the administration of drugs known to prolong the Q
antipsychotics and chloral hydrate is not recommended. Several antipsychotic agents have demonstrated QT
amisulpride (Prod Info Solian(R), 1999l), haloperidol (O'Brien et al, 1999g), quetiapine (Owens, 2001o), rispe
1999o), sertindole (Agelink et al, 2001k), sultopride (Lande et al, 1992k), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloral hydrate and antipsychotics is not recomme
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
torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998b). Periodic electrocard
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 doses (
et al, 1993b). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperido
delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac
haloperidol.

3.5.1.P 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 dos
anticipated if administered with other agents which lengthen the QT interval (Prod Info Aralen(R), 2001). Sev
demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999w), haloperidol (O'Brien et al,
2001z), risperidone (Duenas-Laita et al, 1999ad), sertindole (Agelink et al, 2001s), sultopride (Lande et al, 19

2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT inte
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 rispe
Laita et al, 1999ac; Ravin & Levenson, 1997k).

3.5.1.Q Chlorpromazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the
recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co
Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no
antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999j),
paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001n), risper
1999n), sertindole (Agelink et al, 2001j), sultopride (Lande et al, 1992i), ziprasidone (Prod Info GEODON(R) i
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 phen
not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.R Cimetidine
1) Interaction Effect: increased risperidone bioavailability
2) Summary: Concurrent use of risperidone and cimetidine resulted in a 64% increase in the bioavailability o
active metabolite, 9-hydroxyrisperidone, was not affected (Prod Info RISPERDAL(R) CONSTA(R) long-acting
if these agents are used concomitantly. Monitor patients for increased risperidone adverse events (sedation,
dyspepsia, tachycardia, constipation, or dry mouth).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent treatment with cimetidine and risperidone has resulted in a 64% increas
The AUC of the active metabolite, 9-hydroxyrisperidone, was not affected (Prod Info RISPERDAL(R) CONST
2007). Caution is advised if these agents are used concomitantly. Consider monitoring for increased risperido
sedation, akathisia, parkinsonism, dyspepsia, tachycardia, constipation, or dry mouth.
7) Probable Mechanism: unknown

3.5.1.S Cisapride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated
which lengthen the QT interval (Prod Info Geodon(TM), 2002; Owens, 2001a; Prod Info Orap(R), 1999a). Tor
prolongation have been reported with cisapride (Prod Info Propulsid(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT inte
contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patient
arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pro
interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment
deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis
prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999
b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone (Due
Levenson, 1997).

3.5.1.T 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 I
haloperidol (O'Brien et al, 1999b), quetiapine (Owens, 2001f), risperidone (Duenas-Laita et al, 1999f), sertind
sultopride (Lande et al, 1992c), and zotepine (Sweetman, 2004). Even though no formal drug interaction stud
use of clarithromycin and antipsychotic agents may cause additive effects on the QT interval and is not recon

2002).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of clarithromycin and agents that prolong the QT inte
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 significant in
following administration of quetiapine. The patient, hospitalized for acute psychotic symptoms was treate
with a gradual increase in dosage to 700 mg over 10 days. Psychotic symptoms dissipated within 3 weel
developed a lower airway infection, and was orally treated with 750 mg sultamicillin, 500 mg clarithromyc
quetiapine 400 mg. The following morning, 750 mg sultamicillin, 500 mg clarithromycin, and the morning
given. Within hours the patient became somnolent, and plasma sample testing resulted in 826.8 microgr
microgram/L). The patient developed severe impaired consciousness and respiratory depression. Quetia
and treatment was discontinued. Plasma levels were continually measured over the course of a week un
achieved (Schulz-Du Bois et al, 2008).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (
et al, 1993). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidol
delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac
haloperidol. Four patients developed the dysrhythmia after administration of 170 to 580 mg over 1 to 4 d
bacterial meningitis (1), status asthmaticus (2) or respiratory insufficiency (1). All 4 patients recovered wi
c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info Risperdal

3.5.1.U Clozapine
1) Interaction Effect: decreased risperidone clearance
2) Summary: The manufacturer reports that clozapine may decrease risperidone clearance with chronic com
(R) Consta(TM), 2003g).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for increased adverse effects of risperidone when these drugs are
7) Probable Mechanism: unknown

3.5.1.V Darunavir
1) Interaction Effect: increased risperidone plasma concentrations
2) Summary: Coadministration of ritonavir-boosted darunavir, a CYP2D6 inhibitor, and risperidone, a CYP2D
increased plasma concentrations of risperidone, possibly due to inhibition of CYP2D6-mediated risperidone m
As this may result in risperidone adverse effects, a lower dose of risperidone should be considered with conc
Info PREZISTA(R) film coated oral tablets, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of ritonavir-boosted darunavir and risperidone may increa
concentrations. Consider using a lower risperidone dose when these agents are coadministered (Prod Info P
tablets, 2008).
7) Probable Mechanism: inhibition of CYP2D6-mediated risperidone metabolism by darunavir/ritonavir

3.5.1.W Dehydroepiandrosterone
1) Interaction Effect: reduced effectiveness of risperidone
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/decil
optimal treatment of patients with psychosis (Howard, 1992a). In case reports, patients have been resistant t
levels were elevated (Howard, 1992a). Patients being treated with risperidone should avoid DHEA supplemer
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and risperidone. If DHE
dexamethasone 1 mg orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness
8) Literature Reports
a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 mill
mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient app
acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandro
part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexame
resulted in substantial improvement within one week. The patient appeared calmer, more alert with impro
ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The
DHEA levels were associated with severe psychosis resistant to conventional antipsychotic therapy (Hov
b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accom

hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was dia schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorder, excited type. H trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. He was also resistant to combin chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perphenazine 48 mg with lithium c 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day sup dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psych was well-oriented, conversational, and was making good eye contact. Once dexamethasone was discon and florid psychosis ensued despite "substantial amounts of psychotropic medications". DHEA increased concluded that elevated DHEA levels were associated with florid psychosis resistant to conventional anti 1992).

3.5.1.X 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 I haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stud coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.Y 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 I haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stud coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.Z 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, halop quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets 1999z; O'Brien et al, 1999q; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001ab; Du et al, 2001v; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetma antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent a with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinag
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
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), iloperic 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 ther 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study de

in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol tre
under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/
peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on com
and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors
is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993)

3.5.1.AA Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of dofetilide and risperidone is not recommended due to the risk of additive effe
concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised. Dofetilide should be
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 risperidone is not recommended due
threatening arrhythmias. Dofetilide should be stopped for at least 2 days before any interacting drug is initiate
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
fibrillation, and torsades de pointes. Several antipsychotic agents have also demonstrated QT prolongati
(Duenas-Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as dofetilide and ris
effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.AB 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 I
haloperidol (O'Brien et al, 1999e), quetiapine (Owens, 2001l), risperidone (Duenas-Laita et al, 1999k), sertinc
sultopride (Lande et al, 1992g), and zotepine (Sweetman, 2003). Even though no formal drug interaction stuc
coadministration of dolasetron and other drugs known to prolong the QTc interval, including antipsychotics, is
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 interva
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, and Q
baseline values. Measured changes in ECG parameters were transient, reversible, and asymptomatic. In
intervals may be due to prolongation of maximum upstroke velocity (Vmax) due to binding of dolasetron
cause of QTc interval prolongation appears to be due to prolongation of the QRS interval, increases in h
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 doses (
et al, 1993a). Three patients developed the dysrhythmia after administration of 211 to 825 mg haloperidc
delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac
haloperidol. Four patients developed the dysrhythmia after administration of 170 to 580 mg over 1 to 4 d
bacterial meningitis (1), status asthmaticus (2) or respiratory insufficiency (1). All 4 patients recovered wi
c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info Risperdal

3.5.1.AC 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 I
haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c
sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stuc
coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R
1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr
interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment
deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis
prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.AD 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
(O'Brien et al, 1999l), quetiapine (Owens, 2001w), risperidone (Duenas-Laita et al, 1999z), sertindole (Agelin
et al, 1992t), and zotepine (Sweetman, 2003). Droperidol has been shown to prolong the QTc interval at the
Even though no formal drug interaction studies have been done, the coadministration of droperidol and other
interval, including antipsychotics is not recommended (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.AE Encainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such
approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is a
Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of encainide and risperidone is not recommended du
threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AF 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
which lengthen the QT interval (Agelink et al, 2001y; Owens, 2001af; Prod Info Haldol(R), 1998i; Lande et al,
drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs
the QTc interval, including enflurane (Owens, 2001af).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of enflurane and agents that prolong the QT interval,
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 rispe
Laita et al, 1999ai; Ravin & Levenson, 1997n).

3.5.1.AG Erythromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective s
Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prol
PCE(R), 1997). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Pro
haloperidol (O'Brien et al, 1999p), risperidone (Duenas-Laita et al, 1999ae), sertindole (Agelink et al, 2001t),
and zotepine (Sweetman, 2003). Caution is advised with coadministration of drugs that potentially prolong th
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if erythromycin and antipsychotics are used concomitantly. Moni
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
dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal
or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval
(msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n e
increased from 473 msec to 525 msec (p less than 0.01). In patients with heart disease (n equal to 30), a
QTc interval (mean of 15%), compared with an increase of 8% in patients without heart disease (p less t
the QTc interval was severely prolonged. One patient developed torsades de pointes attributed to erythr
cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

3.5.1.AH Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such
approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is a

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 risperidone is not recommended du threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AI 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 fluconaz Wassmann et al, 1999). Haloperidol (Prod Info Haldol(R), 1998d), risperidone (Prod Info Risperdal(R) risperic Info Solian(R), 1999k), sertindole (Brown & Levin, 1998a); sultopride (Lande et al, 1992j), and zotepine (Swe to prolong the QT interval at therapeutic doses. Even though no formal drug interaction studies have been do 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.AJ Fluoxetine
1) Interaction Effect: increased plasma concentrations of risperidone
2) Summary: Concomitant use of fluoxetine (CYP2D6 inhibitor) and risperidone (CYP2D6 substrate) has res plasma concentrations and an increased risk of risperidone adverse effects such as serotonin syndrome, QT effects. The postulated mechanism of action is inhibition of CYP2D6-mediated metabolism of risperidone by f demonstrated increased risperidone levels in patients treated concurrently with fluoxetine and risperidone (Pr tablets, oral solution, orally disintegrating tablets, 2008; Spina et al, 2002). Monitoring the patient for increase effects may be necessary (Spina et al, 2002). The risperidone dose should be reevaluated if fluoxetine is initi RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 2008) (Spina et al, 2002a).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of fluoxetine and risperidone has resulted in increased risperidone increased risk of risperidone side effects (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegr monitor patients for increased plasma risperidone levels and side effects (serotonin syndrome, extrapyramida when fluoxetine is coadministered with risperidone (Spina et al, 2002). Reevaluate the dose of risperidone wh initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 200
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of risperidone
8) Literature Reports
a) Fluoxetine (a CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concentration of substrate) 2.5- to 2.8-fold. Fluoxetine did not affect the concentration of 9-hydroxyrisperidone. The dosag reevaluated when fluoxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets, oral solut 2008).
b) Fluoxetine, an inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, primarily b alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism of 9-hydr risperidone) or other pathways of risperidone biotransformation. In an open, 4-week, pharmacokinetic stu schizophrenia or schizoaffective disorder, depressive type, risperidone concentrations increased when fl with risperidone. Patients were stabilized on a fixed dose of risperidone 4 to 6 mg/day for at least four we fluoxetine therapy 20 mg/day for the management of concomitant depression. Mean plasma risperidone ng/mL at baseline to 49 nanograms (ng)/mL (p less than 0.01) at week 2, and 56 ng/mL (p less than 0.01 concentrations of 9-hydroxyrisperidone (9-OH-risperidone) showed no significant increase at 4 weeks co weeks of concurrent therapy, the active moiety (risperidone plus 9-OH-risperidone) was increased by 75 than 0.01) compared with baseline. The mean plasma risperidone to 9-OH-risperidone ratio also increas experienced Parkinsonian symptoms during week 2 of concomitant therapy and were treated with antich suggest that monitoring plasma risperidone levels may be warranted in patients receiving concomitant flu treatment (Spina et al, 2002).

3.5.1.AK Foscarnet
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachyca torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation including amisulpride haloperidol (O'Brien et al, 1999r), quetiapine (Owens, 2001ae), risperidone (Duenas-Laita et al, 1999ah), ser sultopride (Lande et al, 1992ab), and zotepine (Sweetman, 2003). Because antipsychotics may also prolong risk of arrhythmias, the concurrent administration of foscarnet and antipsychotics is not recommended (Prod Levenson, 1997m).
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.AL 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 interva not been performed, gemifloxacin should be used cautiously in patients receiving antipsychotic medications (
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of two drugs that prolong the QT interval, such as ge not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AM Ginkgo Biloba
1) Interaction Effect: increased risk of risperidone adverse effects
2) Summary: Concomitant use of risperidone and ginkgo biloba may have precipitated priapism in one case cytochrome P450 isoforms 3A4 and 2C9, both of which are responsible for risperidone metabolism. Increase risperidone may lead to an increased risk of side effects, including priapism, as in this case report (Lin et al, 2
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution patients taking risperidone to discuss the use of nonprescription medicines with their doctor or pharmacist. If a patient presents with symptoms consistent with excessive risperidone, inc nonprescription medicines, herbs, and dietary supplements. It is recommended to avoid ginkgo in patients tal
7) Probable Mechanism: unknown
8) Literature Reports
a) Priapism occurred in a 26-year-old patient treated with risperidone 3 mg/day for 3 years who began g emergency department admission. He reported no other recent trauma, illness, or use of drugs or medic adverse effects related to risperidone therapy. He was treating occasional tinnitus with ginkgo biloba 160

3.5.1.AN Halofantrine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachy torsades de pointes. Some antipsychotic agents prolong the QT interval and an additive effect would be antic agents which lengthen the QT interval (Agelink et al, 2001b; Owens, 2001d; Prod Info Solian(R), 1999c; Proc al, 1992b). The concurrent administration of halofantrine with antipsychotics is not recommended (Prod Info H
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halofantrine and an antipsychotic is not recommer
7) Probable Mechanism: additive cardiac effects

3.5.1.AO Haloperidol
1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 20 2001a). Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe Laita et al, 1999t; Ravin & Levenson, 1997h; Gesell & Stephen, 1997d) and in overdose situations (Lo Vecch 1993d). 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. Screen pa predispose to QT prolongation and torsade de pointes (i.e. cardiomyopathy, alcohol abuse, hypothyroidism). 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 rispe Laita et al, 1999s; Ravin & Levenson, 1997g; Gesell & Stephen, 1997c) and in overdose situations (Lo V 1993c).
b) Numerous case reports have described significant QTc prolongation and torsades de pointes (TdP) a Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death hav appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. Th greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dose as low as intravenously over 4 hours. To prevent haloperidol-induced TdP, screen patients for a history of dilated c testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout the magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperi

an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from b or development of U-waves occurs (Hassaballa & Balk, 2003).

3.5.1.AP 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 which lengthen the QT interval (Agelink et al, 2001i; Owens, 2001m; Prod Info Solian(R), 1999i; Prod Info Ha 1992h). Even though no formal drug interaction studies have been done, antipsychotic agents should not be which may also prolong the QTc interval, including halothane (Owens, 2001m).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halothane and agents that prolong the QT interval 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 rispe Laita et al, 1999m; Ravin & Levenson, 1997d).

3.5.1.AQ 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, halop quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets 1999z; O'Brien et al, 1999q; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001ab; Du et al, 2001v; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetma antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent a with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinag
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
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), iloperic 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 ther 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study de in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol tre under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/ peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on com and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993)

3.5.1.AR Ibutilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of ibutilide and risperidone is not recommended due to the risk of additive effec concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ibutilide and risperidone is not recommended due threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
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 fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as ibutilide and risperidone r QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.AS 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 haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stuc coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).

3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.AT 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 which lengthen the QT interval (Agelink et al, 2001w; Owens, 2001ac; Prod Info Solian(R), 1999aa; Prod Info 1992aa). Even though no formal drug interaction studies have been done, antipsychotic agents should not be which are also known to prolong the QTc interval, including isoflurane (Owens, 2001ac).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isoflurane and agents that prolong the QT interval 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 rispe Laita et al, 1999ag; Ravin & Levenson, 1997l).

3.5.1.AU Isradipine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachyca torsades de pointes, and its use with other drugs known to cause QT prolongation is not recommended (Proc Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), al, 1999c), quetiapine (Owens, 2001h), risperidone (Duenas-Laita et al, 1999h), sertindole (Agelink et al, 200 2004).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isradipine and an antipsychotic is not recommend
7) Probable Mechanism: additive cardiac effects

3.5.1.AV Itraconazole
1) Interaction Effect: increased risperidone concentrations
2) Summary: In an open-label study, coadministration of itraconazole and risperidone in 19 schizophrenic pa serum concentrations of both risperidone and its active metabolite, 9-hydroxyrisperidone. It has been postula P450 2D6 enzymes, risperidone may also be metabolized by cytochrome P450 3A (CYP3A) enzymes. Inhibit mediated metabolism by itraconazole, a potent CYP3A inhibitor, may result in increased serum risperidone c affect clinical symptoms and side effects of risperidone (Jung et al, 2005). If these two agents are coadminist patients for clinical symptoms of risperidone efficacy and potentially, increased risperidone side effects (hypo side effects, arrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Coadministration of itraconazole and risperidone can result in increased serum con and its active metabolite, 9-hydroxyrisperidone. If these two agents are coadministered, consider monitoring risperidone efficacy and potentially, increased risperidone side effects (hypotension, sedation, extrapyramida
7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated risperidone metabolism
8) Literature Reports
a) Concurrent administration of itraconazole with risperidone resulted in increased serum risperidone co patients (n=19, mean age 41.4 years) who were being treated with 2 to 8 milligrams (mg) of risperidone pm) for at least 2 months were administered itraconazole 200 mg per day (dosed at 8 pm) for 1 week an open-label study indicated that the dose-normalized, steady-state plasma concentrations of both risperid hydroxyrisperidone, were significantly increased by 82% and 70%, respectively (p less than 0.01). Upon both concentrations returned to the levels prior to itraconazole administration. Scores on the Brief Psych improvement in clinical symptoms, decreased by 6% (p=0.017). However, there was no increase in adve Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating scale. It has been postulated that in addition enzymes, risperidone may also be metabolized by cytochrome P450 3A (CYP3A) enzymes. The propose is inhibition of risperidone's CYP3A-mediated metabolism by itraconazole, a potent CYP3A inhibitor (Jun

3.5.1.AW Lamotrigine

1) Interaction Effect: increased risperidone plasma concentrations and risk of adverse effects

2) Summary: Increased risperidone plasma concentrations, with signs of toxicity, developed in a patient adm to a stable dose-regimen of risperidone and clozapine (Bienentreu & Kronmuller, 2005).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Clinicians should be aware of the increased risk of risperidone adverse effects in pa together with risperidone. When concomitant lamotrigine is initiated, discontinued, or the dose of lamotrigine of risperidone.

7) Probable Mechanism: unknown

8) Literature Reports

a) Increased risperidone plasma concentrations and subsequent toxicity were reported in a patient recei stable dose-regimen of risperidone and clozapine. The patient, a 26-year-old woman diagnosed with sch partial response to her established regimen of clozapine 550 milligrams (mg) daily and risperidone 8 mg concentrations of risperidone and clozapine were 55-70 nanograms/milliliter (ng/mL) and 800-1100 ng/m initiated, with the dose incrementally titrated up to 200 mg daily. Clozapine and risperidone plasma conc ng/mL and 263 ng/mL, respectively; no symptoms of intoxication were observed. Lamotrigine was furthe daily, after which risperidone plasma concentration increased to 412 ng/mL, accompanied by symptoms risperidone dose was reduced to 2 mg daily and completely withdrawn shortly thereafter (Bienentreu & K

3.5.1.AX Levodopa

1) Interaction Effect: loss of levodopa efficacy

2) Summary: Because risperidone is an antagonist with a high affinity for dopamine type 2 receptors, it is exp of levodopa (Prod Info Stalevo(TM), 2003; Prod Info Risperdal(R) Consta(TM), 2003d).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of risperidone in patients with parkinsonism should be avoided. If c monitor the patient for loss of levodopa therapeutic efficacy.

7) Probable Mechanism: pharmacologic antagonism

3.5.1.AY Levomethadyl

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

2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levom pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such QT interval (Prod Info Orlaam(R), 2001).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Levomethadyl is contraindicated in patients being treated with risperidone as it may interact with levomethadyl.

7) Probable Mechanism: additive cardiac effects

3.5.1.AZ Levorphanol

1) Interaction Effect: precipitation of opioid withdrawal symptoms in opioid-dependent patients

2) Summary: A patient stabilized on levorphanol 14 mg daily for neck pain experienced opioid cravings and d risperidone therapy. Discontinuing risperidone resolved her symptoms of withdrawal. Possible mechanisms fo accelerating opioid metabolism via the cytochrome P450 system, interference with the gastrointestinal absorp altered opioid distribution, or opioid displacement from plasma protein binding sites (Wines & Weiss, 1999a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Opioid-dependent patients should be monitored for signs of opioid withdrawal if risp prescribed.

7) Probable Mechanism: unknown

8) Literature Reports

a) A 31-year-old female with a lengthy history of drug dependency, including opioids, was being treated depression and levorphanol 14 mg daily for chronic severe neck pain. Because of recurring nightmares a mg daily was initiated and increased to 1.5 mg daily within two days. While her dissociative symptoms im cramps, gooseflesh, and opioid cravings. Risperidone was decreased to 1 mg daily but her dissociative s risperidone was again increased to 2 mg daily, but she experienced an increase in her withdrawal sympt Risperidone therapy was eventually discontinued (Wines & Weiss, 1999).

3.5.1.BA 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 though no formal drug interaction studies have been done, the coadministration of antipsychotics and other d

interval is not recommended. Several antipsychotic agents have demonstrated QT prolongation including am
1999), haloperidol (O'Brien et al, 1999), quetiapine (Owens, 2001), risperidone (Duenas-Laita et al, 1999), se
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.BB Linezolid

1) Interaction Effect: increased risk of serotonin syndrome
2) Summary: In a review of post-marketing data, 1 case of serotonin toxicity was reported with the concurrer
which was coadministered with other serotonergic agents (Lawrence et al, 2006) . Risperidone, in combinatio
has been associated with the serotonin syndrome (Springuel & McMorran, 2003). There have been spontane
syndrome associated with concomitant use of linezolid and serotonergic agents (Wigen & Goetz, 2002; Prod
tablets, oral suspension, 2008). Although coadministration of linezolid and serotonergic agents did not result
1, 2, or 3 clinical trials, linezolid is a reversible, non-selective MAOI and can potentially interact with serotone
serotonin syndrome. If concurrent use of linezolid and a serotonergic agent is clinically warranted, monitor pa
symptoms of serotonin syndrome. Consider discontinuing either one or both agents if these symptoms occur,
discontinuation of the concomitant serotonergic agent may result in associated discontinuation symptoms (Pr
oral tablets, oral suspension, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Serotonin toxicity has been reported in 1 individual with the concurrent use of linezo
coadministered with other serotonergic agents (Lawrence et al, 2006). If concurrent use of linezolid and rispe
serotonergic agents, is clinically necessary, monitor patients closely for signs and symptoms of serotonin syn
abnormalities (including hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering
(including tachycardia, mydriasis, diaphoresis, and diarrhea), and mental status changes (including agitation
syndrome can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and prov
therapy as necessary (Boyer & Shannon, 2005). Keep in mind that discontinuation of the concomitant seroto
associated discontinuation symptoms (Prod Info ZYVOX(R) IV injection, oral tablets, oral suspension, 2008).
7) Probable Mechanism: inhibition of serotonin metabolism by monoamine oxidase
8) Literature Reports
a) In a review of post-marketing data, one case of serotonin toxicity was reported in the concurrent use
which was coadministered with other serotonergic agents. A review was conducted of post-marketing ad
Food and Drug Administration's Adverse Event Reporting System (AERS) database between November
regarding serotonin toxicity with linezolid use. A serotonin toxicity case was defined as having: (a) linezo
(b) concomitant administration of 1 or more secondary suspect drug with CNS serotonergic activity, and
by the modified Hunter Serotonin Toxicity Criteria or by the reporter of the adverse event. A total of 29 ca
17 to 83 years), where linezolid was used concomitantly with 1 drug (n=20), with 2 drugs (n=6), and with
SSRIs were the most common class of drugs received concomitantly with linezolid (n=26), other drug cla
antidepressants (n=6), and atypical antidepressants (n=4). Additionally, drugs used concurrently include
dextromethorphan (n=1), lithium (n=1), metoclopramide (n=1), risperidone (n=1), and tramadol (n=1). Sy
included tremor, fever, seizure, clonus, sweating, agitation, akathesia, rigors, twitching, and muscle rigidi
hospitalization was required in 13 patients, and 3 deaths were reported with concurrent SSRI use. For th
concurrent use linezolid and risperidone, additional coadministered serotonergic drugs included bupropio
(Lawrence et al, 2006).

3.5.1.BC Lithium

1) Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brai
2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few pat
dopamine-2 antagonist, particularly haloperidol. A causal relationship between these events and the concomi
dopamine-2 antagonist and lithium has not been established (Prod Info LITHOBID(R) slow-release oral tablet
lithium and a number of antipsychotic drugs has caused a wide variety of encephalopathic symptoms, brain d
symptoms, and dyskinesias in isolated case reports. In most cases, these effects have occurred with therape
1982; Prakash, 1982; Addonizio et al, 1988a). However, many series and trials have reported using such con
adverse consequences (Goldney & Spence, 1986). The mechanism is not fully understood, but chronic lithiu
neostriatal dopaminergic activity, probably through a direct action on the G protein and the capacity of the G
stimulate adenyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined ph
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, espec
antagonists, particularly haloperidol, and lithium are used. Serum lithium levels should be monitored periodica
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, fever in several patients with mania (Cohen & Cohen, 1974; Loudon & Waring, 1976; Thomas, 1979). Irr have been reported (Sandyk & Hurwitz, 1983; Keitner & Rahman, 1984).

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

c) The addition of lithium to neuroleptic therapy exacerbated extrapyramidal symptoms (EPS) in a small The patients had received at least five days of treatment with either oral thiothixene, haloperidol, or fluph chlorpromazine equivalents prior to initiation of the lithium and were experiencing drug-induced extrapyra was added when clinically indicated in sufficient doses to achieve a therapeutic serum concentration. Th 0.65 to 1.27 mEq/L. The EPS ratings increased in all ten patients following the addition of lithium. Howev marked symptoms and no patient developed lithium toxicity. Significantly increased symptoms included g rigidity, and tremor.

d) Ten patients treated with clozapine and lithium were studied (Blake et al, 1992). Of the ten patients, f neurologic effects, including jerking of limbs, facial spasms and tics, tremor of hands and arms, tongue tv of these also experienced delirium. These effects reversed when lithium was discontinued or given at a l of two patients suffered recurrence of symptoms. By keeping serum lithium no greater than 0.5 mEq/L, c coadministered.

e) Chlorpromazine serum levels can be significantly reduced in the presence of lithium treatment. If use of lithium may result in rebound elevation of chlorpromazine levels, resulting in chlorpromazine toxicity. I chlorpromazine combination, abrupt withdrawal of the lithium may precipitate chlorpromazine cardiotoxic was manifested as sudden ventricular fibrillation associated with prolongation of the QTc interval. Hypote in this situation (Stevenson et al, 1989).

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

g) A 69-year-old patient with oxygen-dependent chronic obstructive pulmonary disorder and a 25-year h started on risperidone 3 mg for the treatment of new-onset auditory and visual hallucinations. She had al regimen of lithium (450 mg daily) for more than 10 years. In addition, she was given amantadine (100 mg weeks after the start of risperidone, the patient experienced a decline in mental status in addition to dizzi and vomiting, polyuria, depression, and visual and auditory hallucinations. She was then admitted to the serum level was 1.36 mEq/L at the time of the admission. All medications were discontinued. Although h mEq/L, she continued to experience profound delirium, tremors, lethargy, and hallucinations for almost o respond to commands, she was restarted on lithium (300 mg at bedtime) because of the onset of mild hy was discharged with a regimen of lithium and low-dose lorazepam for treatment of insomnia. It is sugges caused by the concurrent use of lithium and risperidone. Other factors could also have caused delirium, lithium level and the underlying pulmonary pathology. In addition, amantadine, which facilitates the relea has a mild anticholinergic effect, may have contributed (Chen & Cardasis, 1996).

3.5.1.BD Lorcainide

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

2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is a Larochelle et al, 1984).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of lorcainide and risperidone is not recommended du threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BE 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 mefloquir can prolong the QTc interval (Prod Info Lariam(R), 1999). Mefloquine was associated with significant QT prol subjects (Davis et al, 1996). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998f), quetiapine (Ow Info Risperdal(R) risperidone, 2000b), amisulpride (Prod Info Solian(R), 1999r), sertindole (Agelink et al, 200 1992r), 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 mefloquine and antipsychotics are used concomitantly.

7) Probable Mechanism: additive effect on QT interval

3.5.1.BF Mesoridazine

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

3.5.1.BG Methadone

1) Interaction Effect: precipitation of opioid withdrawal symptoms in opioid-dependent patients
2) Summary: A patient stabilized on methadone 50 mg daily experienced aches, nasal congestion, and irrital risperidone therapy. Discontinuing risperidone resolved his symptoms of withdrawal. Possible mechanisms fo accelerating opioid metabolism via the cytochrome P450 system, interference with the gastrointestinal absorp altered opioid distribution, or opioid displacement from plasma protein binding sites (Wines & Weiss, 1999c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Opioid-dependent patients should be monitored for signs of opioid withdrawal if risp prescribed.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 26-year-old male with a long history of chemical dependency was receiving a methadone maintena was hospitalized for an exacerbation of paranoia and agitation. Risperidone 0.5 mg twice daily was initia patient complained of feeling "dope sick", with symptoms of aches, nasal congestion, and irritability. The risperidone was increased to 2 mg daily and dissipated when risperidone was discontinued. His paranoia chlorpromazine with no further signs of opioid withdrawal (Wines & Weiss, 1999b).

3.5.1.BH Midodrine

1) Interaction Effect: an increased risk of acute dystonia
2) Summary: A case report described development of acute dystonia in a 33-year-old female following conco midodrine and risperidone (Takahashi, 2000). Patients receiving this combination may need to be monitored events, including signs and symptoms of acute dystonia.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution if midodrine and risperidone are prescribed concurrently. Monitor for si dystonia or other risperidone adverse events.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 33-year-old female developed acute dystonia after addition of midodrine to treat orthostatic hypoter therapy. The patient had a 12-year history of catatonic schizophrenia, which was adequately controlled v mg/day. Two days after addition of midodrine 4 mg/day to treat complaints of orthostatic hypotension, the of acute dystonia, including tongue protrusion, retrocollis, and oculogyric crisis. Intramuscular injection of resolved all symptoms. Midodrine was discontinued and risperidone 6 mg/day monotherapy was continu dystonic symptoms, midodrine 4 mg/day was added again to therapy to treat continuing complaints of or acute dystonic reaction recurred one day later and was successfully treated with one intramuscular injec midodrine was discontinued and the patient remained on risperidone 6 mg/day without dystonic sympton risperidone dose was decreased to 3 mg/day due to persistent orthostatic hypotension, and the patient w symptoms at a 3-month follow-up. Increased risperidone-associated central noradrenergic activity due to activity of midodrine was a postulated mechanism for this interaction (Takahashi, 2000).

3.5.1.BI 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 I haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stuc coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects

8) Literature Reports

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

3.5.1.BJ 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 (Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and o QTc interval, including octreotide, is not recommended. Several antipsychotic agents have demonstrated QT amisulpride (Prod Info Solian(R), 1999u), haloperidol (O'Brien et al, 1999m), risperidone (Duenas-Laita et al, al, 2001q), quetiapine (Owens, 2001x), 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.BK Paroxetine

1) Interaction Effect: increased plasma concentrations of risperidone

2) Summary: Concomitant use of paroxetine (potent CYP2D6 inhibitor) and risperidone (CYP2D6 substrate) risperidone plasma concentrations and an increased risk of risperidone adverse effects such as serotonin syn extrapyramidal effects. The postulated mechanism of action is inhibition of CYP2D6-mediated metabolism of studies demonstrated increased risperidone levels resulting in a greater frequency of extrapyramidal symptom concurrently with paroxetine and risperidone (Saito et al, 2005; Spina et al, 2001a). One of these studies sho paroxetine dose increases and greater risperidone plasma concentrations (Spina et al, 2001a). In a case rep observed in a patient who had already been receiving risperidone and was initiated on paroxetine (Hamilton & patient for increased risperidone plasma levels side effects may be necessary. The risperidone dose should b initiated or discontinued. Concomitant use of a low dose of paroxetine with risperidone may be safe and effec with negative symptoms (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegrating tablets, 20

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of paroxetine and risperidone has resulted in increased risperidon increased risk of risperidone side effects (Prod Info RISPERDAL(R) oral tablets, oral solution, orally disintegr 2005; Spina et al, 2001a; Hamilton & Malone, 2000). Carefully monitor patients for increased plasma risperid (serotonin syndrome, extrapyramidal symptoms, and cardiotoxicity) when paroxetine is coadministered with r of risperidone when concomitant paroxetine is initiated or discontinued (Prod Info RISPERDAL(R) oral tablets disintegrating tablets, 2008). Coadministering a low dose of paroxetine with risperidone may be safe and effe with negative symptoms (Saito et al, 2005).

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

8) Literature Reports

a) Paroxetine (a potent CYP2D6 inhibitor) 20 mg/day has been shown to increase the plasma concentra substrate) by 3- to 9- fold. Paroxetine also lowered the concentration of 9-hydroxyrisperidone by about 1 surveillance of risperidone, torsade de pointes has been reported with combined overdose of risperidone risperidone should be reevaluated when paroxetine is initiated or discontinued (Prod Info RISPERDAL(R disintegrating tablets, 2008).

b) Risperidone plasma concentrations increased when risperidone-treated inpatients (n=12) with schizo were coadministered incremental doses of paroxetine. Prior to initiating paroxetine, patients were receivi for at least 6 weeks and steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone (9- achieved. Paroxetine doses were administered in 3 consecutive 4-week increments of 10 mg/day, 20 mg risperidone plasma concentrations during 10-, 20-, and 40-mg paroxetine treatment were 3.8- (95% conf less than 0.01) , 7.1- (95% CI, 5.3 to 16.5; p less than 0.01), and 9.7-fold (95% CI, 7.8 to 22.5; p less tha baseline. Increases in 9-OH-risperidone concentrations were not significant with paroxetine use. Mean a OH-risperidone) plasma concentrations increased by 1.8-fold (95% CI, 1.4 to 2.7; p less than 0.05) durin increases were not significant with 10- or 20-mg doses. Metabolic ratio was significantly increased (p les 3.4 to 6.2) with 10 mg of paroxetine, by 8.2-fold (95% CI, 6 to 16) with 20 mg, and by 12.6-fold (95% CI, symptom scores were significantly improved during all paroxetine doses; however, extrapyramidal sympt higher during 20- and 40-mg doses. The authors suggest that low-dose coadministration of paroxetine w effective for treating schizophrenia with negative symptoms (Saito et al, 2005).

c) Paroxetine, a potent inhibitor of cytochrome CYP2D6, may impair the elimination of risperidone, prim mediated alpha-hydroxylation and, to a lesser extent, by simultaneously affecting the further metabolism risperidone) or other pathways of risperidone biotransformation. In a study including 10 patients diagnos schizoaffective disorder depressive type (n=3), risperidone plasma concentrations increased when parox risperidone. Patients were stabilized on risperidone therapy 4 to 8 mg/day and received adjunctive parox symptoms, concomitant depression, or both. Risperidone dosage remained constant throughout the dura elevation in risperidone plasma concentrations (p less than 0.01) and a slight, nonsignificant decrease in

4 weeks of paroxetine treatment, the total concentration of risperidone and 9-OH-risperidone was increa
The mean plasma risperidone to 9-OH-risperidone ratio also changed significantly (p less than 0.001) wi
treatment. Extrapyramidal side effects occurred in one patient during the second week of paroxetine coa
of risperidone in this patient increased 62% over baseline values during paroxetine coadministration. The
symptoms in patients after addition of SSRIs to antipsychotics might also be caused by an additive pharr
(Spina et al, 2001a).

d) Serotonin syndrome occurred in a patient using concomitant paroxetine and risperidone, an antipsycl
antagonism and dopamine blocking activity . A 53-year-old male with a 7-month history of psychotic depr
risperidone 3 mg/day and paroxetine 20 mg/day for 10 weeks before presentation. Nine weeks into thera
decreased motivation and bilateral jerking movements of the mouth and legs. The patient discontinued h
before his admission. Upon presentation he was apathetic, confused, disorganized, and talked to himsel
risperidone were doubled to 40 mg/day and 6 mg/day, respectively. Within 2 hours of taking his medicati
jerking movements, ataxia, tremor, and shivering. He presented to the emergency room with involuntary
His mental status exam was notable for depression with psychomotor agitation, difficulty being aroused,
Differential diagnosis included recurrent psychotic depression, neuroleptic malignant syndrome (NMS), c
syndrome. Nortriptyline 100 mg at bedtime, haloperidol 10 mg twice daily and diphenhydramine 50 mg a
discharge. The patient returned to baseline 9 months after discharge and is without symptoms of depres
Malone, 2000).

3.5.1.BL 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 dos
though no formal drug interaction studies have been done, the coadministration of antipsychotics and other d
interval, including pentamidine, is not recommended (Agelink et al, 2001e; Owens, 2001g; Prod Info Haldol(R
1999e; Duenas-Laita et al, 1999g; Duenas-Laita et al, 1999g; Prod Info Nipolept(R), 1996a; Metzger & Friedr
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of pentamidine and antipsychotics is not recommend
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BM Phenobarbital

1) Interaction Effect: decreased plasma concentrations of risperidone and the active metabolite 9-hydroxyris
2) Summary: Concomitant use of phenobarbital may reduce plasma concentrations of risperidone. Patients s
Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the planned discontinua
adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Prod Info
2003e).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of phenobarbital du
therapy; higher risperidone doses may be needed. Patients may be placed on a lower dose of risperidone be
discontinuation of phenobarbital therapy to adjust for the expected increase in plasma concentrations of rispe
hydroxyrisperidone. For patients currently maintained on the lowest available dose (25 mg) risperidone, it is r
that dose unless an interruption of treatment is necessary.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of risperidone by phenobarbita

3.5.1.BN Phenylalanine

1) Interaction Effect: increased incidence of tardive dyskinesia
2) Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dysl
Abnormal phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain a
availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines (Gardo
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monito
tardive dyskinesia.
7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with ca
8) Literature Reports

a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics ir
patients were studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients w
current or past exposure to greater than or equal to 100 milligrams (mg) of a chlorpromazine equivalent f
(3) patients with no tardive dyskinesia not previously exposed to a neuroleptic drug (n=10). Neuroleptic a
study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered phenylalanine 100
juice after an overnight fast. Blood samples were obtained just prior to phenylalanine administration and
Three patients in group 1 (with tardive dyskinesia) had the highest postloading phenylalanine plasma lev
higher (though nonsignificant) mean phenylalanine levels than the other groups. Tardive dyskinesia scor
Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phenylalanine l

scores were significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlatic 0.05). Postloading phenylalanine level and baseline AIMS scores demonstrated a trend toward correlatic correlation coefficient 0.679, p less than 0.05). In all patients, phenylalanine loading increased plasma pl eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of phenylalanine to tyrosine large neutral amino acids such as tryptophan decreased slightly (Gardos et al, 1992).

3.5.1.BO Phenytoin

1) Interaction Effect: decreased plasma concentrations of risperidone and the active metabolite 9-hydroxyris
2) Summary: Concomitant use of phenytoin may reduce plasma concentrations of risperidone. Upon initiatio patients should be closely monitored during the first 4-8 weeks, since the dose of risperidone may need to be placed on a lower dose of risperidone between 2 to 4 weeks before the planned discontinuation of phenytoin expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Prod Info Risperdal(R)
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of phenytoin highe needed. Monitor patients during the first 4-8 weeks of coadministration with phenytoin and risperidone; highe needed. Patients may be placed on a lower dose of risperidone between 2 to 4 weeks before the discontinua adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patie lowest available dose (25 mg) risperidone, it is recommended to continue with that dose unless an interruptio
7) Probable Mechanism: induction of risperidone metabolism through cytochrome P450 enzymes by phenyto

3.5.1.BP Pimozide

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

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, halop quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets 1999z; O'Brien et al, 1999q; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001ab; Du et al, 2001v; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetma antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent a with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinag
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
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), iloperic 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 ther 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study de in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol tre under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/ peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on com and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors is more likely responsible for the plasma level changes than an elimination 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, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets 1999z; O'Brien et al, 1999q; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001ab; Du et al, 2001v; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetma antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent a with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinag
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
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), iloperic 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 ther 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study de in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol tre under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/ peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on com and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors is more likely responsible for the plasma level changes than an elimination 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 interval is not recommended. Probucol has been shown to prolong the QTc interval (Gohn & Simmons, 1992 Antipsychotics including haloperidol (Prod Info Haldol(R), 1998e), quetiapine (Owens, 2001s), risperidone (Pr 2000a), amisulpride (Prod Info Solian(R), 1999p), sertindole (Brown & Levin, 1998c); sultopride (Lande et al, (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, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets 1999z; O'Brien et al, 1999q; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001ab; Du et al, 2001v; Lande et al, 1992z; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetma antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent a with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinag
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
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), iloperic 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 ther 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study de in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol tre under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/ peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on com and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors is more likely responsible for the plasma level changes than an elimination 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 on the recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co

Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though nc antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999j), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001n), risper 1999n), sertindole (Agelink et al, 2001j), sultopride (Lande et al, 1992i), ziprasidone (Prod Info GEODON(R) i 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 phen not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.BV Propafenone
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of risperidone with other drugs that potentially prolong the QTc interval, such approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is a Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of propafenone and risperidone is not recommended life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring i
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BW 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 haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), c sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stuc coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.BX Quetiapine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Risperidone can prolong the QT interval in some patients, which may result in ventricular tachy torsades de pointes, and its use with other agents that may prolong the QT interval, such as quetiapine, is no Risperdal(R), 2002c; Owens, 2001q). Coadministration of risperidone 3 mg twice daily with quetiapine 300 m steady-state pharmacokinetics of quetiapine (Prod Info Seroquel(R), 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Because of the potential additive effects on the QT interval, the concurrent administ risperidone is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risper Laita et al, 1999u; Ravin & Levenson, 1997i; Gesell & Stephen, 1997e; Lo Vecchio et al, 1996e; Brown e

3.5.1.BY Ranitidine
1) Interaction Effect: increased risperidone bioavailability
2) Summary: Concurrent use of risperidone and ranitidine resulted in a 26% increase in the bioavailability of active metabolite, 9-hydroxyrisperidone, and risperidone combined was increased by 20% (Prod Info RISPER IM injection, 2009). Use caution if these agents are used concomitantly. Monitor patients for increased risperi akathisia, parkinsonism, dyspepsia, tachycardia, constipation, or dry mouth).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concurrent treatment with ranitidine and risperidone has resulted in increased rispe

RISPERDAL(R) CONSTA(R) long-acting IM injection, 2009). Caution is advised if these agents are used con
for increased risperidone adverse events, including sedation, akathisia, parkinsonism, dyspepsia, tachycardia
7) Probable Mechanism: unknown

3.5.1.BZ Rifampin

1) Interaction Effect: decreased plasma concentrations of risperidone and the active metabolite 9-hydroxyris
2) Summary: Concomitant use of rifampin may reduce plasma concentrations of risperidone (Prod Info RISP
RISPERDAL(R) M-TAB(R) orally disintegrating tablets, 2008). Patients should be closely monitored if concon
may be placed on a lower dose of risperidone between 2 to 4 weeks before the planned discontinuation of rif
expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Prod Info RISPERDAL
injection, 2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of rifampin during t
higher risperidone doses may be needed. Patients may be placed on a lower dose of risperidone 2 to 4 week
rifampin therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyris
maintained on the lowest available dose of risperidone long-acting injection (25 mg), it is recommended to co
interruption of treatment is necessary (Prod Info RISPERDAL(R) CONSTA(R) long-acting IM injection, 2008).
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of risperidone by rifampin

3.5.1.CA Ritonavir

1) Interaction Effect: increased risperidone serum concentrations and potential toxicity (hypotension, sedatio
arrhythmias)
2) Summary: Coadministered ritonavir may increase serum concentrations of risperidone, resulting in risperi
Kelly et al, 2002a)A risperdal dose decrease may be required when coadministered with ritonavir (Prod Info N
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs and symptoms of neuroleptic toxicity (hypotension, sedati
arrhythmias). Reduce doses of risperidone as required.
7) Probable Mechanism: decreased risperidone metabolism
8) Literature Reports

a) Increases in risperidone serum concentration occurred in a patient taking concomitant ritonavir. A 48-
diagnosed with acquired immunodeficiency syndrome (AIDS) was admitted to a psychiatric hospital for n
medications included zidovudine 250 mg twice daily, didanosine 300 mg once daily, indinavir 400 mg twi
twice daily. He was given risperidone 3 mg twice daily upon admission. After receiving two doses of rispe
progressively drowsy and disoriented. He then became lethargic and comatose. Physical exam revealed
points with miotic pupils. Laboratory tests were normal. A toxic or metabolic etiology was suspected to be
medication was discontinued. Twenty-four hours later, his neurologic status returned to baseline and pro
reappeared. The author suggests that an interaction between risperidone, indinavir and ritonavir may hav
coma (Jover et al, 2002).

b) Extrapyramidal symptoms (EPS) occurred in a patient initiated on ritonavir and indinavir while taking
35-year-old white male with AIDS received risperidone 2 mg twice daily for treatment of Tourette's-like tic
month history of hand tremor, twitching and jerky involuntary movements of the face, shoulders, arms, an
were dapsone, pyrimethamine, azithromycin, and hydroxyzine. Risperidone was initiated at 1 mg twice d
increased to 2 mg twice daily. Indinavir 800 mg twice daily and ritonavir 200 mg twice daily was initiated
dosage was increased. One week later he experienced significantly impaired swallowing, speaking, and
existing tremors. Ritonavir and indinavir were discontinued. One month later the patient agreed to try ind
the same time he increased the risperidone dose to 3 mg twice daily. Symptoms worsened over the next
parameters were unremarkable and vital signs were stable. Risperidone was discontinued and clonazep
patients symptoms improved. Caution is warranted when risperidone is prescribed with ritonavir/indinavir

3.5.1.CB Ropinirole

1) Interaction Effect: diminished effectiveness of ropinirole
2) Summary: Theoretically, risperidone may oppose the dopaminergic effect of dopamine agonists, such as r
(R) oral tablets, 2007; Prod Info REQUIP(R) oral tablets, 2006). If concurrent use of ropinirole and a dopamin
warranted, monitor patients closely for loss of ropinirole efficacy.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the concurrent use of risperidone and ropinirole as this may result
ropinirole due to the antagonistic dopaminergic effect of risperidone (Prod Info REQUIP(R) oral tablets, 2006)
and a dopamine antagonist is clinically warranted, monitor patients closely for signs and symptoms of diminis
such as worsening of extrapyramidal movements, rigidity, tremor, or gait disturbances.
7) Probable Mechanism: pharmacological antagonism

3.5.1.CC Sematilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of sematilide and risperidone is not recommended due to the risk of additive ef concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of sematilide and risperidone is not recommended du life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring i
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 fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as sematilide and risperidon the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CD Sertindole

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of sertindole with other drugs that potentiallly prolong the QTc interval, such a approached with caution (Brown & Levin, 1998e; Prod Info Risperdal(R), 2002e).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as risper 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 rispe Laita et al, 1999aj; Ravin & Levenson, 1997o; Gesell & Stephen, 1997g; Lo Vecchio et al, 1996g; Brown
b) Thirty, otherwise healthy, schizophrenic patients participated in an open, dose titration (4 to 16 mg/da cardiovascular effects of sertindole. At the end of the 3-week study it was concluded that resting heart ra times increased in a dose-related manner, while there was no change in PQ-conduction times, autonomi pressure. Conduction times increased an average 3.5% to 6.5% over the dosing range (Agelink et al, 20
c) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998d). Periodic electrocard in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997a).

3.5.1.CE Simvastatin

1) Interaction Effect: increased simvastatin serum concentrations with an increased risk of myopathy or rhab
2) Summary: Concomitant use of risperidone and simvastatin may increase the bioavailability of simvastatin. are both metabolized by cytochrome P450-3A4 (CYP3A4). Although risperidone is predominantly metabolize a slow metabolizer phenotype due to possession of a CYP2D6 polymorphic genotype may convert to CYP3A risperidone metabolism. As a result, risperidone may competitively inhibit simvastatin metabolism, thereby in rhabdomyolysis. In a case report, a patient developed rhabdomyolysis complicated by acute compartment sy simvastatin concomitantly with risperidone (Webber et al, 2004).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of risperidone with simvastatin is not recommended. If concurrent patient for signs and symptoms of myopathy or rhabdomyolysis (muscle pain, tenderness, or weakness). Mo and discontinue use if CK levels show a marked increase, or if myopathy or rhabdomyolysis is diagnosed or
7) Probable Mechanism: competitive inhibition of cytochrome P450-3A4-mediated simvastatin metabolism
8) Literature Reports
a) Rhabdomyolysis occurred in a 22-year-old man after simvastatin 10 milligrams (mg) daily was added comprising clonazepam 2 mg and risperidone 4 mg daily. Approximately 5 days after beginning simvasta presented with right ankle and heel pain. Over the next 24 hours, the pain advanced proximally and incre extremity showing signs of warmth, erythema, rash, and pronounced tenseness of the distal muscle com kinase (CK), aspartate and alanine aminotransferase concentrations were 12, 408 units/liter (L), 296 Inte IU/L, respectively. CK concentrations peaked at 25, 498 units/L. Simvastatin was withdrawn and the pati decompression fasciotomies due to acute compartment syndrome of the right lower extremity. Risperido continued without incident (Webber et al, 2004).

3.5.1.CF Sotalol

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of sotalol and risperidone is not recommended due to the risk of additive effect 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 sotalol and risperidone is not recommended due t threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
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 fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as sotalol and risperidone m QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CG 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 Even though no formal drug interaction studies have been done, the coadministration of antipsychotics and o QTc interval, including spiramycin, is not recommended. Several antipsychotic agents have demonstrated QT amisulpride (Prod Info Solian(R), 1999v), haloperidol (O'Brien et al, 1999n), quetiapine (Owens, 2001y), rispe 1999ab), 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 recommende
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CH Sulfamethoxazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic do though no formal drug interaction studies have been done, the coadministration of antipsychotics and other d interval, including cotrimoxazole, is not recommended. Several antipsychotic agents have demonstrated QT p amisulpride (Prod Info Solian(R), 1999g), haloperidol (O'Brien et al, 1999d), quetiapine (Owens, 2001i), rispe 1999i), 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 recommer
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CI Sultopride

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of sultopride with other drugs that potentiallly prolong the QTc interval, such a approached with caution (Lande et al, 1992m; Montaz et al, 1992a; Harry, 1997b; Prod Info Risperdal(R), 20
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as risper recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone thera 1999p; Ravin & Levenson, 1997e; Gesell & Stephen, 1997a; Lo Vecchio et al, 1996a; Brown et al, 1993a
b) Sultopride may induce prolongation of the QT interval and ventricular arrhythmias including torsades or toxic doses (Lande et al, 1992l; Montaz et al, 1992; Harry, 1997a).

3.5.1.CJ Tedisamil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of tedisamil and risperidone is not recommended due to the risk of additive effe concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of tedisamil and risperidone is not recommended due threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is ac
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 fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation in Laita et al, 1999a). Concomitant use of Class III antiarrhythmic agents such as tedisamil and risperidone QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CK 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 which lengthen the QT interval (Agelink et al, 2001g; Owens, 2001j; Prod Info Haldol(R), 1998b; Lande et al, drug interaction studies have been done, antipsychotic agents should not be coadministered with other drugs 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 administra 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 thera 1999j; Ravin & Levenson, 1997b).

3.5.1.CL 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 therap (TM), 2002b; Owens, 2001ad; Prod Info Orap(R), 1999g). Even though no formal drug interaction studies hav coadministration of terfenadine and other drugs known to prolong the QTc interval, including antipsychotics, i
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT int agents, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.CM Tetrabenazine

1) Interaction Effect: increased risk of QT interval prolongation, neuroleptic malignant syndrome, extrapyram
2) Summary: Tetrabenazine causes a small increase in the correct QT interval. As the degree of prolongatio develop into torsade de pointes-type VT. The concomitant use of tetrabenazine with other drugs known for Q should be avoided. In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive control. The 50 mg d approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008) In addition to QT may also cause adverse reactions such as neuroleptic malignant syndrome and extrapyramidal disorders, wh coadministered with neuroleptic drugs (eg, risperidone) (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with risperidone or other neuroleptic drugs may i reactions, such as QT interval prolongation and increased risk of torsade de pointes. Other adverse reactions syndrome and extrapyramidal disorders may be enhanced when given with a dopamine agonist such as rispe oral tablets, 2008).
7) Probable Mechanism: increased dopamine levels; additive effects on QT interval prolongation

3.5.1.CN 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 interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstrated QT amisulpride (Prod Info Solian(R), 1999q), haloperidol (O'Brien et al, 1999j), pimozide (Prod Info Orap(R), 200 paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1 2001n), sultopride (Lande et al, 1992q), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral cap (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 antips contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CO Topiramate

1) Interaction Effect: decreased risperidone exposure
2) Summary: Concurrent administration of topiramate (200 mg/day) with a single, 2 mg dose of risperidone i

in a 25% decrease in risperidone exposure. Patients receiving risperidone and topiramate together should be response to risperidone (Prod Info TOPAMAX(R) oral tablets, oral sprinkle capsules, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: If risperidone and topiramate are administered concurrently, monitor patients closel risperidone (Prod Info TOPAMAX(R) oral tablets, oral sprinkle capsules, 2008).
7) Probable Mechanism: unknown

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

3.5.1.CQ Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999j), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001n), risper 1999n), sertindole (Agelink et al, 2001j), sultopride (Lande et al, 1992i), ziprasidone (Prod Info GEODON(R) i 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 phen not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.CR Trimethoprim
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic do though no formal drug interaction studies have been done, the coadministration of antipsychotics and other d interval, including cotrimoxazole, is not recommended. Several antipsychotic agents have demonstrated QT p amisulpride (Prod Info Solian(R), 1999g), haloperidol (O'Brien et al, 1999d), quetiapine (Owens, 2001i), rispe 1999i), 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 recommer
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CS 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 haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001a), o sultopride (Lande et al, 1992a), and zotepine (Sweetman, 2003). Even though no formal drug interaction stud coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod Info Pamelor(R 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experiment deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanis prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999

3.5.1.CT Valproic Acid

1) Interaction Effect: increased plasma valproic acid concentrations
2) Summary: The addition of risperidone to valproic acid produces a significant increase in the peak plasma acid (Prod Info Risperdal(R) Consta(TM), 2003c) as well as marked increases in ammonia levels (Carlson et capacity of risperidone could lead to a competition for protein-binding with the high protein-binding capacity o displacement of valproic acid from plasma protein-binding sites (van Wattum, 2001). However, Valproic acid treatment regimen consisting of risperidone (Spina et al, 2000c). Monitoring of ammonia levels may be warra new or increased manic behavior when taking valproic acid and risperidone, especially in patients vulnerable hyperammonemia, including the young, on valproate polytherapy, severely handicapped, or suffering from m decreased free serum carnitine (Carlson et al, 2007). In patients prescribed this combination of drugs, monitc OH-risperidone concentrations does not appear to be warranted.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Monitor for increased ammonia levels and plasma valproic acid concentrations with drug therapy or changes in risperidone dose.
7) Probable Mechanism: unknown
8) Literature Reports
a) In 2 case reports of 11 year-old boys, there were marked exacerbations in manic behavior and a 2 to ammonia levels when risperidone and valproic acid were concomitantly administered. The first patient, w disorder, attention-deficit/hyperactivity disorder (ADHD), psychosis, and manic symptoms, was admitted behavior. Chlorpromazine was added as needed and risperidone was added to replace his aripiprazole. acid 250 mg twice daily, the patient experienced a qualitative exacerbation of manic behavior. The risper adjusted to 2 mg/day and valproic acid to 625 mg/day. The patient's valproate level ranged from 87 to 9C When valproic acid was discontinued, and the ammonia level fell to 55, his manic behavior stopped. The absence epilepsy and ADHD, was on stable doses of valproic acid. Because of his psychotic symptoms, increased to 1.125 mg/day over 5 weeks. The patients exhibited markedly pronounced manic behavior a 113, despite a normal valproic acid level of 71. Upon discontinuation of risperidone and valproic acid, the and the manic behavior resolved. One month later when the patient was rechallenged with risperidone (i there was no return of either mania or hyperammonemia (Carlson et al, 2007).
b) A study was performed to evaluate the pharmacokinetic interaction between risperidone and valproic concentrations of risperidone and 9-hydroxyrisperidone (9-OH risperidone) were compared in patients tre patients comedicated with valproic acid. Thirty-three patients with a DSM-IV diagnosis of schizophrenia, bipolar disorder, were stabilized with risperidone alone or in combination with valproic acid. The results c given at doses up to 1200-1500 mg/day had clinically insignificant effects on plasma concentrations of ris metabolite. Valproic acid can be added safely to a treatment regimen consisting of risperidone. In patient drugs, monitoring of plasma risperidone or 9-OH-risperidone concentrations does not appear to be warra
c) The combination of valproic acid and risperidone led to significantly increased levels of valproic acid i suffered from mood swings and increasingly aggressive behavior. Valproic acid treatment was initiated a Valproate serum levels were in the therapeutic range. After 10 days of treatment, risperidone 2 mg/day w to 3 mg/day on day 4. On day 5 after risperidone was started, the patients symptoms improved but valpr therapeutic range at 191 mg/L. Valproic acid was decreased to 1000 mg/day and the level normalized to subsequently stabilized. The author concludes that the high-protein-binding capacity of risperidone could binding with the high protein-binding capacity of valproic acid, leading to displacement of valproic acid fro (Van Wattum, 2001).
d) In 21 patients, repeated oral doses of risperidone 4 mg daily did not affect the pre-dose or average pl (area under the concentration-time curve) of valproate 1000 mg daily compared to placebo. There was, h valproate maximum plasma concentration (Cmax) after risperidone coadministration (Prod Info Risperda

3.5.1.CU 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 recommen 2001b; Prod Info Solian(R), 1999a; Duenas-Laita et al, 1999c; Brown & Levin, 1998; Harry, 1997; Prod Info N Friedman, 1993; Mauro et al, 1988). Even though no formal drug interaction studies have been done, the coa 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 antipsy recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CV 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 Antipsychotics including haloperidol (Prod Info Haldol(R), 1998g), quetiapine (Owens, 2001aa), risperidone (I risperidone, 2000c), amisulpride (Prod Info Solian(R), 1999y), sertindole (Agelink et al, 2001u); sultopride (La (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses. Even though no formal 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 recommende
7) Probable Mechanism: additive effect on QT interval

3.5.1.CW Zotepine
1) Interaction Effect: increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Zotepine used concurrently with neuroleptics may increase the risk of seizures (Hori et al, 1992 drugs that potentiallly prolong the QTc interval, such as zotepine and risperidone, should be approached with Info Risperdal(R), 2002d).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitoring for seizures is particularly important in those patients who: (1) are taking have a history of seizure disorders; (3) are of young age; or (4) have a past history of brain injury. The concu prolong the QT interval, such as zotepine and risperdone, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Since zotepine can prolong the QT interval it is recommended that an ECG is performed before starti existing prolongation of the QT interval should not be given zotepine (Sweetman, 2004).
b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone thera 1999w; Ravin & Levenson, 1997j; Gesell & Stephen, 1997f; Lo Vecchio et al, 1996f; Brown et al, 1993f).

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic
1) Physical Findings
a) Bipolar Disorder
1) A prolonged time to relapse to any mood episode (depression, mania, hypomania, or mixed) is indica risperidone (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
2) Closely monitor effectiveness during the first 4 to 8 weeks of starting carbamazepine or other known inducers. The dose of risperidone may need to be titrated upward (Prod Info RISPERDAL(R) CONSTA(R
b) Schizophrenia
1) Positive and Negative Syndrome Scale (PANSS), which measures positive symptoms, negative symp uncontrolled hostility/excitement, and anxiety/depression, evaluates response to therapy (Prod Info RISP acting injection, 2009).
a) Positive psychotic symptoms (delusions, auditory hallucinations, racing thoughts)
b) Negative psychotic symptoms (anhedonia, apathy, amotivation, ambivalence).
2) Closely monitor effectiveness during the first 4 to 8 weeks of starting carbamazepine or other known inducers. The dose of risperidone may need to be titrated upward (Prod Info RISPERDAL(R) CONSTA(R
B) Toxic
1) Laboratory Parameters
a) Fasting blood glucose testing should be measured prior treatment and periodically during treatment in pat obesity, family history of diabetes) for diabetes mellitus. Patients with known diabetes mellitus should be regu glucose control during risperidone treatment. When symptoms of hyperglycemia develop, fasting blood gluco (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).
b) Complete blood count should be monitored frequently during the first few months of risperidone. If there a a decrease in CBC, then risperidone should be discontinued at the first sign of decline in WBC. For absolute 1000/mm(3), discontinue risperidone and perform follow-up WBC until recovery. Patients with preexisting low induced leukopenia/neutropenia are potentially at greatest risk for leukopenia, neutropenia, and agranulocyto

CONSTA(R) long acting injection, 2009).

2) Physical Findings

a) Tardive dyskinesia should be observed for in patients on risperidone particularly the elderly (elderly wome patients on chronic risperidone (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

b) Hyperglycemia symptoms including polydipsia, polyuria, polyphagia, and weakness should be monitored f (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

c) Monitor ECG at baseline and periodically during treatment (Pacher & Kecskemeti, 2004).

d) Cerebrovascular events (eg, stroke, transient ischemic attack) should be observed for in elderly patients v (not an indication) because of the higher incidence of cerebrovascular events observed with oral risperidone

e) Neuroleptic malignant syndrome (NMS) (hyperpyrexia, muscle rigidity, altered mental status, and evidenc (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) should be monitored fc should be immediately discontinued in the presence of NMS. Carefully monitor for NMS recurrence if risperid RISPERDAL(R) CONSTA(R) long acting injection, 2009).

f) Orthostatic hypotension symptoms including heart rate and blood pressure should be monitored for in all p during the initial dose-titration phase of oral risperidone. A dose reduction may be necessary if hypotension o predisposed to hypotension include those with known cardiovascular disease (history of myocardial infarction conduction abnormalities), cerebrovascular disease, who are dehydrated and hypovolemic, and in the elderly hepatic impairment (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

g) Fever and other symptoms or signs of infection should be monitored for in patients on risperidone becaus neutropenia or agranulocytosis (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

h) Patients at high-risk for suicide should be closely supervised during therapy because of the increased risk with schizophrenia or bipolar disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009).

i) Confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical featu neuroleptic malignant syndrome are manifestation of increased sensitivity in patients with Parkinson's Diseas

4.2 Patient Instructions

A) Risperidone (By mouth)

Risperidone

Treats schizophrenia and certain problems caused by bipolar disorder.

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

How to Use This Medicine:
Tablet, Liquid, Dissolving Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed what works best for you. Do not use more medicine or use it more often than your doctor tells you to.

Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup. You may mi milk, coffee, or orange juice. Do not mix with cola or tea.

If you are using the disintegrating tablet, make sure your hands are dry before you handle the tablet. Do not c contains the tablet until you are ready to take it. Remove the tablet from the blister pack by peeling back the f not push the tablet through the foil. Place the tablet in your mouth. It should melt quickly. After the tablet has water.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next c medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Do Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after treatment. You will also need to throw away old medicine after the expiration date has passed.

Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

There are many other medicines that you should not use while you are taking risperidone. Taking risperidone may be dangerous, even life-threatening. Make sure your doctor and your pharmacist knows about all other r

Make sure your doctor knows if you are taking carbamazepine (Tegretol®), cimetidine, furosemide (Lasix®), paroxetine (Paxil®), phenobarbital, ranitidine, or valproate (Depakene®, Depakote®). Tell your doctor if you a quinidine, phenytoin (Dilantin®), or rifampin (Rifadin®). Make sure your doctor knows if you are also using m

Some blood pressure medicines are atenolol, hydrochlorothiazide (HCTZ), lisinopril, metoprolol, quinapril, Ac Lotrel®, Norvasc®, Toprol®, and Zestril®.

Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a 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, plan to become pregnant, or if you are breast feeding. Tell
of liver disease, kidney disease, stroke, or breast cancer. Make sure your doctor knows if you have heart prol
seizures, or trouble swallowing.
Make sure your doctor knows if you have a family history of a heart condition called congenital long QT syndı
ever had Neuroleptic Malignant Syndrome (NMS) caused by other antipsychotic medicines.
This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your
are using medicine for diabetes, your doctor may need to change your dose.
This medicine is not approved to treat behavior disorders in older people who have dementia. Using this med
increase the risk of death. This risk has not been shown for the approved uses of this medicine.
Some side effects are more likely to happen in elderly people who have memory problems or other reduced r
doctor knows if the person who will be using this medicine has Alzheimer's disease or similar problems (ofter
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
alert.
This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If
might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too hot whil
places that are very hot. Call your doctor if you are too hot and cannot cool down.
This medicine may make your skin more sensitive to sunlight. Use a sunscreen when you are outdoors. Avoi
Risperdal® M-Tab® contains aspartame (phenylalanine). If you have phenylketonuria (PKU), talk to your doc

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

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, c
Change in how much or how often you urinate.
Confusion, weakness, and muscle twitching.
Constant muscle movement that you cannot control (often in your lips, tongue, arms, or legs).
Dry mouth, increased thirst, muscle cramps, nausea or vomiting.
Fast, slow, irregular (uneven), or pounding heartbeat.
Fever, sweating, muscle stiffness.
In males: Painful, prolonged erection of your penis.
Lightheadedness, fainting, or seizures.
Severe diarrhea, vomiting, or stomach pain.
Skin rash.
Sudden or severe headache, problems with vision, speech, or walking.
Twitching or muscle movements you cannot control (often in your eyes, jaw, neck or upper body).
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:

Anxiety, trouble sleeping, increased dreaming.
Constipation, diarrhea, nausea, or upset stomach.
Darkening of your skin.
Drooling, or stuffy nose.
In women: Unusually heavy bleeding during your menstrual period.
Severe tiredness.
Trouble having sex.
Weight gain.

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

B) Risperidone (Injection)

Risperidone

Treats schizophrenia and certain problems caused by bipolar disorder.

When This Medicine Should Not Be Used:
You should not receive this medicine if you have had an allergic reaction to risperidone.

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 given as
A nurse or other trained health professional will give you this medicine. This medicine is usually given every 2

If a Dose is Missed:

This medicine needs to be given on a fixed schedule. If you miss a dose or forget to use your medicine, call y
instructions.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

There are many other medicines that you should not use while you are taking risperidone. Taking risperidone may be dangerous, even life-threatening. Make sure your doctor and your pharmacist knows about all other r
Make sure your doctor knows if you are taking carbamazepine (Tegretol®), cimetidine (Tagamet®), furosemi (Larodopa®), fluoxetine (Prozac®), paroxetine (Paxil®), phenobarbital (Luminal®), ranitidine (Zantac®), or va Depakote®). Tell your doctor if you are using clozapine (Clozaril®), quinidine, phenytoin (Dilantin®), or rifamp doctor knows if you are also using medicine to lower blood pressure (such as atenolol, hydrochlorothiazide (H quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, or Zestril®).
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a 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 if you plan to become pregnant while you are using this r after you stop using it. Do not breastfeed while you are using this medicine and for at least 12 weeks after yo
Make sure your doctor knows if you have kidney disease, liver disease, diabetes, breast cancer, bone proble Reye's syndrome, Parkinson's disease, trouble with swallowing, or a history of seizures or neuroleptic malign doctor if you have any kind of blood vessel or heart problems, including low blood pressure, heart failure, a lo problems, or a history of a heart attack or stroke.
This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your are using a medicine for diabetes, your doctor may need to change your dose.
This medicine is not approved to treat behavior disorders in older people who have dementia. Using this med increase the risk of death. This risk has not been shown for the approved uses of this medicine.
Some side effects are more likely to happen in elderly people who have memory problems or other reduced r doctor knows if the person who will be using this medicine has forgetfulness or confusion related to aging (su dementia).
Stop taking this medicine and check with your doctor right away if you have any of the following symptoms wh convulsions (seizures), difficulty with breathing, a fast heartbeat, a high fever, high or low blood pressure, inc control, severe muscle stiffness, unusually pale skin, or tiredness. These could be symptoms of a serious cor malignant syndrome (NMS).
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine away if you have any of the following symptoms while taking this medicine: lip smacking or puckering, puffing movements of the tongue, uncontrolled chewing movements, or uncontrolled movements of the arms and leg
This medicine may make you dizzy, lightheaded, or drowsy. Avoid driving, using machines, or doing anything you are not alert. Change positions slowly when getting up from a lying or sitting position.
This medicine lowers the number of some types of blood cells in your body. Because of this, you may bleed c help with these problems, avoid being near people who are sick or have infections. Wash your hands often. S other situations where you could be bruised, cut, or injured. Brush and floss your teeth gently. Be careful whe razors and fingernail clippers.
This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too hot whil places that are very hot. Call your doctor if you are too hot and cannot cool down.
This medicine may cause some people to be agitated, irritable, or display other abnormal behaviors. It may a suicidal thoughts and tendencies or to become more depressed. If you or your caregiver notice any of these a right away.
This medicine may increase your weight. Your doctor may need to check your weight regularly during treatme
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, c
Change in how much or how often you urinate.
Chills, cough, sore throat, and body aches.
Dry mouth, increased hunger or thirst, or muscle cramps.
Fast, slow, pounding, or uneven heartbeat.
Feeling depressed, agitated, or nervous.
Fever, sweating, confusion, or muscle stiffness.
Lightheadedness, dizziness, or fainting.
Mood or behavioral changes, or thoughts of hurting yourself or others.
Numbness or weakness in your arm or leg, or on one side of your body.
Painful, prolonged erection of your penis (in males).
Problems with balance or walking.
Seizures or tremors.
Swelling in your hands, ankles, or feet.
Trouble with speaking or swallowing.
Twitching or muscle movements you cannot control (often in your eyes, jaw, neck or upper body).
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:
Blurred vision or change in vision.
Constipation, diarrhea, nausea, vomiting, or stomach pain or upset.
Dry mouth or drooling.
Headache.
Pain, swelling, or a lump under your skin where the shot is given.
Rash or itching skin.
Stuffy or runny nose.
Weight gain.

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

4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs (including risperidone) and typical antipsychotic drugs had a similar d cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched c patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least on outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as occurring in the community and admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or causes not related to ventricular tachy defined as the interval between the time the prescription was filled and the end of the day's supply. Low and high dose less than 100 milligrams (mg) of chlorpromazine, and doses comparable to chlorpromazine 300 mg or greater, respec sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic drugs in 79,589 person-years was less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 person-years wh 2.34, p less than 0.001). The risk of sudden cardiac death in current risperidone users in 24,589 person-years was 2.9 than 0.001). The risk of sudden cardiac death significantly increased with increasing dose in both the typical and atypi atypical antipsychotic use, the incidence rate ratio increased from 1.59 (95% CI, 1.03 to 2.46) in low-dose use to 2.86 dose use. To limit the effects of confounding of the study results, there was a secondary analysis performed in a coho propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In a Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence populations with cardiac risk profiles (eg, elderly patients), there should an age-dependent justification required prior to suggested (although not formally tested) that ECGs be performed before and shortly after initiation of antipsychotic the emergent QT interval prolongation (Schneeweiss & Avorn, 2009).

B) Schizophrenia

1) Risperidone is a benzisoxazole derivative. It is approved for the treatment of schizophrenia. It blocks both serc (2) receptors. It is effective in chronic schizophrenia for positive and negative symptoms with a response rate of 5 Rossi et al, 1997; Smith et al, 1996). At doses of 8 milligrams or less risperidone is associated with a lower risk of conventional antipsychotics (Foster & Goa, 1998). Comparative efficacy with haloperidol and other conventional n shown that risperidone has a significantly higher clinical response rate and allows for significantly less prescribing (Davies et al, 1998; Bech et al, 1998; Luebbe, 1996). Risperidone has also shown some efficacy in psychotic disc HIV, levodopa, and other medical conditions. Refractory obsessive-compulsive disorder and refractory depressior risperidone in select cases.

C) Bipolar Mania

1) Long-acting injection risperidone alone or in combination with lithium or valproate is approved for the maintena disorder (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 2009). Oral risperidone alone or in combina approved for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder (Prod I oral solution, orally-disintegrating tablets, 2006).

D) Irritability associated with Autistic Disorder

1) Risperidone is approved for the treatment of irritability associated with autistic disorder in children and adolesc aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods (Prod Info oral solution, orally-disintegrating tablets, 2006).

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

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) In vitro studies have shown that risperidone acts primarily as a serotonin (5-HT2) and dopamine (D2) antagoni serotonergic receptors. Risperidone also binds to alpha-1 and alpha-2 adrenergic and histamine H1 receptors, alt Dissociation from 5-HT2 and H1 receptors is slow; however, the drug rapidly dissociates from dopaminergic and a potency of risperidone as a dopamine D2 antagonist is less than that of haloperidol, and its 5-HT2 antagonist pote ritanserin. Risperidone interacts weakly or not at all with other receptor and neurotransmitter systems, including cl Anon, 1993a; Gerlach, 1991; Leysen et al, 1988; Niemegeers et al, 1988).

2) Studies have shown that there is an exponential dose-response relationship between the daily dose of risperid receptor occupancy (Dresel et al, 1998; Remington et al, 1998). The slope of the curve is between that of haloper closely resembles haloperidol. One study did find that extrapyramidal effects were linked to D(2) occupancy with t symptoms having the highest percentage of binding (Remington et al, 1998). The other study found no clear relati D(2) occupancy. They hypothesized that the decreased incidence of extrapyramidal effects seen with risperidone the D(2) receptor but to risperidone's high 5-HT(2) affinity providing a relative protection from symptoms (Dresel e

3) Animal studies have shown that risperidone inhibits tryptamine- and serotonin-induced cyanosis and 5-hydroxy twitching; it also blocks central and peripheral manifestations of dopaminergic stimulation, including apomorphine-

apomorphine- or amphetamine-induced stereotypy or hypermotility (Anon, 1991; Megens et al, 1988). Risperidon
than haloperidol in the inhibition of locomotion and induction of catalepsy; in addition, risperidone causes a signifi
corresponding to the effect of ritanserin (Gerlach, 1991).
4) Potent alpha-2 adrenoceptor blockade has been demonstrated with risperidone, as it reverses clonidine inhibit
norepinephrine release in occipital cortex. It also exhibits complete and potent lysergic acid diethylamide (LSD) a
1991; Leysen et al, 1988; Niemegeers et al, 1988).

B) REVIEW ARTICLES

1) The use of atypical antipsychotic medications in adults (Markowitz et al, 1999)(Brown et al, 1993h), and childre
1998; Toren et al, 1998) has been reviewed.
2) A pharmacoeconomic review of risperidone's use in schizophrenia has been published (Foster & Goa, 1998a).
3) Meta-analyses of risperidone versus haldoperidol's efficacy and safety (Davies et al, 1998) and cost-effectiven
been published.
4) Risperidone's role in the treatment of schizophrenia has been reviewed by the American Psychiatric Associatio
5) Risperidone controlled trials, clinical observations, and reports of side effects have been reviewed (Marder, 19
6) The Consensus Study Group on Risperidone Dosing has published guidelines on transitioning patients to rispe
7) A review of new neuroleptics with emphasis on risperidone as a new prototype is published in the German liter
8) New generation neuroleptics in the treatment of patients with negative symptomology are reviewed in the Gerr
9) Risperidone is examined with respect to its clinical profile and its place in therapy; in the German literature (Ta
10) A literary review rating the therapeutic actions of risperidone with a focus on negative symptomology, cognitiv
aspects is published in the German literature (Franz & Gallhofer, 1997).

4.5 Therapeutic Uses

Agitation, acute - Psychotic disorder

Anorexia nervosa

Autistic disorder - Irritability

Behavioral syndrome - Dementia

Behavioral syndrome - Mental retardation

Bipolar I disorder

Borderline personality disorder

Catatonia

Cocaine dependence

Cognitive function finding

Delusional disorder

Dementia

Dementia - Psychotic disorder

Depression, Refractory; Adjunct

Drug-induced psychosis - Levodopa adverse reaction

Gilles de la Tourette's syndrome

Huntington's disease

Inhalant abuse

Obsessive-compulsive disorder, Refractory

Organic psychotic condition

Parkinson's disease - Psychotic disorder

Pervasive developmental disorder

Pick's disease

Posttraumatic stress disorder

Schizophrenia

Schizotypal personality disorder

Stuttering

Tardive dyskinesia

Trichotillomania

Water intoxication syndrome

4.5.A Agitation, acute - Psychotic disorder

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Olanzapine orally disintegrating tablets and risperidone oral solution yielded similar improvements on the and Negative Syndrome Scale and the Clinical Global Impression scale in 87 patients treated for acute p emergency setting, according to an open-label, flexible-dose study(Hatta et al, 2008)

3) Adult:

a) Olanzapine orally disintegrating tablets (ODT) and risperidone oral solution (OS) yielded similar improvem for Positive and Negative Syndrome Scale (PANSS-EC) and the Clinical Global Impression (CGI) scale in 87 psychotic agitation in a psychiatric emergency setting, according to an open-label, flexible-dose study. Patien score of 15 or higher who accepted oral medication were assigned to receive initial doses of either olanzapin or risperidone OS 3 mg (n=53). Treatment group assignments were based on previous effective treatments, olanzapine or risperidone according to the time of study trial entry. Patients who experienced continued agita time, and after 1 hour could receive adjunctive drug therapy. PANSS-EC scores in both groups decreased ov from baseline was similar between the olanzapine and risperidone group (2.8 vs 3.2; p=0.22). Repeated mea score over time ANOVA (at baseline and every 15 minutes for 1 hour) revealed no significant main effect of t treatment over time (p=0.09 and p=0.41, respectively). There was a significant mean change in heart rate in t compared with risperidone OS group (-9.2 vs 1.1 beats/minute, p=0.03). There were no significant differences for adverse effects including extrapyramidal symptoms (Hatta et al, 2008).

4.5.B Anorexia nervosa

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

4.5.C Autistic disorder - Irritability

FDA Labeled Indication

1) Overview

FDA Approval: Adult, no; Pediatric, yes (5 years and older)
Efficacy: Pediatric, Effective
Recommendation: Pediatric, Class IIa
Strength of Evidence: Pediatric, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone was more effective than placebo in improving the emotional and behavioral symptoms of au towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods in short-ter studies (Prod Info RISPERDAL(R) oral tablets, oral solution, orally-disintegrating tablets, 2006; McCrack

continued risperidone therapy maintained efficacy up to 6 months and led to lower relapse rates compar
2002).
Treatment with oral risperidone was well tolerated and more effective in improving autism symptoms con
randomized, double-blind study (n=40) (Nagaraj et al, 2006).

3) Pediatric:

a) Risperidone was more effective than placebo for the short-term treatment of severe behavioral problems i
randomized, double-blind, placebo-controlled study (n=101). Patients (ages 5 to 17 years) with autism accom
problems (tantrums, aggression, or self-injurious behavior) received placebo (n=49) or risperidone 0.5 to 3.5
dose during last week, 1.8 mg/day) for 8 weeks. Primary efficacy measures were the score at eight weeks on
Aberrant Behavior Checklist and the rating on the Clinical Global Impressions-Improvement (CGI-I) scale. A p
a 25% or greater reduction in the Irritability score and a rating of much improved or very much improved on th
Irritability score for the risperidone group decreased by 56.9% following 8 weeks of treatment as compared w
placebo group (p less than 0.001). The rate of positive response was significantly higher in risperidone-treate
placebo (69% vs 12%, respectively; p less than 0.001). Risperidone was generally well tolerated and most ac
transient. Due to the uncertainty of a clear benefit with regard to the core symptoms of autism the authors rec
reserved for the treatment of moderate-to-severe behavioral problems accompanying autism (McCracken et a
endpoints, risperidone significantly decreased the overall score on the Ritvo-Freeman scale, which was modi
measure to a parent rating scale and included subscales for assessing sensory motor behaviors, social relate
sensory responses, and language (subscales I, II, III, IV, and IV, respectively). Specifically, significant treatm
noted for subscales I (effect size, 0.45; p=0.002), III (effect size, 1.1; p less than 0.001), and IV (effect size, 0
statistically significant effect on the subscales scores for social relatedness (subscale II) or language (subsca
deviation Children's Yale-Brown Obsessive Compulsive scale score (modified to only assess the compulsion
20) decreased from a baseline score of 15.51 +/- 2.73 to 11.65 +/- 4.02 in the risperidone group compared to
14.21 +/- 4.81 in the placebo group. For the total Maladaptive Behavior Domain (measured using the Vinelan
there was a significant treatment and time interaction during the 8-week trial (effect size, 1.03; p less than 0.0
baseline scores of 33.26 and 33.51 to 7.93 and 8.87 for the risperidone and placebo groups, respectively (Mc

1) Long-Term Extension

a) In a 24-week extension of the aforementioned study that included a 4-month, open-label extensio
placebo-controlled discontinuation phase, continued risperidone therapy maintained efficacy for auti
compared to the placebo group. Following 8 weeks of double-blind therapy in 101 patients, a total of
years) from both the risperidone and placebo groups received open-label risperidone for another 16
adjustments were allowed up to a maximum total daily dose of 3.5 milligrams (mg)/day in children w
and up to 4.5 mg/day for children weighing over 45 kg. Response was defined as at least 25% reduc
the Aberrant Behavior Checklist (ABC) and a rating of much improved or very much improved on the
Improvement (CGI-I) scale). Responders to the 4-month open-label extension therapy were random
either to continue risperidone at the same dose or to gradual placebo substitution (risperidone dose
weeks and assessed for relapse (defined as a 25% increase in the ABC-Irritability (ABC-I) subscale
much worse or very much worse for at least 2 consecutive weeks). At the end of the 4-month, open-
treat analysis revealed a minor but clinically insignificant increase in ABC-I score, going from a base
therapy) mean +/- standard deviation (SD) score of 9.5 +/- 6.8 to 10.8 +/- 7.1. There was a significar
at the end of the 4-month extension phase (p=0.02), Additionally, among 51 patients who completec
a much improved or very much improved rating on the CGI-I scale. A preplanned interim analysis du
revealed higher relapse rates in the placebo group compared to the risperidone group (62.5% (n=10
median time to relapse was 34 days and 57 days, respectively. This prompted early termination of th
Pediatric Psychopharmacology Autism Network, 2005). For secondary outcomes, improvements see
scores of the modified Ritvo-Freeman scale, the Children's Yale-Brown Obsessive Compulsive scale
the Maladaptive Behavior Domain of the Vineland Adaptive Behavior Scales, after 8 weeks of initial
the 4-month extension phase (McDougle et al, 2005).

b) Risperidone was more effective than placebo in improving the irritability symptoms of autism in an 8-week
children and adolescents with autistic disorder. Children (n=55; 5 to 12 years of age) with autistic disorder rec
0.02 to 0.06 mg/kg/day once or twice daily, starting at 0.01 mg/kg/day (mean modal dose of 0.05 mg/kg/day,
Efficacy was evaluated using the Aberrant Behavior Checklist (ABC). The change from baseline to endpoint i
ABC (ABC-I) was the primary outcome measure. This subscale evaluated the emotional and behavioral symp
aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. Risp
scores on the ABC-I subscale compared with placebo (Prod Info RISPERDAL(R) oral tablets, oral solution, o

c) Treatment with oral risperidone was more effective in improving autism symptoms compared to placebo ir
double-blind study (n=40). Consecutive children up to 12 years of age diagnosed with autism according to the
symptoms that included hyperactivity, aggression, stereotypies, and language difficulties were randomized to
either risperidone (initiated at 0.5 milligrams (mg)/day, increased to 1 mg/day 2 weeks later; n=19; mean age
(n=20; mean age, 63 months) for 6 months. The primary efficacy measures were changes from baseline in th
Rating Scale (CARS) and the mean Children's Global Assessment Scale (CGAS) scores at end of treatment.
irritability was the most common autism symptom (92%). At endpoint, 63% (n=12/19) of children in the risperi
improvement of at least 20% from baseline CARS scores compared to none in the placebo group. Median CA
(range, 32.5 to 46) at baseline to 32 (range, 24.5-40.5) at the end of treatment for the risperidone group comp
(range, 31.5-43 at baseline to 37.5 (30-42.5) at end of treatment for the placebo group (p less than 0.001). O
patients in the risperidone group had improvements (ie, increase in CGAS score of at least 20% from baselin
group (n=17 vs n=2). Mean CGAS scores increased from 29.79 and 32.65 at baseline in the risperidone and
40.94 and 35.2, respectively, at the end of treatment (p =0.035). Among secondary endpoints, based on an ir

questionnaire, risperidone improved functioning in domains of social responsiveness (n=7/19; p=0.014), nonv
p=0.008), decreased hyperactivity symptoms (n=7/19; p=0.002), and aggression and irritability (n=5/19; p=0.(
significant improvements in the domains of restricted interests, emotional interaction, or verbal communicatio
was well tolerated. Mild and transient dyskinesias occurred in 3 children. There was a nonstatistically significa
increase from baseline among risperidone-treated children (2.81 kilograms (kg; 17%) vs 1.71 kg (9.3%)) (Nag

4.5.D Behavioral syndrome - Dementia

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Improved target symptoms of agitation, aggression, hallucinations, and delusions in demented elderly
Cerebrovascular adverse events (stroke, transient ischemic attack) have occurred in elderly individuals (
received risperidone for treatment of dementia-related psychosis (Prod Info Risperdal(R), 2004)
Improved management of behavioral and psychological symptoms in elderly patients with dementia (De

3) Adult:

a) Risperidone and haloperidol produced similar reductions in severity of behavioral symptoms, especially ag
patients (DeDeyn et al, 1999). In a double-blind, 12-week study, agitated patients (55 years and older) with A
dementia, or a mixed dementia were randomized to receive risperidone (n=115), haloperidol (n=115), or plac
assessed using the Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). Both medicatior
milligrams (mg) daily and increased by 0.25 mg every 4 days up to 1 mg twice daily. If indicated, the patient's
to a maximum of 2 mg twice daily. At the end of 12 weeks mean doses were risperidone 1.1 mg/day and halo
patients having at least a 30% improvement at 12 weeks was similar at 72% for risperidone, 69% for haloperi
significant). However, risperidone showed significantly greater improvements in mean BEHAVE-AD total scor
(p=0.05). Risperidone also had a significantly greater improvement than placebo and haloperidol in the BEHA
(p=0.002; p=0.05). Somnolence occurred in 18% of haloperidol patients, 12% of risperidone, and 4% of place
b) In a retrospective chart review, demented patients treated with risperidone were shown to benefit from the
al, 1999). Charts of patients with Alzheimer's disease, Lewy body dementia, or a mixed dementia who had re
problems were reviewed. The average dose of risperidone used was 1.8 milligrams for a mean duration of 4 r
occurred in 15% of patients treated, 41% had a partial response, and 44% had no response. Approximately h
adverse effects including extrapyramidal symptoms in 32%, sedation in 17%, or worsening agitation in 7%.
c) In a case series of 22 patients with dementia and behavioral disturbances, risperidone in doses ranging fr
other day to 3 mg twice daily resulted in substantially improved behavior in 11 patients (50%). All patients me
14 patients with dementia of the Alzheimer's type, 6 with vascular dementia, and 2 with Lewy body dementia.
target symptoms were agitation, aggression, hallucinations, and delusions. The mean dose of risperidone use
Clinical Global Impression scale, 6 patients (27%) were rated as very much improved, 5 patients (23%) were
patients (27%) were rated as minimally improved. Eleven patients (50%) experienced extrapyramidal sympto
therapy within the first two weeks due to side effects (Herrmann et al, 1998).
d) In a pooled analysis, risperidone therapy was superior compared to placebo in managing behavioral and p
dementia in elderly nursing home residents. The pooled data was from three randomized, placebo-controlled
parallel group, Phase III trials. The efficacy analysis was preceded by a one week single-blind washout perio
psychotropic medications were discontinued. Patients were then randomized to receive risperidone (n=722) o
at a dose range of 0.25 to 1 milligram (mg) twice daily. Overall, the demographics and baseline characteristic
patients being women, Caucasian, and suffering from dementia for an average of 5 or more years. Agitation a
assessed using the Cohen-Mansfield agitation inventory (CMAI) scores. Risperidone produced significantly g
to placebo in CMAI total scores from week 4 through week 12 (mean change from baseline to end point: -11.
than 0.001). Decreases in the total aggression and total non-aggression scores were also both statistically sig
less than 0.001). The severity of behavioral and psychological symptoms associated with dementia were ass
behavioral pathology in Alzheimer's disease (BEHAVE-AD). At all evaluation points, scores on the BEHAVE-
more improved with risperidone versus placebo (mean change from baseline to end point: -6.1 versus -3.6, re
The psychotic symptoms subscale of the BEHAVE-AD found that risperidone produced significantly greater in
patients with psychosis at baseline (mean change from baseline: -3.5 +/- 0.21 (n=434) versus -2.5 +/- 0.32 (n
The paranoid and delusional symptoms were significantly improved in the risperidone group compared to pla
0.002). However, there was no significant difference between the groups regarding improvement in hallucinat
0.3; p=0.191). The clinical global impression (CGI) scores were also significantly improved in the risperidone
A subgroup analysis on dementia type (Alzheimer's disease, vascular dementia and mixed dementia) found t
total scores were significantly improved in the risperidone group in both Alzheimer's disease and vascular de
dementia subjects. Treatment-emergent adverse events were comparable between risperidone (84.3%) and
number of patients who discontinued therapy due to treatment-emergent adverse events was higher in the ris
versus placebo (11.2%). Common adverse events leading to discontinuation in the risperidone group were so
extrapyramidal disorders, aggressive reaction, pneumonia, injury, cerebrovascular disorder, and fall (De Deyn

4.5.E Behavioral syndrome - Mental retardation

1) Overview

FDA Approval: Adult, no; Pediatric, no

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

2) Summary:
Useful for the adjunctive therapy of behavioral disturbances in patients with mental retardation
Effectively reduced severe behavior problems in children with below average intelligence

3) Adult:
a) Seven patients with Prader-Willi Syndrome and behavioral disturbances responded favorably to risperidor average dose was 1.64 milligrams daily). Six patients were adults and 1 was an adolescent. The patients hac antipsychotic medications (Durst et al, 2000).
b) In one double-blind, placebo-controlled crossover study, 37 patients with behavioral abnormalities such as irritability, agitation, hyperactivity, automutilation, and autism despite current therapy improved on risperidone medications were given orally for 3 weeks, followed by 3 weeks of crossover treatment. Doses of risperidone day; at weekly evaluations, daily dosage was increased by 4 mg/day up to a maximum total dose of 12 mg/da Global Impression (CGI) scores occurred. Risperidone caused significant improvement in CGI parameters th study; placebo was not effective. No extrapyramidal symptoms occurred. No significant cardiovascular, bioch were reported (Vanden Borre et al, 1993a).

4) Pediatric:
a) Risperidone was safe and effective as a short- and long-term therapy for the reduction of severe behavior moderate intellectual disabilities. In a 6-week, randomized, double- blind, placebo controlled study, patients (average intelligence (IQ, 36 to 84) and a diagnosis of conduct disorder, oppositional defiant disorder, or disru otherwise specified received placebo (n=63) or risperidone (n=55) 0.02 to 0.06 milligrams (mg)/kilogram/day Efficacy of risperidone was assessed according to the change in score from baseline to endpoint on the cond Nisonger Child Behavior Rating Form. Patients treated with risperidone showed a significantly larger reductio subscale scores from baseline to endpoint as compared with placebo (-15.2 vs -6.2, respectively; p less than patients also showed significantly better improvements than did placebo-treated patients on all other subscal Rating Form. Risperidone was generally well tolerated and most adverse effects were mild to moderate, inclu headache (29%). As a long-term, open-label extension, 107 patients from this controlled study received rispe titrated up to maximum of 0.06 mg/kg/day; mean dose 1.51 mg/day) for 48 weeks. Throughout the 48-week e was maintained in patients treated with risperidone during the controlled trial and significant symptom improv who had received placebo during the controlled trial. Risperidone was generally well tolerated throughout the Adverse events included headache (32.7%), somnolence (32.7%), rhinitis (28%), increased appetite (9.3%), increase from baseline, 5.5 kilograms), and transient, mild elevations in prolactin levels (mean maximum leve (ng/mL) in boys; 23.9 ng/mL in girls). Additional studies are needed to investigate the safety and efficacy of ri for the treatment of severe, disruptive behavior in pediatric patients (Findling et al, 2004; Aman et al, 2002).

4.5.F Bipolar I disorder

FDA Labeled Indication

1) Overview
FDA Approval: Adult, yes (oral and intramuscular); Pediatric, yes (10 years and older, oral only)
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Intramuscular long-acting risperidone is indicated as monotherapy or in combination with lithium or valpr treatment of bipolar I disorder in adults (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 200
Oral risperidone is indicated for the short-term treatment of acute manic or mixed episodes associated w aged 10 years of age and older and adults (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPI disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).
Oral risperidone, at doses ranging from 0.5 to 6 milligrams per day for 3 weeks, was effective in the treat episodes of bipolar I disorder in children aged 10 to 17 years in a multicenter, randomized, double-blind, Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20 oral solution, 2007).

3) Adult:
a) Monotherapy
1) Intramuscular
a) In a multicenter, randomized, double-blind, placebo-controlled study of adult patients who met DS bipolar disorder type I and who were stable on medications or experiencing an acute manic or mixed intramuscular (IM) risperidone was effective for the maintenance treatment of bipolar I disorder. Dur a total of 501 patients were treated with IM risperidone at the starting dose of 25 mg and titrated up in patients not tolerating the starting dose). Of the 501 treated patients, 303 (60%) were deemed to to double-blind treatment with either the same dose of IM risperidone or placebo. The results of the compared to placebo, patients receiving monotherapy IM risperidone were delayed to reaching the was the time to relapse to any mood episode (depression, mania, hypomania, or mixed). The majori rather than depressive symptoms and based on their history of bipolar disorder, these patients had, episodes than depressive episodes (Prod Info RISPERDAL(R) CONSTA(R) long acting injection, 20

2) Oral

a) Risperidone monotherapy was effective in the acute and continuation treatment of mania in patie open- label, multicenter study, patients with acute mania and a score of at least 20 on the Young Ma received six months of risperidone monotherapy at a mean dose of 4.2 milligrams (mg) daily (range improvements in the YMRS score were observed from baseline to weeks 1, 2, 4, 6, 12, and 24 (p les improvements in Clinical Global Impression and Positive and Negative Syndrome Scale scores were as compared with baseline (p less than 0.0001). Extrapyramidal symptoms (ie, dystonia, hypokinesi week 4 (p=0.015) (correlating with the highest mean doses of risperidone), but then decreased signi (p=0.027). Other adverse events included impotence, drowsiness, weight gain (mean increase, 3.2 l dizziness, hypotension, incontinence, and galactorrhea. Within the initial 4 weeks of treatment, incre symptoms was seen in four patients (4.2%) and the appearance of a depressive episode was obser Randomized, controlled studies are needed to confirm the safety and efficacy of risperidone monoth of bipolar mania (Vieta et al, 2004).

b) In two placebo-controlled trials, risperidone monotherapy was more effective than placebo in red patients with bipolar disorder. Patients meeting DSM-IV criteria for bipolar I disorder with manic or m without psychotic features received risperidone (1 to 6 milligrams (mg)/day; mean modal dose, 4.1 t weeks (n=246; n=286). In both trials, risperidone was more effective than placebo in the reduction o (YMRS) scores of these patients (Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDA tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) Combination Therapy

1) Intramuscular

a) In a multicenter, randomized, double-blind, placebo-controlled study of adult patients who met DS bipolar disorder type I and who experienced at least 4 episodes of mood disorder requiring psychiat previous 12 months and at least 2 episodes in the 6 months prior to starting the trial, long-acting intr effective for bipolar I disorder when used as combination therapy with lithium or valproate. During a total of 240 patients were treated with IM risperidone at the starting dose of 25 mg and titrated up if patients not tolerating the starting dose) in addition to continuing their usual bipolar disorder therapy discontinued after the first 3 weeks of the initial injection of IM risperidone. Of the 240 treated patien be stable for at least the last 4 weeks and were randomized to double-blind treatment with either the placebo in addition to their usual bipolar disorder therapy for 52 weeks. The results of the 52-week s compared to placebo, patients receiving IM risperidone as combination therapy were delayed to rea which was the time to relapse to any new mood episode (depression, mania, hypomania, or mixed) RISPERDAL(R) CONSTA(R) long acting injection, 2009).

2) Oral

a) The efficacy of risperidone as a combination therapy for the treatment of manic or mixed episode disorder was established in one controlled trial, while a second controlled trial failed to show efficacy combination trial, patients (n=148) on lithium or valproate therapy (therapeutic range, 0.6 to 1.4 mEq respectively) with bipolar I disorder with or without psychotic features and with inadequately controlle received risperidone (1 to 6 mg/day; mean modal dose, 3.8 mg/day), an active comparator, or place original therapy. Combination therapy with adjunctive risperidone was more effective than lithium or of the YMRS total score. However, in a second combination trial in 142 patients on lithium, valproate inadequately controlled manic or mixed symptoms, the addition of risperidone (1 to 6 mg/day; mean not superior to lithium, valproate, or carbamazepine (therapeutic range, 0.6 to 1.4 mEq/L, 50 to 125 respectively) alone in the reduction of the YMRS total score. The failure of this trial could be due to i hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 20 oral solution, 2007).

b) Risperidone (median modal dose of 4 milligrams) may be more effective in the treatment of mani bipolar disorder than placebo when combined with mood stabilizing drugs. Bipolar patients, aged 18 with a manic or mixed episode and a score of at least 20 on the Young Mania Rating Scale (YMRS) double-blind, placebo-controlled study. To be eligible for this study the patient also had to be taking divalproex or carbamazepine) for a minimum of 2 weeks prior to randomized assignment into treatm measure was the change in YMRS score from baseline to endpoint. There was a decrease of 14.5 a score for the risperidone and placebo groups, respectively, at the end of the 3 weeks (p=0.089). Ris patients with or without psychotic features. When combined with carbamazepine, risperidone media concentrations decreased by 40%. Due to a high number of dropouts in both groups the study was i determine the true treatment effects. Additional studies are ongoing (Yatham et al, 2003).

c) Risperidone was associated with significantly greater improvement compared with placebo. A mu group study investigated adding risperidone, haloperidol, or placebo to a mood stabilizer (lithium or acute mania. After completing the 3 week, double-blind phase of the study, patients were offered op an additional 10 weeks of follow-up. Improvement on the Young Mania Rating Scale and the Clinica Improvement scale was greater with risperidone at 3 weeks. The investigators concluded that risper addition to lithium or valproate for the treatment of bipolar mania (Ghaemi & Sachs, 1997).

d) An improvement was seen in all patients who completed another small, 6-week, open label study (mean dose, 3 mg per day) and concurrent mood-stabilizing drugs in the treatment of acute psychot enrolled and by week 6, all of the completers had a 50% improvement as assessed by the Young M 1996).

e) As an add-on therapy, risperidone brought significant improvement to patients with bipolar disorc

bipolar type. In a 6-month, open study, patients with a diagnosis of bipolar or schizoaffective disorde hypomanic, depressive, or mixed episode (n=541; 430 completed the study) were given risperidone anticonvulsants, and antidepressants to clinical response and tolerability. The average dose of rispe was 4 milligrams (mg) per day and at the end of the study, 3.9 mg/day. For all patients, scores on th (YMRS) were significantly reduced at week 1 and at every point thereafter (p less than 0.001 for all patients, for whom p was less than 0.05). Mean scores on the YMRS decreased from 25.6 at baseli scores on the Hamilton Rating Scale for Depression (HAM-D) were significantly reduced from baseli than 0.0001), with scores declining from 12.8 at baseline to 4.1 at 6 months. Scores on the Positive (PANSS) declined from 72 at baseline to 40 at 6 months (p less than 0.0001). According to the Clini (CGI), no patients were free from symptoms at baseline and only 5% were rated as "mildly ill." At st showed no symptoms of mania or depression and a further 30% were "mildly ill." During the study, 2 relapses into a mood state different from that at the start of the trial. Scores for extrapyramidal symp study than at baseline (p less than 0.0001). There were significant reductions in dystonia, rigidity, hy dyskinesia, tremor, and akathisia subscores. There were no cases of new-emergent tardive dyskine reactions included increase in weight (2.4% of patients), drowsiness (1.3%), impotence (0.7%), and very low incidence of exacerbation mania in the first 6 weeks (1.8%) (Vieta et al, 2001).

f) Long-term use of adjunctive risperidone for breakthrough episodes of mania or depression was re study. A group of outpatients (n=12) with bipolar disorder type I, who experienced breakthrough epis maintenance medication, were treated with a mean dose of 2.75 mg per day of risperidone. Scores Functioning scale improved from 10 to 25 points in 4 of the 8 patients who completed 6 months of tr worsening of mania (Sachs G, 1999).

g) In an open study, 10 patients with rapid cycling bipolar disorder (type I or type II) improved with r 1998). Patients were allowed to continue thyroid medications and benzodiazepines but had all antid discontinued. Risperidone was started at 1 milligram twice daily and titrated as needed. After 6 mon 5.5 affective episodes during the previous 6 months to 2 episodes while receiving risperidone (p less Rating Scale for Depression scores also decreased from 14 to 6.

h) Open studies using risperidone 1 to 6 milligrams as adjunct therapy in the treatment of refractory some efficacy. In one study, 9 out of 14 patients were rated as much improved on the Clinical Globa Among the other 5 patients, 3 stopped due to ataxia and dizziness or weight gain and 2 experienced al, 1997). In another study, 4 of 7 patients had a mild to moderate improvement on the CGI rating sc change after therapy (McIntyre et al, 1997). A controlled trial is needed to establish the benefits of ri

4) Pediatric:

a) Monotherapy

1) In a multicenter, randomized, double-blind, placebo-controlled trial, oral risperidone, at doses ranging day, was effective in the treatment of mania in children aged 10 to 17 years. Patients who were experien bipolar I disorder were randomized to receive either risperidone 0.5 to 2.5 mg/day (n=50; mean modal do mg/day (n=61; mean modal dose, 4.7 mg), or placebo (n=58) for 3 weeks. Risperidone was initiated at 0 target dose by day 7, with further increases to the maximum tolerated dose by day 10. Compared to plac groups showed a significant reduction from baseline in the total Young Mania Rating Scale (YMRS) scor seen in the 3 to 6 mg/day dose group were comparable to those seen in the 0.5 to 2.5 mg/day dose grou evident at doses higher than 2.5 mg/day. Adverse events reported at a higher incidence than placebo in fatigue (18%-30%), dizziness (13%-16%), dystonia (8%-13%), abdominal pain (15%-18%), nausea (13% somnolence (42%-56%), and abnormal vision (4%-7%) (Prod Info RISPERDAL(R) oral tablets, 2007; Pr orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007).

b) Combination Therapy

1) In a case series including 11 children and adolescents aged 5 to 16 years with difficult to manage mo bipolar disorder) and aggressive behavior, 8 had therapeutic responses to risperidone 0.75 to 2.5 milligra symptoms were clinically very diverse and most were taking concurrent medications, such as mood stab psychometric instruments were used for assessment, so improvement was purely subjective. Seven pati marked improvement and one patient was considered moderately improved. Side effects reported includ anxiety (Schreier, 1998).

4.5.G Borderline personality disorder

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Has reduced aggressive behavior and hostility in patients with borderline personality disorder

3) Adult:

a) Treatment with risperidone was associated with improvement in aggression, mood, and anergy in 13 patie disorder. In an 8-week open label study, patients were given risperidone, starting at 1 milligram (mg) per day basis to a maximum of 4 mg/day. The average final dose was 3.27 mg/day. Scores on the Brief Psychiatric R reduced by an average of 21% (p=0.003), with improvements specifically on the anergia scale (p=0.0033) an (p=0.0144). Depression was reduced (p=0.0025) and, according to the self-rated Aggression Questionnaire, by 18% (p=0.0057). Four patients experienced insomnia and 3 experienced agitation. Somnolence, anxiety,

reported by 2 patients (Rocca et al, 2002).

b) A 31-year-old woman with comorbid borderline personality disorder and dysthymia was successfully treat
(Szigethy & Schulz, 1997). She had been hospitalized 5 times and had failed therapy with fluoxetine, sertralir
perphenazine. She had been maintained on fluvoxamine but after an exacerbation of symptoms, risperidone
sustained improvement over the next 3 months. Risperidone was increased and a fluvoxamine taper was uns
resumption of fluvoxamine she was again able to return to her full-time job.

c) A 31-year-old woman was successfully treated with risperidone for her extreme impulsivity associated witl
personality disorder (Khouzam & Donnelly, 1997). After being refractory to multiple antipsychotics, antidepres
carbamazepine and valproate, she went into remission on risperidone 4 milligrams daily.

4.5.H Catatonia

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

One case report documents the successful use of risperidone for catatonia

3) Adult:

a) A 47-year-old man with persistent organic catatonia responded to risperidone 4 milligrams twice daily ther
with psychotherapy and pharmacologic therapy that included antidepressants, lithium carbonate, and various
1996).

4.5.I Cocaine dependence

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone is not effective in reducing cocaine use
Risperidone reduced craving and relapses in cocaine-dependent patients with schizophrenia

3) Adult:

a) Cocaine Dependence Only

1) There was no reduction in cocaine use associated with risperidone. A 12-week, randomized, double-l
evaluated using risperidone for the treatment of cocaine dependence. Cocaine-dependent subjects (n=1
or 8 mg of risperidone, with a subsequent change to active doses of 2 mg and 4 mg. Subjects attended t
provided urine samples, obtained medication, and underwent one behavioral therapy session per week.
interim analysis. Retention was worse for the 4 and 8 mg medication groups. Side effects were primarily
although neither the 2 nor 4 mg dose was well accepted by subjects. Risperidone is unlikely to find broa
cocaine dependence (Grabowski et al, 2000).

b) Schizophrenia With Concomitant Cocaine Dependence

1) The results of a pilot study suggest that risperidone therapy reduced craving and relapses in cocaine-
schizophrenia. In this 6-week, open label trial, patients with a dual diagnosis of schizophrenia and cocair
of cocaine/month) received risperidone (n=8; initial, 2 milligrams (mg)/day, titrated to maximum dose of 6
neuroleptic medication treatment (n=10; haloperidol, fluphenazine, or chlorpromazine). Patients in the ris
less cue reactivity in regard to the intensity (p=0.005) and depression (p=0.031) dimensions of craving a
therapy, but there was no statistical difference on the energy and feeling sick dimensions. Risperidone-tr
significantly lower rate of relapse (defined as any substance abuse) than did patients on typical neurolep
respectively; p=0.025). Although not significant, a tendency toward a greater reduction in negative and g
was seen in risperidone-treated patients. Larger, double-blind studies are needed to substantiate these f

4.5.J Cognitive function finding

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone-treated patients have shown some positive results in their neurocognitive abilities

3) Adult:

a) In a small randomized study (n=13), risperidone demonstrated an advantage over haloperidol for improvir
(Addington & Addington, 1997). Patients received either risperidone or haloperidol over a 6 week period. The
risperidone subjects on executive functioning (Wisconsin Card Sorting Test), on a measure of sustained atter
test), and on delayed verbal recall.

b) Risperidone therapy appeared to exert a more favorable effect on verbal working memory in treatment-res than did haloperidol therapy (Green et al, 1997a). In a randomized, double-blind comparison of treatment witl haloperidol (n=29), verbal working memory was measured at baseline and after 4 weeks of both a fixed dose Risperidone patients showed a significant improvement in memory using a Digit Span Distractibility Test from the fixed-dose (p less than 0.0001) and the flexible dose (p less than 0.0003) phases. The haloperidol-treated significantly. Results suggest that treatment of schizophrenia could be broadened to include the impact on ne
c) Risperidone improved neuropsychological impairment in withdrawn cocaine-dependent patients (Smelson patients received either risperidone 2 to 4 milligrams or no drug. Neuropsychological testing was done before group receiving risperidone showed improvement in the Digit Symbol test (p less than 0.01), the Trails Part A Grooved Peg Board dominant (p less than 0.003) and nondominant tests (p less than 0.06). No difference wa

4.5.K Delusional disorder

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone has been effective in the treatment of delusional disorder in case reports and open trials
Risperidone was effective treatment of monosymptomatic hypochondriacal psychosis

3) Adult:

a) Risperidone reduced most delusional parameters in a 50-year-old female with persecutory delusions (Fea treatment with sulpiride, 200 to 800 milligrams (mg) daily, produced side effects and resulted in patient noncc patient was originally part of a 24-week, double-blind, randomized, placebo-controlled, crossover trial (1 to 4 placebo) with 4 participants; all other participants dropped out of the study. A collaborative approach was use in the study. In this approach the delusions are not challenged from the outset. The certainty with which the p change, but these beliefs were qualitatively different; the persecution had happened in the past, but was not tools used were the Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS) of Delusions Schedule (MADS). During the placebo phase (weeks 0 to 11) there was no change in delusiona (weeks 12 to 24), the patient received 2 weeks of 1 mg risperidone, which was then titrated to 2 mg accordin trial crossover, MADS results indicated improvement in delusional condition had begun; substantial improvem risperidone treatment. The final trial dose was 2 mg of risperidone at night. By the end of the 24-week trial, ef marked reduction or absence of delusions, suspicions, anxiety, tension, and depression.
b) Risperidone eliminated or reduced delusions of theft in 17 of 18 patients treated for 12 weeks in an open- burden on the caretaker was evaluated for 16 of the responding patients. The mean daily risperidone dose fo milligrams. There were significant reductions in Neuropsychiatric Inventory (NPI) scores for delusion (p less t (p=0.002), anxiety (p=0.017), irritability/lability (p=0.023), and aberrant motor behavior (p=0.011) with risperid Zarit Caregiver Burden Interview (ZBI) dropped from 41 at the start of the study to 23 at 12 weeks (p less tha
c) An 81-year-old male presented with tactile hallucinations and DELUSIONS OF INFESTATION at which tir initiated and started gradually. The patient was asymptomatic 3 months later. After 9 months he returned with haloperidol that had been prescribed by another physician. Haloperidol was discontinued and low dose risper later his symptoms recurred and the risperidone dose was increased. At the time of publication he was sympt
d) A 23-year-old male presented with ocular complaints. He was suffering from continuous pain and the feeli down his face. Risperidone 2 milligrams per day was started and increased to 4 milligrams per day 3 days lat after 2 weeks and discharged at 4 weeks (Cetin et al, 1999).

4.5.L Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.M Dementia - Psychotic disorder

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Reduces frequency and severity of delusions and agitation
Cerebrovascular adverse events (stroke, transient ischemic attack) have occurred in elderly individuals (received risperidone for treatment of dementia-related psychosis (Prod Info RISPERDAL(R), RISPERDA solution, orally disintegrating tablets, 2005)

3) Adult:

a) Low-dose risperidone was efficacious in the treatment of behavioral and psychological symptoms of deme 8-week study included 34 patients, ranging in age from 53 through 89 years (35% between 70 and 79 years; exhibiting dementia and at least one of the following symptoms: delusions, hallucinations, agitation/aggressio primary diagnosis of 59% of the patients was Alzheimer's type dementia. At baseline, the illness of 71% of pa "severe" or "very severe." By the end of the study, the mean dose of risperidone was 1.1 milligram (mg) per d

received 1 mg/day, 18% received 0.5 mg/day, and 32% more than 1 mg/day. Both frequency and severity of
were significantly reduced by week 8 (p=0.0002 and p=0.0033, respectively for the product of frequency and
was also significantly reduced (p=0.0452). Fifty-nine percent of patients were rated as "much" or "very much
some degree of improvement, according to the Clinical Global Impression of Change scale. Cognition was ur
The mean increase in the Extrapyramidal Symptom Rating Scale (ESRS) score was 0.8 (p less than 0.01). O
sedation, and vertigo occurred in a few patients. No patient withdrew because of extrapyramidal symptoms o
al, 2001).

b) Risperidone was effective and well-tolerated for the treatment of psychotic symptoms and behavioral distu
comorbid medical illnesses and medications (Zarate et al, 1997). In a review of medical records, 122 hospital
newly treated with risperidone were assessed. Patients received risperidone for agitation or psychosis associ
major mood disorder (29%), or other disorder (18%). Most were also medically ill and received other psychot
drugs (70%). Risperidone appeared to be effective in 85% of cases. In the demented group of patients with a
82% were rated as improved. Patients starting on low doses and undergoing slow dosage increases, were le
drug events (p=0.002). Risperidone was discontinued in 11% due to side effects and in 7% due to lack of effi

c) Two cases of patients with psychotic symptoms secondary to Lewy-Body dementia responsive to risperid
& Hussain, 1998; Geizer & Ancill, 1998). The first was a 59-year-old man with depressive illness, anxiety, agg
hallucinations, and hallucinations (Hussain & Hussain, 1998). He had some relief of symptoms with trifluoper
Risperidone 2 milligrams twice daily increased to 3 mg twice daily made the visual hallucinations disappear a
74-year-old male with visual hallucinations, persecutory delusions, and agitation. He was started on risperido
psychotic experiences. He then had donepezil added and within 2 weeks had complete resolution of psychos

4.5.N Depression, Refractory; Adjunct

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Improvement was demonstrated with risperidone compared with placebo augmentation of antidepressan
depression in a double-blind, 4-week, placebo-controlled, study (n=97); however, the treatment effect wa
(Keitner et al, 2009).

There were modest but statistically significant improvements in treatment-resistant depression with 6 we
to antidepressant drugs compared with placebo in a multicenter, double-blind, randomized trial in adults

Short-term benefit of risperidone augmentation in patients with treatment-resistant depression was not su
months) in a multinational, double-blind, placebo-controlled study (n=243) (Rapaport et al, 2006).

3) Adult:

a) General Information

1) Risperidone, as augmentation to antidepressant medication, has provided some benefit in the short-t
with treatment-resistant or difficult-to-treat depression (Mahmoud et al, 2007), (Keitner et al, 2009); howe
augmentation for 24 weeks failed to prevent relapse of depression (Rapaport et al, 2006). There were m
improvements with 6 weeks of risperidone augmentation compared with placebo in a multicenter, double
randomized trial (n=274) (Mahmoud et al, 2007). In another double-blind, 4-week, placebo-controlled, stu
demonstrated with risperidone compared with placebo augmentation diminished around 4 weeks (Keitne
augmentation did not prevent relapse in the long-term (9 months) in a multinational, double-blind, placeb
(Rapaport et al, 2006).

b) Clinical Trials

1) Improvement was demonstrated with risperidone compared with placebo augmentation of antidepres
depression in a double-blind, 4-week, placebo-controlled study (n=97); however, the treatment effect wa
Patients (n=147) with unipolar, nonpsychotic major depression were enrolled in an open-label treatment
monotherapy for 5 weeks if they were currently not on antidepressant drugs, if they were not currently re
an adequate dose and duration, or if they had poorly documented antidepressant therapy. At the end of t
responders and non-responders with a Montgomery-Asberg Depression Rating Scale (MADRS) rating of
double-blind, randomized phase (n=43). Additionally, patients (n=54) with well documented failure of cur
adequate dose and duration were enrolled in the double-blind phase directly, without going through the o
bipolar I, bipolar II, or psychotic features were among those excluded. During the double-blind phase, pa
dose of their antidepressant drug and were randomized to additionally receive either risperidone (n=62) o
Risperidone was initiated at 0.5 milligrams (mg) per day, and the dose was increased, if necessary, to 2
thereafter (mean dose at end of 4 weeks, 1.6 mg/day). Based on Clinical Global Impression (CGI) scores
moderately ill at baseline (risperidone, 68.8%; placebo, 69.7%) and mean baseline MADRS scores were
the risperidone and placebo groups, respectively. In the modified intent-to-treat population (received at le
competed at least 1 set of assessments), the primary outcome of remission (MADRS rating of 10 or less)
(n=32/62) and 24.2% (n=8/33) of patients in the risperidone- and placebo-treated groups, respectively, a
The corresponding rates of remission for those who completed all 4 weeks of treatment (n=82) were 52.7
(p=0.052). Treatment difference was evident after 2 weeks, with remission rates of 37.3% and 15.6% in t
groups, respectively. Notably, while both treatments demonstrated improvement over time, the difference
significant at week 4. The odds ratio for remission with risperidone compared with placebo was 3.33 (95%
Among other outcomes, rates of response (50% decrease from baseline MADRS rating) at 4 weeks were

risperidone and placebo groups, respectively (p=0.049), with significant differences seen after 1 week of respectively; p=0.031). When remission and response were evaluated on the Hamilton Depression Scale between risperidone and placebo were not statistically significant. Patient ratings of overall life satisfactio significantly better in the risperidone group compared with the placebo group (from 1.3 to 2.5 and 1.2 to differences apparent by 2 weeks of treatment. The overall frequency of side effects was similar in the risp (81.8%) groups (Keitner et al, 2009).

2) There were modest but statistically significant improvements in treatment-resistant depression with 6 augmentation to antidepressant drugs compared with placebo in a multicenter, double-blind, randomized label, 4-week, run-in period identified 274 patients (age range, 18 to 65 years) with unremitting major dep Impression-Severity of Illness (CGI-S) score of 4 or more, and a Carroll Depression Scale score of 20 or antidepressant monotherapy at the recommended dosage. These patients were then randomized to 6 w with either oral risperidone (n=141) or placebo (n=133). The risperidone dose was 0.25 milligrams (mg) e every day for days 4 to 15, followed by 1 mg every day for days 16 to 28. At the investigator's determinat day 29, risperidone was either continued at 1 mg/day or the dose was increased to 2 mg/day, or double- At the start of randomization, the mean time since diagnosis of depression was 16.7 +/- 12.3 years, and Depression 17-item (HRSD-17) scores for the risperidone- and placebo-treated patients were 24.3 and 2 patients continued on their baseline antidepressant regimen, which consisted of a selective serotonin reu group, 59.1%; placebo group, 59.5%), a serotonin-norepinephrine reuptake inhibitor (22.6% and 19.8%, such as bupropion and trazodone (17.6% and 19.9%, respectively). The primary outcome was the chang HRSD-17 total score; response was defined as a 50% or more reduction in score and remission was def The final risperidone dose was 1 mg for 65.7% and 59.5% of risperidone- and placebo-treated patients, r primary outcome are listed in the table below (Mahmoud et al, 2007).

Outcome	Risperidone	Placebo	Difference (95% CI)
Mean (+/- SE) HRSD-17			
Week 4*	15.4 +/- 0.52	17.3 +/- 0.52	-1.9 +/- 0.69 (95% CI, -3.3 t
Week 6**	13.4 +/- 0.54	16.2 +/- 0.53	-2.8 +/- 0.72 (95% CI, -4.2 t
Remission Rates			
Week 4*	13.6%	6%	--
Week 6**	24.5%	10.7%	--
Response Rates			
Week 4*	35.6%	18.8%	--
Week 6**	46.2%	29.5%	--

KEY: SE = standard error; CI = confidence interval; HRSD-17 = Hamilton Rating Scale for Depress
*risperidone: n=118; placebo: n=117
** risperidone: n=106; placebo: n=112.

Secondary outcomes, which included clinician-rated measures (measured by CGI-S) and patient-rat Quality of Life Enjoyment and Satisfaction Questionnaire, Patient Global Improvement Scale, Sheeh significantly more with risperidone compared with placebo at week 6. The number needed to treat w augmentation to achieve 50% baseline symptom improvement in treatment-resistant depression wa tolerated, with premature study discontinuation due to adverse effects occurring in 5.8% of risperido placebo-treated patients. Frequency of motor events was similar between the risperidone and place 0%, respectively; dystonia, 0% and 0.8%; tremor, 0.7% and 0.8%) and did not require use of benztr

3) Short-term benefit of risperidone augmentation in patients with treatment-resistant depression was nc months) in a multinational, double-blind, placebo-controlled study (n=243). The study design consisted o weeks of open-label citalopram monotherapy (initial dose, 20 milligrams (mg); target dose range, 40 mg label risperidone augmentation, and a 24-week double-blind, placebo-controlled continuation of the rispe enrolled in the open-label citalopram monotherapy phase had major depressive disorder, single or recur psychotic features, a score of 20 or more on the Hamilton Rating Scale for Depression (HAMD-17), and to respond to at least 1 but not more than 3 antidepressant trials of at least 6 weeks' duration at the labe failed to respond (less than 50% reduction in HAMD-17 total score) after 6 weeks or were unchanged or citalopram were augmented with open-label, oral risperidone (n=390). For patients aged 18 to 54 years, mg/day and increased up to 2 mg/day (goal, 1 mg/day); patients aged 55 to 85 years old received 0.25 n increases permitted up to 1 mg/day (goal, 0.5 mg/day). Patients achieving a HAMD-17 score of 7 or less (CGI)-Severity score of 1 or 2 during the risperidone augmentation (n=243, 63% of the open-label risperi randomized to receive either placebo (n=120; mean age, 48.4 years) or to continue on risperidone (n=12 weeks. Time to relapse, the primary outcome, was defined as 1 or more of the following: 6 (much worse) CGI-Change score, 16 or higher on the HAMD-17 score, lack of efficacy leading to discontinuation, or int ideation. There were more women than men in the double-blind continuation phase (71.3% vs 56.3%). T risperidone and placebo groups at baseline was 17.9 +/- 12.3 years and 17.6 +/- 13.9 years, respectively double-blind phase, 63.1% were complete non-responders (less than 25% reduction in HAMD-17 score) responders (25% to 49% reduction in HAMD-17) to open-label citalopram. Based on Kaplan-Meier analy was 102 days and 85 days (p=0.52) for the risperidone augmentation group and placebo augmentation g

rates of 53.3% and 54.6%, respectively. The HAMD-17 baseline scores worsened by 7.6 +/- 8.8 points fr
blind phase) score of 6 +/- 3 in the risperidone group and by 7.9 +/- 8.1 points from a baseline score of 6
(for both, p less than 0.001 compared with baseline). The Montgomery-Asberg Depression Rating Scale
12.6 points from a baseline score of 6.8 +/- 4.7 in the risperidone group and 10.4 +/- 11.2 points from a b
both, p less than 0.001 compared with baseline) in the placebo group. The mean prolactin concentration
nanograms/milliliters (ng/mL) and 6.6 +/- 21 ng/mL (p less than 0.001) in the risperidone and placebo gro
occurred in 2.5% and 0%, respectively. During the double-blind phase, the mean weight increase was 1.
risperidone group compared with a mean loss of 0.5 +/- 2.9 kg in the placebo group (Rapaport et al, 200
4) Adjunctive risperidone therapy was effective in the treatment of nonpsychotic depressive disorders in
a case series, five female patients (ages 48 to 61 years) with treatment-resistant depression and suicida
(maximum dose, 1 milligram/day) in addition to their current antidepressant medication for at least 5 mor
Impressions-Severity of illness scores were reported as "markedly ill" or "among the most extremely ill" a
adjunctive therapy, all patients were rated as "very much improved" on the Clinical Global Impressions-Ir
patients did not report further suicidal ideation. Risperidone was well tolerated. Larger, controlled studies
these findings (Viner et al, 2003).
5) Eight cases were described of risperidone therapy augmenting selective serotonin reuptake inhibitor
major depressive episodes without psychotic features (Ostroff & Nelson, 1999). All patients had incomple
therapy with Hamilton Rating Scale for Depression (HAM-D) scores of 16 to 27. Risperidone 0.5 to 1 mill
and HAM-D scores decreased to a range of 0 to 6 within 1 to 7 days.

4.5.O Drug-induced psychosis - Levodopa adverse reaction

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective for levodopa-induced psychotic symptoms

3) Adult:

a) In an open-label trial in 10 patients, low dose risperidone was useful for levodopa-induced psychotic symp
with advanced Parkinson's disease and cognitive decline (Meco et al, 1997b). Nine patients improved signific
Rating Scale and the Hallucinosis Questionnaire after 2 weeks and peaked after 6 weeks (p less than 0.01).
risperidone due to worsening Parkinson's disease.
b) In a 26 week-trial, 23 of 39 parkinsonism patients treated with risperidone demonstrated complete or near
hallucinations and delusions and an approximately 50% to 75% reduction was seen in another 4 patients. Six
improvement and an additional 6 had rapid and pronounced deterioration of parkinsonism which required risp
mean dose of risperidone was 1.10 milligrams (mg) with a mean duration of treatment of 16.2 weeks. Sixteen
trial (Leopold, 2000). Similar results were found in a 12-week open pilot study involving 17 patients receiving
day (Mohr et al, 2000).

4.5.P Gilles de la Tourette's syndrome

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

May be an effective alternative for treatment of Tourette's syndrome

3) Adult:

a) Risperidone was effective in treating patients with Tourette's Syndrome (TS). In a randomized, double-blir
patients with moderate to severe TS received either risperidone 0.5 to 6 milligrams/day or placebo for 8 week
0.25 mg once daily and increased to 0.5 mg twice daily. Thereafter, the dose could be altered for an individua
exceed 6 mg/day. Sixty-one percent of patients in the risperidone group and 26% in the placebo group impro
Tourette's Syndrome Severity Scale (TSSS) by 8 weeks (p=0.04). The severity of disease at baseline did not
risperidone group also showed significantly greater improvement in functioning than did the placebo group (p
occurring in patients with greater impairment in functioning at baseline. Patients treated with risperidone shov
parkinsonism than did patients treated with placebo (p=0.004. An increase in parkinsonism occurred only in p
average parkinsonism at baseline. Risperidone caused a greater incidence of fatigue than did placebo (57%
(35% vs 4%, p=0.02). Depression also occurred more frequently with risperidone, resulting in discontinuation
group (Dion et al, 2001).
b) Risperidone treatment resulted in improvement in the severity of Tourette's syndrome tics in an open trial
1996). All subjects (age range 8 to 53 years) had been treated with clonidine and neuroleptics and had exper
unacceptable side effects. The mean risperidone dose was 2.7 milligrams/day (range 0.5 to 9 mg/d). Twenty-
took neuroleptics during the study period. Eight patients dropped out because of side effects; of the original 3
experienced improvement. Reported side effects included sedation (18% of patients), akathisia/agitation (10%
weakness, insomnia, depression, anxiety, and aggressive behavior (3% each). Risperidone dose, other medi

diagnoses did not significantly affect response, and there was no correlation between those factors and the ty

4) Pediatric:

a) Tourette syndrome patients demonstrated a reduction in aggression in 78.5% of 28 patients and a decrea of tics in 61.7% of 28 patients. The average daily dose of risperidone was 2 milligrams daily. The tics and agg at baseline and 2 weeks to 4 months later (average 2 months) (Sandor & Stephens, 2000).

4.5.Q Huntington's disease

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective for the involuntary movements per case reports

3) Adult:

a) Four patients with involuntary movements secondary to Huntington Chorea (and no psychotic symptoms) therapy (Dallocchio et al, 1999). Patients received an initial dose of risperidone 1 milligram (mg) every 8 hour were increased in 0.5-mg increments per day to 3 mg every 8 hours. There was no significant improvement s higher doses produced a significant reduction in choreic disturbances as seen on the Marsden and Quinn Sc Symptoms worsened again as the patients were withdrawn from risperidone. Another patient with genetically but only with psychosis and no movement disorder also received risperidone 3 mg/day. Her psychiatric condi any side effects.

4.5.R Inhalant abuse

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone was effective in the treatment of inhalant abuse

3) Adult:

a) A 25-year-old male had a 5-year history of inhalant (gasoline and carburetor cleaning fluid) abuse. Risperi daily was started which effectively reduced hallucinations and paranoia and eliminated aggressive behavior c After an increase to 1 mg twice daily paranoid thoughts ceased and craving for inhalants was reduced. He ha follow-up (Misra et al, 1999).

4.5.S Obsessive-compulsive disorder, Refractory

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Adjunctive therapy may be effective for obsessive-compulsive disorder refractory to serotonin reuptake i 2008; McDougle et al, 2000; Agid & Lerer, 1999; Stein et al, 1997; Saxena et al, 1996).

3) Adult:

a) Adjunctive therapy of risperidone or olanzapine with serotonin-reuptake inhibitors (SRI) were equally effec compulsive symptoms in SRI monotherapy-resistant outpatients, according to an 8-week, single-blind, rando conclusion may be limited by the lack of a placebo arm, single-arm design, and underpowered nature of the t prospective, open-label phase of SRI monotherapy (n=96), patients who were treatment-resistant (defined as the total score of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and a Clinical Global Impression Seve entered an 8-week single-blind phase (n=50). Patients in the single-blind phase received SRI daily doses of c citalopram 50 to 80 mg, fluoxetine 60 mg, fluvoxamine 200 to 300 mg, paroxetine 50 to 60 mg, or sertraline 2 receive either risperidone 1 to 3 mg/day (n=25), or olanzapine 2.5 to 10 mg/day (n=25) in addition to the SRI personnel and assessor-blinding constituted the single-blind study design; patients were not blinded. In an int carried forward analysis of the primary endpoints, both treatments significantly improved Y-BOCS and CGI-S The magnitude of change in mean Y-BOCS total scores, CGI-S scores, and responder rates (35% or greater versus baseline, and a CGI-I score of 2 or less) was similar between groups.

Primary Efficacy Endpoints at 8 Weeks		
	Risperidone (n=25)	Olanzapine (n=25)

Responder rates*	44% (11/25)	48% (12/25)
Mean end-point Y-BOCS score	22.6 +/- 7.2	22.2 +/- 7.4
Change in mean Y-BOCS score from baseline	-7.5; p less than 0.001	-8.4; p less than 0.0
Mean end-point CGI-S score	3.2 +/- 1.7	3.1 +/- 1.8
Change in mean CGI-S score from baseline	-1.7; p less than 0.001	-1.9; p less than 0.0
* p=1; Y-BOCS=Yale-Brown Obsessive Compulsive Scale; CGI-S=Clinical Global Impression Severity s		

b) Adverse effects of risperidone compared with olanzapine-treated patients included tension/inner unrest (2 (16% vs 52%, p=0.016), and amenorrhea (66.7% vs 10%, p=0.02), respectively. The small sample size and t calculation may have contributed to the limitations of this study (Maina et al, 2008).
c) Obsessive compulsive disorder (OCD) patients with and without comorbid chronic tic disorders or schizoty respond to the addition of low-dose risperidone to ongoing serotonin reuptake inhibitor (SRI) therapy. A doub was designed to determine the short-term efficacy and tolerability of potent SRIs in combination with risperid refractory to SRIs alone. Seventy adult patients with a primary diagnosis of OCD received 12 weeks of treatm patients were refractory to 6 weeks of risperidone (n=20) or placebo (n=16) addition. Behavioral ratings, inclu Compulsive Scale, were obtained at baseline and throughout the trial. Placebo-treated patients subsequently trial of risperidone addition. For study completers, 9 (50%) of 18 risperidone-treated patients were responder mg per day) compared to 0 of 15 in the placebo addition (p less than 0.005). Seven (50%) of 14 patients who addition responded. Risperidone addition was superior to placebo in reducing OCD (p less than 0.001), depre anxiety (p=0.003) symptoms. Other than mild, transient sedation, risperidone was well tolerated (McDougle e
d) Risperidone (initial dose of 2 milligrams/day) was effective in a 24-year-old patient with methamphetamine compulsive disorder-like symptoms (Iyo et al, 1999).
e) Fourteen of 16 patients with obsessive-compulsive disorder had substantial reductions in obsessive-comp within 3 weeks of initiating risperidone. Result were usually seen within the first few days. Before the addition received a serotonin reuptake inhibitor (SRI) for at least 12 weeks either alone or in combination with mood s anxiolytics. In addition to the OCD, patients had horrific mental imagery, comorbid schizophrenia, schizoaffec disorder (Saxena et al, 1996).
f) In a case series, 3 of 8 patients with obsessive- compulsive disorder (DSM-IV criteria) showed significant i Global Impression Change Scale after receiving augmentation with risperidone 1 to 2 milligrams/day. Of the noted minimal to much improvement, 3 patients had no change in symptoms and 1 patient was unable to tole 1997).
g) A 25-year-old man with obsessive compulsive disorder refractory to multiple medications improved with ri paroxetine (Agid & Lerer, 1999). Risperidone 1.5 milligrams (mg)/day was added to paroxetine 60 mg/day. Hi Obsessive Compulsive Scale for obsessions went from 14 to 4 and for compulsions went from 20 to 2. After The depressed symptoms responded to a decreased dose of risperidone of 0.5 mg/day.

4.5.T Organic psychotic condition

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

2) Summary:
Has reduced symptoms of psychosis caused by medical conditions

3) Adult:
a) A case series reports the successful use of risperidone in five patients who fulfilled DSM-IV criteria for psy condition and two who met the criteria for mood disorder due to a general medical condition with severe psyc 1997). All seven responded to treatment including four patients who had previously failed initial treatment wit antipsychotic agent.
b) In a case series of 21 patients with HIV-related psychotic disorders, 20 patients treated with risperidone h (Singh et al, 1997). Most responded to low doses (mean 3.3 milligrams) and required only a short course (me adverse effects were reported and no hematological effects were observed.

4.5.U Parkinson's disease - Psychotic disorder

See Drug Consult reference: THERAPY OF PSYCHOTIC DISTURBANCES IN PARKINSONIAN PATIENTS

4.5.V Pervasive developmental disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; 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

2) Summary:

Effective for the treatment of symptoms related to pervasive developmental disorders and autism in adul
In children with autism spectrum disorder, responders to 24 weeks of open-label therapy with oral risperi
rates when randomized to continue additional 8 weeks of double-blind treatment with risperidone versus
Treatment with oral risperidone relieved several behavioral symptoms associated with pervasive develop
to 12 years in an 8-week, multicenter, randomized, double-blind, placebo-controlled study (n=79) (Shea

3) Adult:

a) Risperidone therapy was effective in 3 autistic disorder patients. All 3 patients tolerated risperidone well a
effects. Effective doses in each patient were 5 milligrams daily, 4 milligrams daily, and 1 milligram daily, resp
2 of the patients and both showed no increase in seizure frequency. Improved social relations and reduced a
observed in all patients and decreased repetitive behavior in 1 patient (McCartney et al, 1999).

b) In a double-blind, placebo controlled trial including adults with autistic disorder (n=17) or pervasive develo
patients treated with risperidone (mean dose 2.9 milligrams per day) were considered responsive to therapy
recipients (p less than 0.002). At the end of the 12 week trial, patients initially randomized to placebo were tre
During open-label treatment, 60% of patients were considered responders. Repetitive behaviors were evalua
the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and aggression was evaluated with the Self-injurious
Q). The Clinical Global Impression (CGI) Scale and the Rivto-Freeman Real-life Rating Scale were also used
the CGI, Y-BOCS, SIB-Q, and overall Rivto-Freeman Scale were significantly improved with risperidone com
0.05 for all analyses). Improvements became evident at 4 weeks and continued throughout the 12-week stud
effect was transient sedation. Other than one patient who developed gait abnormalities, extrapyramidal side e
(McDougle et al, 1998).

4) Pediatric:

a) In a double-blind extension phase, continued treatment with risperidone was more effective than placebo
spectrum disorder symptoms among responders to 24 weeks of open-label risperidone therapy. Children age
the DSM-IV (Third Revision) criteria for a pervasive development disorder (PDD) and who demonstrated clini
aggression, self-injurious behavior, or a combination of these problems were enrolled in the open-label phase
children weighing under 45 kilograms (kg), risperidone was initiated at 0.5 milligrams (mg) at bedtime, increas
later, and subsequently increased in 0.5-mg increments to a maximum dose of 2.5 mg/day by day 29. Doses
mg/day by day 29 in children weighing more than 45 kg. Patients with an at least 25% reduction from the bas
(ABC) Irritability score (baseline mean score, 23) and a rating of much improved or very much improved on th
(CGI) of Severity scale after 8 weeks were classified as responders (26/36) and allowed to continue taking ris
At 24 weeks of open-label treatment, 69% (18/26) of patients were rated as much improved or very much imp
Change (CGI-SC) scale, with significant decreases in ABC Irritability subscores as well; most improvements
Completers of the additional 16 weeks of therapy were randomized in a double-blind fashion to either continu
placebo (gradual withdrawal for 3 weeks and placebo only for 5 weeks; n=12) for 8 weeks. Relapse was defir
Symptom Change (CGI-SC) scores of much worse or very much worse for at least 2 consecutive weeks and
the last ABC Irritability score. An intention-to-treat analysis revealed relapses (primary endpoint) in 3 and 8 pa
placebo groups, respectively (p=0.049), with a longer mean time to relapse in patients maintained on risperid
Compared to mean +/- standard deviation (SD) ABC Irritability subscale scores of 11.1 +/- 8.1 and 12.7 +/- 7.
groups, respectively, at week 24, scores at the end of the study (week 32) were 12.6 +/- 9.8 (14% increase) a
p=0.043), respectively. Improvements noted at week 24 among other ABC subscales, such as social withdra
inappropriate speech, were fairly well maintained until the end of the study in the risperidone, there were no s
between the groups at study end. Treatment-emergent adverse events were mild to moderate and included i
(39%), fatigue (35%), and increased thirst (26%). At week 24, the mean weight gain from baseline was 5.7 +/
less than 0.0001). It should be noted that the majority (75%; n=18/24) of the study population had a form of P
and 63% (n=15/24) had average or above-average intelligence (Troost et al, 2005).

In an 8-week, multicenter, randomized, double-blind, placebo-controlled study (n=79) in children, treatme
several behavioral symptoms associated with pervasive development disorder (PDD). Pediatric outpatie
age, 7.5 years; greater than 75% male) with a DSM-IV Axis I diagnosis of PDD and a total score of 30 or
Rating Scale (CARS), with or without mental retardation were randomized to receive either an oral soluti
placebo (n=39) in 1 or 2 divided doses for 8 weeks. Risperidone was initiated at 0.01 milligram/kilogram/
0.02 mg/kg/day on day 3. At day 8, the dose was further increased at a maximal increment of 0.02 mg/kg
increments or decrements were allowed up to a maximum daily dose of 0.06 mg/kg/day. Using the Aberr
efficacy was primarily assessed for change in irritability from baseline to endpoint on the irritability subsc
assessments included scores on the other 4 ABC subscales (hyperactivity/noncompliance, inappropriate
withdrawal, and stereotypic behavior), the parent-rated Nisonger Child Behavior Rating Form (N-CBRF),
Impression-Change (CGI-C; 7-point scale ranging from very much improved to very much worse). At bas
most common form of PDD (risperidone, 67.5%; placebo, 71.8%), and 57.5% and 53.8% of patients in th
groups, respectively, were diagnosed with severe autism. At endpoint, patients in the risperidone group h
daily dose was 0.05 mg/kg/day (mean daily dose, 1.48 mg) for a mean duration of 52.7 days (range, 2 to
analysis (included all patients receiving at least 1 study dose and with at least 1 postbaseline assessmer
decreases from baseline irritability scores in the risperidone group (64% improvement) compared to plac
Based on CGI-C scores, global improvements occurred in 87.2% and 39.5% of risperidone- and placebo
with 54% and 18% of patients, respectively, reporting a rating of much improved or very much improved
there was a greater decrease in the Visual Analog Scale score of aggression (most frequently reported t
the risperidone-treated patients compared to placebo (mean score decrease, 38.4 vs 26.2, respectively;
Results of the primary and key secondary endpoints are listed in the table below. Treatment-emergent a
severity, with somnolence (72.5% vs 7.7%), upper respiratory tract infection (37.5% vs 15.4%), rhinitis (2

appetite (22.5% vs 10.3%) being the most commonly reported among risperidone-treated patients (Shea

Efficacy measure	Risperidone (n=39)		Placebo (n=38)
	Baseline	Endpoint (change from baseline)	Baseline
ABC subscale (mean +/- SD)			
Irritability	18.9 +/- 8.8	-12.1 +/- 5.8*	21.2 +/- 9.7
Hyperactivity/noncompliance	27.3 +/- 9.7	-14.9 +/- 6.7*	30.9 +/- 8.8
Inappropriate speech	4.6 +/- 3.4	-2.6 +/- 2.6**	4.8 +/- 3.7
Lethargy/social withdrawal	13.7 +/- 7	-8.6 +/- 5.9***	14.3 +/- 8.2
Stereotypic behavior	7.9 +/- 5	-4.3 +/- 3.8**	8.1 +/- 5.6
N-CBRF (parent version) subscale (mean +/- SD)			
Conduct problem	16.8 +/- 9.4	-10.4 +/- 7.4*	23.3 +/- 12
Hyperactive	17.2 +/- 5.8	-8.1 +/- 4.6**	18.9 +/- 5.3
Self-Isolated/ritualistic	7.5 +/- 4.1	-4.8 +/- 3.9	8.2 +/- 4.5
Insecure/anxious	8.7 +/- 8.1	-4.6 +/- 6.5**	10.6 +/- 7.6
Overly sensitive	6.9 +/- 3.4	-3.8 +/- 2.8**	7.4 +/- 3.5
Self-injurious/sterotypic	4.2 +/- 4.2	-2.6 +/-3.3	3.5 +/- 4.2

Key: n=number of subjects; ABC=Aberrant Behavior Checklist ; N-CBRF=Nisonger Child Behavior Rati
deviation
*p less than or equal to 0.001 vs placebo
**p less than or equal to 0.05 vs placebo
***p less than or equal to 0.01 vs placebo

b) Risperidone improved functionality on the Children's Global Assessment Scale in 13 out of 14 cases in an adolescents (ages 9 to 17 years) treated for pervasive developmental disorders. Starting doses of 0.25 milligi increased in 0.25 mg/day increments every 5 to 7 days to optimal doses ranging from 0.75 to 1.5 mg daily in occurred in attention, lessening of obsessional behaviors, decrease in agitation and anxiety and improvemen Steele, 1996).

c) Behavioral symptoms improved in a series of 6 children (ages 7 to 15) with pervasive developmental diso treatment for 5 months (range 1-8 months) at a mean optimal dose of 2.7 milligrams (mg) daily (range 1 to 6 patient rating scores decreased, which reflected improvements in aggression, temper tantrums, and mood ins followed for more than 2 years, of whom one discontinued risperidone due to increased liver enzymes; one p new agent, and the third patient continued risperidone with good response (Perry et al, 1997)

4.5.W Pick's disease

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in one case report

3) Adult:

a) A 42-year-old woman with a presumptive diagnosis of Picks Disease was treated with risperidone (titrated demonstrated significant improvements and cognitive stabilization. The author suggested that controlled trials antipsychotics in treating Picks Disease need to be performed and might produce promising results (Curtis &

4.5.X Posttraumatic stress disorder

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Possibly effective in treating patients with irritable aggression in posttraumatic stress disorder
Possibly effective in treating intrusive thoughts associated with posttraumatic stress disorder

3) Adult:

a) Risperidone was effective in a 48-year-old male war veteran demonstrating increased irritability and anger stress disorder. Fluoxetine and diazepam were ineffective. With the addition of risperidone 1 milligram daily t reported less intensity in his anger and more confidence in his ability not to act on it (Monnelly & Ciraulo, 199
b) Two patients with posttraumatic stress disorder responded favorably to risperidone 6 milligrams daily and Other agents were ineffective (Krashin & Oates, 1999).

4.5.Y Schizophrenia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (oral and intramuscular); Pediatric, yes (13 years and older, oral only)
Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIa; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone is indicated for the treatment of schizophrenia in adults (Prod Info RISPERDAL(R) CONSTA Prod Info RISPERDAL(R) oral tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating table (R) oral solution, 2007)and pediatric patients 13 years of age and older (Prod Info RISPERDAL(R) oral ta RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007) Approved for maintenance treatment of schizophrenia in adults (Prod Info RISPERDAL(R) oral tablets, 2 M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007; Prod Info RISPE acting injection, 2009)
Oral risperidone, at doses ranging from 1 to 6 milligrams per day, was effective in the treatment of schizo to 17 years in 2 short-term (6 and 8 weeks), double-blind, controlled trials (Prod Info RISPERDAL(R) ora RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R) oral solution, 2007)

3) Adult:

a) General Information

1) Risperidone is effective for the positive and negative symptoms associated with chronic schizophreni 75% (Foster & Goa, 1998b; Rossi et al, 1997a; Smith et al, 1996a). Dose ranges of risperidone 4 to 16 m greater improvement than placebo in Clinical Global Impression (CGI) and total Positive and Negative Sy The 4 to 6 milligram dose appears to be the most effective (Marder & Meibach, 1994a; Chouinard et al, 1 Spahn, 1992a). At doses of 8 milligrams or less risperidone is associated with a lower risk of extrapyram antipsychotics (Foster & Goa, 1998b). Comparative efficacy with haloperidol and other conventional neu risperidone has a significantly higher clinical response rate and allows for significantly less prescribing of (Davies et al, 1998)(Bech et al, 1998a; Luebbe, 1996a). Patients treated with risperidone have a lower re with haloperidol (Csernansky et al, 2002a). Patients have also been successfully switched from depot an et al, 1999).

b) Monotherapy

1) Intramuscular

a) Long-acting injectable risperidone was significantly more effective than placebo in the treatment a randomized, double-blind, placebo-controlled, multicenter study, patients (n=400) with schizophre injections of long-acting risperidone (25 milligrams (mg), 50 mg, or 75 mg) or placebo every two wee week run-in period, patients received oral risperidone (titrated to a dose of 4 mg/day) for at least 3 d risperidone (2 mg/day, 4 mg/day, or 6 mg/day) or placebo for the first three weeks of the double-blin Positive and Negative Syndrome Scale (PANSS) total scores were significantly more improved in pa risperidone 25 mg, 50 mg, or 75 mg as compared with those who received placebo (p=0.002, p less respectively). Improvements in positive and negative symptoms were also significantly greater in all groups as compared with the placebo group (p less then or equal to 0.05, all values). Clinical improv 20% reduction in PANSS total scores and was observed in only 17% of placebo patients as compar patients in the 25 mg, 50 mg and 75 mg long-acting risperidone groups, respectively (p less then 0.0 long-acting risperidone was efficacious, it offered no additional benefit over the 25 mg and 50 mg do well tolerated and extrapyramidal adverse events were mild throughout the study period. Small incre baseline to endpoint were observed in risperidone-treated patients and these changes appeared to 2003).

2) Oral

a) Olanzapine and risperidone were equally safe and effective therapies in the treatment of schizop international, multicenter, double-blind study, 175 elderly patients (mean age, 71 years) were rando risperidone (mean dose, 1.9 milligrams (mg)/day) or olanzapine (mean dose, 11.1 mg/day) for 8 wee period of all psychotropic medications. Mean duration of illness was 36.5 years and Positive and Ne scores were between 50 and 120 at baseline. Clinical improvement was defined as a decrease of at score. Both treatment groups showed significant reductions from baseline in the total PANSS score 0.005) and significant differences were not observed between groups. Fifty-eight percent of risperido olanzapine-treated patients achieved clinical improvement as defined by the study. Both groups also improvement in four of the five PANSS factor scores (p less than 0.001). The greatest mean change occurred in the 93 patients who had received conventional antipsychotic medications in the thirty da less than 0.001). The rate of extrapyramidal symptoms (EPS) was similar between the risperidone a (9.2% vs 15.9%, respectively, p=nonsignificant). The severity of EPS symptoms was reduced in both endpoint with no significant difference between groups. A 7% or higher increase in weight occurred

treated patients as compared with those who received risperidone (14.8% vs 5.1%, p=0.043). No ne
observed in this patient population and mean QTc changes were not considered clinically relevant (
b) Risperidone treatment resulted in mild to substantial improvement in psychotic symptoms in appr
elderly Chinese patients (age 65 years or greater) participating in an open, 4-week study. Doses of r
basis of clinical responses and adverse effects and ranged from 0.25 to 7 milligrams (mg) per day (r
dose for functional psychoses was greater than that for organic mental disorders (2.8 mg/day vs 1.6
schizophrenia received the highest mean dose (4.1 mg/day). With improvement defined as a reducti
scores on various rating instruments, improvement occurred in 61% to 78% of patients. Patients witl
better than Alzheimer's patients. Of the 110 patients, 81 had one or more adverse effects. Weaknes
dizziness, and peripheral edema were the most common side effects (Hwang et al, 2001a).
c) Risperidone is beneficial in the treatment of patients with chronic schizophrenia, compared with c
and these benefits may appear only after longer-term treatment. A randomized, open, parallel, multi
term (12 months) effectiveness of risperidone with that of CNs. One hundred eighty-four subjects we
risperidone or CN and 165 of them completed the follow-up. Outcome measures were taken at 3, 6,
the Positive and Negative Syndrome Scale (PANSS) and the Extrapyramidal Symptom Rating Scale
risperidone was found to be superior to CNs in terms of both the average change in score from base
and the proportion of good responders (as defined by a 20% decrease in total PANSS scores; p=0.0
effectiveness of the risperidone treatment tended to increase over time and at 12 months, the perce
risperidone group was twice as large as that in the CN group (30% vs 15%; p=0.03). A worsening of
subjects receiving risperidone than in those receiving CNs (p=0.02) (Bouchard et al, 2000).
d) In an open, multicenter trial, risperidone was found to be effective in outpatients (Chouinard et al
subchronic or chronic schizophrenia treated on an outpatient basis were screened initially while on t
Their current therapy was discontinued and risperidone started at 2 milligrams (mg) daily and increa
After 2 weeks the dose could be titrated to a maximum of 10 mg or a minimum of 4 mg. At the end o
risperidone dose was 6.1 mg daily in 244 patients completing the study. The mean total Positive and
(PANSS) for schizophrenia decreased significantly from 86.3 to 63.6 (p=0.0001). Clinical improveme
baseline in total PANSS score) was seen in 85% of patients. The most frequent adverse events repo
headache, somnolence, dizziness, fatigue, anxiety, vomiting, and ejaculation failure/disorder.
e) In an open multicenter trial, risperidone was viewed as an efficacious and well tolerated medicati
overall antipsychotic action and above standard improvement in negative symptomology in 254 chro
and without exacerbation who were treated with risperidone 1 to 5 milligrams twice daily for 8 weeks
discontinuation of previous psychotropic medications; significant improvement in the overall Brief Ps
observed at every evaluation time (p less than 0.0001); 73% of patients showed improvement in neg
significant improvement was noted in the extrapyramidal symptom scores in all patients, including th
early (p less than 0.0001); the Clinical Global Impression scores significantly improved for those finis
0.0001); 98% of those finishing the study tolerated risperidone very well or well; 32% of patients disc
which 51% dropped out within the first 2 weeks, probably due to adverse reactions stemming from tl
previous psychotropics; the research team now recommends initial overlapping of therapies, especia
medicated with sedatives (Phillip, 1997).

c) Combination Therapy

1) Addition of celecoxib to risperidone therapy for patients with an acute exacerbation of schizophrenia r
than did risperidone therapy alone. In a randomized, double-blind study, 25 patients were given risperido
plus celecoxib 400 mg/day and 25 patients were given risperidone plus placebo. Both groups showed im
over the 5- week study, mainly with reductions in scores on the positive symptoms subscale of the Positi
(PANSS) (p=0.006) and on the general psychopathology subscale (p=0.01). Negative symptoms were n
Celecoxib therapy resulted in an improvement in total PANSS score relative to that of the placebo group
significant effects of celecoxib on the group-by-time interaction on any of the subscales, although a trend
on all subscales. The main influence of celecoxib occurred in weeks 2 to 4, resulting in earlier improvem
treating side effects of risperidone was not significantly different for the 2 groups. The use of benzodiaze
agitation appeared less in the celecoxib group, but the difference for the 2 groups was not statistically sig
were not observed (Muller et al, 2002).
2) In an open trial, risperidone added to clozapine was well tolerated and produced significant reduction
measured by the Brief Psychiatric Rating Scale (42.2 to 30.3, p=0.0002). Patients enrolled had either pe
symptoms despite optimal doses of clozapine (n=10) or a maximal clozapine dose limited by significant s
doses were kept constant while risperidone doses were increased to a maximum of 6 milligrams (mg) pe
tolerated, however, complaints included mild akathisia, hypersalivation, and worsening fatigue (Henderso
cases of refractory schizophrenic patients responding to combination therapy have been reported (More
clozapine 300 mg with risperidone 4.5 mg, and clozapine 400 mg with risperidone 6 mg.
3) As an add-on therapy, risperidone brought significant improvement to patients with bipolar disorder a
bipolar type. In a 6-month, open study, patients with a diagnosis of bipolar or schizoaffective disorder wh
depressive, or mixed episode (n=541; 430 completed the study) were given risperidone in combination w
antidepressants to clinical response and tolerability. The average dose of risperidone at the start of the s
day and at the end of the study, 3.9 mg/day. For all patients, scores on the Young Mania Rating Scale (Y
at week 1 and at every point thereafter (p less than 0.001 for all but the subgroup of depressed patients,
Mean scores on the YMRS decreased from 25.6 at baseline to 2.4 at 6 months. Likewise, scores on the
Depression (HAM-D) were significantly reduced from baseline at all evaluation times (p less than 0.0001
at baseline to 4.1 at 6 months. Scores on the Positive and Negative Syndrome Scale (PANSS) declined
months (p less than 0.0001). According to the Clinical Global Impressions scale (CGI), no patients were

and only 5% were rated as "mildly ill." At study endpoint, 44% of patients showed no symptoms of mania were "mildly ill." During the study, 25% of the patients experienced relapses into a mood state different fr Scores for extrapyramidal symptoms were lower at the end of study than at baseline (p less than 0.0001 reductions in dystonia, rigidity, hypokinesia, hyperkinesia, dyskinesia, tremor, and akathisia subscores. T emergent tardive dyskinesia. Nonextrapyramidal adverse reactions included increase in weight (2.4% of impotence (0.7%), and dysarthria (0.7%). There was a very low incidence of exacerbation mania in the fi 2001).

d) Refractory

1) Among patients who had been hospitalized for schizophrenia for longer than 5 years and who were c approximately 45% showed sufficient clinical improvement after 3 months of treatment with olanzapine o from the hospital. The 79 patients were not suited to treatment with clozapine either because of medical unwillingness to submit to the weekly blood drawings. Patients were given olanzapine 10 to 30 milligram 10 mg/day. Treatments were titrated quickly to the maximum tolerated dose and continued for 3 months. Psychiatric Rating Scale decreased from 67 to 53 for the olanzapine group (n=32) and from 63 to 52 for less than 0.001 for both groups). Of the 34 patients who were discharged from the hospital, only 3 requir 90-day follow-up. No significant side effects (such as weight change) were observed during the 3 months

e) Schizophrenia With Concomitant Cocaine Dependence

1) The results of a pilot study suggest that risperidone therapy reduced craving and relapses in cocaine- schizophrenia. In this 6-week, open label trial, patients with a dual diagnosis of schizophrenia and cocair of cocaine/month) received risperidone (n=8; initial, 2 milligrams (mg)/day, titrated to maximum dose of 6 neuroleptic medication treatment (n=10; haloperidol, fluphenazine, or chlorpromazine). Patients in the ris less cue reactivity in regard to the intensity (p=0.005) and depression (p=0.031) dimensions of craving a therapy, but there was no statistical difference on the energy and feeling sick dimensions. Risperidone-tr significantly lower rate of relapse (defined as any substance abuse) than did patients on typical neurolep respectively; p=0.025). Although not significant, a tendency toward a greater reduction in negative and g was seen in risperidone-treated patients. Larger, double-blind studies are needed to substantiate these f

4) Pediatric:

a) In 2 short-term (6 and 8 weeks), double-blind, controlled trials, oral risperidone, at doses ranging from 1 to effective in the treatment of schizophrenia in adolescents aged 13 to 17 years. Patients met the DSM-IV diag and were experiencing an acute episode at the time of enrollment. In the first trial (trial 1), patients were rand risperidone 1 to 3 mg/day (n=55; mean modal dose, 2.6 mg), risperidone 4 to 6 mg/day (n=51; mean modal d for 6 weeks. In the second trial (trial 2), patients were randomized to receive either risperidone 0.15 to 0.6 mg 0.5 mg) or risperidone 1.5 to 6 mg/day (n=125; mean modal dose, 4 mg). In both studies, risperidone was init up to the target dose range by approximately day 7 (except for the risperidone 0.15 to 0.6 mg/day group in tri initiated at 0.05 mg/day). Eventually, the dosage was increased to the maximum tolerated dose by day 14. C reduction occurred in the Positive and Negative Syndrome Scale (PANSS) score in all risperidone dose group (primary efficacy endpoint). Reductions in the PANSS scores in the 1 to 3 mg/day group were comparable to and to the 1.5 to 6 mg/day group in trial 2. The 1.5 to 6 mg/day group showed statistically significantly greater mg/day group in trial 2, with no additional benefit evident beyond the 3 mg/day dose. Adverse events reported placebo in both the risperidone 1 to 3 mg/day and 4 to 6 mg/day dose groups in trial 1 included parkinsonism dystonia (9%-18%), dizziness (7%-14%), akathisia (7%-10%), somnolence (12%-24%), and anxiety (6%-7%) tablets, 2007; Prod Info RISPERDAL(R) M-TAB orally disintegrating tablets, 2007; Prod Info RISPERDAL(R)

b) The results of a small study suggest that risperidone may be effective in the treatment of schizophrenia in prospective, open-label trial, eleven patients (mean age, 17.27 years) with first-episode, early-onset schizoph 0.5 milligrams (mg)/day, titrated based on clinical response and adverse effects; mean dose, 3.14 mg/day) fo Positive and Negative Syndrome Scale (PANSS) total score and positive symptoms score were significantly r than 0.01 and p less than 0.0001, respectively), however, a significant reduction was not observed for the ne PANSS (p=ns). Total scores for the Brief Psychotic Rating Scale were significantly reduced from baseline to baseline to endpoint, Clinical Global Impression-Severity (CGI-S) scores decreased by 31.6% (p less than 0.(scores decreased by 45.5% (p less than 0.0001). The most common adverse events observed were weight g depression (63%), orthostatic hypertension (45%), emotional indifference (45%), akathisia (36%). Because th improved significantly at a dose of only 1 mg/day, the authors suggest that lower initial doses of risperidone s as compared with adults, in order to minimize the risk of extrapyramidal side effects. Larger, controlled studie the safety and efficacy of risperidone for the treatment of schizophrenia in pediatric patients (Zalsman et al, 2

c) A 15-year old boy, with a diagnosis of simple deteriorative disorder (DSM-IV criteria or simple schizophrer improvement following risperidone therapy. He was started on 2 mg daily and this dosage was increased to 3 He did not report any significant side effects and showed clinical improvement. The author advocates the furt risperidone in the treatment of simple schizophrenia (Hirose, 2000).

4.5.Z Schizotypal personality disorder

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Appeared to effective in the treatment of schizotypal personality disorder

3) Adult:

a) Risperidone treatment was more effective than placebo in reducing the symptoms of schizotypal personal randomized, double-blind, placebo-controlled study, patients (n=25) with schizotypal personality disorder rece (0.25 milligrams (mg)/day for 1 week, then titrated by 0.5 mg/day every 2 weeks for 8 weeks; final dose, 2 mg comorbid borderline personality disorder. Weekly measurements of symptoms were taken using the Positive (PANSS), the Hamilton Rating Scale for Depression (HAM-D), and the Clinical Global Impressions Scale (CG Questionnaire (SPQ) was administered biweekly. Total PANSS scores were significantly lower in risperidone with placebo at weeks 3, 5, 7, and 9 (p=0.021, p=0.003, p=0.003, and p=0.013, respectively). PANSS negativ patients in the risperidone group than in the placebo group at all time points, with the difference reaching sign (p=0.027, p=0.006, and p=0.01, respectively). Patients in the risperidone group had significantly lower PANS patients in the placebo group at weeks 3, 5, 7, and 9 (p=0.042, p=0.007, p=0.005, and p=0.013, respectively) had significantly lower PANSS positive symptom scores at weeks 7 and 9 as compared with placebo (p=0.02 the end of treatment, SPQ and CGI scores showed greater reductions in the risperidone group than in the pla difference was not significant. The change in HAM-D scores was non- significant in both groups. Adverse eve decreased sexual arousal, delayed ejaculation, mild dystonic reaction and dry mouth. Larger studies are nee (Koenigsberg et al, 2003).

4.5.AA Stuttering

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Risperidone may be beneficial

3) Adult:

a) Risperidone may be effective in the treatment of developmental stuttering. A small, randomized, double- b was conducted to assess the efficacy of risperidone in the treatment of developmental stuttering in 16 adults. and eight received risperidone at 0.5 mg once daily at night, increased to a maximum of 2 mg per day. After 6 in all measures of stuttering severity were greater in the risperidone group than in the placebo group; the betw significant (p less than 0.05) on the most important measure, the percentage of syllables stuttered. In the risp baseline in scores for the percentage of syllables stuttered, time stuttering as a percentage of total time spea severity were significant (p less than 0.01); changes in scores on the fourth measure of stuttering, duration, w differences occurred in the placebo group. Five of the eight patients in the risperidone group responded best stuttering recurring at higher doses. Risperidone was generally well-tolerated (Maguire et al, 2000).

b) In one small study (n=21), patients were randomized to receive risperidone (n=10) up to 2 milligrams daily Every 2 weeks stuttering severity, adverse events, compliance, and tolerability were assessed. Risperidone t the mean stuttering severity compared to placebo (3.93 and 5.23, respectively (p less than 0.05). However, e social alienation-personal disorganization did not (Maguire et al, 1999).

4.5.AB Tardive dyskinesia

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in reducing tardive dyskinesia in some patients when substituted for conventional antipsychotic

See Drug Consult reference: TARDIVE DYSKINESIA - DRUG THERAPY

3) Adult:

a) Risperidone treatment was more effective than withdrawal of antipsychotic therapy in reducing symptoms randomized, double-blind, placebo-controlled study (n=42), schizophrenic patients with persistent, severe tar risperidone (initial, 2 milligrams (mg)/day titrated in 2 mg increments to 6 mg/day over 6 weeks) or placebo fo washout period from all original conventional antipsychotic medications. Response was defined as a decreas Involuntary Movement Scale (AIMS) total score. Risperidone- treated patients showed a significantly greater score from baseline to endpoint, as compared with placebo (5.5 vs 1.1, respectively; p=0.001). This significar AIMS score between groups was observed from week 8 to endpoint, and grew more distinct over time. In add significantly higher in the risperidone group as compared with the placebo group (68%(15) vs 30%(6), respec dyskinesia improvement in the risperidone group was noted mainly in the buccolinguomasticatory area rather movement of the extremities. Additional studies are needed to evaluate the long-term efficacy of risperidone f dyskinesia and whether symptoms reemerge when the risperidone dosage is withdrawn or reduced (Bai et al

b) Five of nine patients with tardive dyskinesia showed a lessening of severity of tardive dyskinesia when ris conventional antipsychotic drug they had been taking. After a tapering of the previous antipsychotic and antip patients were prescribed risperidone 2 milligrams (mg) per day. The dose was gradually increased over 4 we adjusted to maintain the least severity of tardive dyskinesia. Over the year-long study, 5 patients showed imp in score on the Abnormal Involuntary Movement Scale (AIMS) (responders). The dose for maximum effect in

improvement in AIMS score was 7 for responders and 0.5 for nonresponders (Chen et al, 2001).
c) Tardive movements were resolved with the addition of risperidone and a reduction in doses of trihexypher
old schizophrenic patient (Chong et al, 1999).
d) Tardive dyskinesia was diminished in a 54-year-old schizophrenic woman after switching to risperidone th
Risperidone 2 milligrams daily resolved her schizophrenic symptoms. At 8 months, her tardive dyskinesia wa
months, her parkinsonism had also resolved.

4.5.AC Trichotillomania

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
2) Summary:
Augmented therapy in patients with trichotillomania
3) Adult:
a) In a case series, 3 of 5 patients with trichotillomania disorder (DSM-IV criteria) showed significant improve
Impression Change Scale after receiving augmentation with risperidone 1 milligram/day (Stein et al, 1997).

4.5.AD Water intoxication syndrome

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Ineffective
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
2) Summary:
No effect on self-induced water intoxication
3) Adult:
a) Risperidone had no significant effect in treating self-induced water intoxication. In a prospective, 11 month
in 8 men with chronic schizophrenia and a history of polydipsia and episodic water intoxication, fluid intake wa
4 times daily weights. Risperidone was increased in doses up to 16 milligrams per day. Though there was a t
intake, there was no significant change in body weight over the study period (Milson et al, 1996).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amisulpride

Chlorpromazine

Clozapine

Haloperidol

Lithium

Olanzapine

Paroxetine

Perphenazine

Quetiapine

Ziprasidone

4.6.A Amisulpride

4.6.A.1 Schizophrenia

a) Amisulpride and risperidone therapies were equally effective in the treatment of positive and negative sym
with schizophrenia. In a randomized, double-blind, multi-center study, schizophrenic patients with productive

amisulpride 400 to 800 milligrams (mg) per day (mean dose, 630 mg/day) or risperidone 4 to 8 mg per day (n
weeks following a 3-to-6-day washout period. At 6 weeks, patients in both treatment groups showed significa
and Negative Symptom Scale (PANSS) total score and the three PANSS sub- scale scores, but no significan
treatment groups. The occurrence of adverse events was also similar between groups. Akathisia (16%), trem
were most commonly reported with risperidone administration while insomnia (17.3%) and constipation (17.3
in the amisulpride group (Hwang et al, 2003).

4.6.B Chlorpromazine

4.6.B.1 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo- controlled, fixed-dose and f
development trials, the minimum effective dose of risperidone was 4 milligrams/day (equivalent to chlorproma
SW, 2003).

4.6.C Clozapine

Bipolar disorder

Hostile behavior

Parkinson's disease - Psychotic disorder

Schizophrenia

4.6.C.1 Bipolar disorder

a) In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic r
olanzapine (n=20), and risperidone (n=25), along with standard mood stabilizers, showed similar efficacy. Ov
improvement of at least 1 point in their Clinical Global Impressions assessment over the 12-week study. Mea
(mg) per day for clozapine, 11.7 mg/day for olanzapine, and 1.7 mg day for risperidone. The only serious adv
study was a seizure in a patient taking clozapine. Extrapyramidal symptoms (EPS) were reported in 12 of 42
occurred in 4 of 25 patients taking risperidone, 1 of 20 taking olanzapine, and 1 of 5 taking clozapine. Weight
patients taking clozapine and olanzapine than in those taking risperidone. Weight gain, which was greater tha
have been affected by concurrent mood enhancing medications (Guille et al, 2000a).

4.6.C.2 Hostile behavior

a) Clozapine reduced hostility in patients with schizophrenia and was superior to haloperidol and risperidone
seven patients with a diagnosis of schizophrenia or schizoaffective disorder and a history of poor response to
assigned to receive clozapine, olanzapine, risperidone, or haloperidol in cross-titration with the antipsychotic
study. Concomitant mood stabilizers and antidepressants had been phased out earlier. Daily doses of olanza
haloperidol were escalated within the first week to the target doses of 20, 8, and 20 milligrams (mg), respecti
were scheduled to achieve the target daily dose of 500 mg on day 24. Doses remained fixed for the remainde
second (6-week) period, doses were allowed to vary: 200 to 800 mg for clozapine, 10 to 40 mg for olanzapine
10 to 30 mg for haloperidol. Hostility, measured by the hostility item of the Positive and Negative Syndrome S
significantly (in comparison to baseline) in the clozapine group only (p=0.019). This effect was independent o
(delusional thinking, hallucinations) or on sedation. The effect of clozapine on hostility was superior to that of
risperidone (p=0.012) but not to that of olanzapine (Citrome et al, 2001).

4.6.C.3 Parkinson's disease - Psychotic disorder

a) In subjects with Parkinson's Disease (PD), risperidone may be considered as an alternative to clozapine h
extrapyramidal symptoms more than clozapine and therefore must be used with caution. A small (n=10) doub
efficacy and safety of risperidone and clozapine for the treatment of psychosis in patients with PD. Five patie
clozapine and five patients received risperidone. Clozapine was started at 12.5 mg at bedtime and risperidon
and both were titrated to symptomatic improvement was achieved or intolerable side effects emerged. Each s
months and was assessed prior to initiation of treatment and after 2, 4, 8, and 12 weeks of treatment. Assess
the Brief Psychiatric Rating Scale and the Unified Parkinson's Disease Rating Scale. Mean improvement in th
psychosis score was similar in the clozapine and the risperidone groups (p=0.23). Although the mean motor U
Rating Scale scores worsened in the risperidone group and improved in the clozapine group, this difference d
significance. Risperidone may be a reasonable alternative to clozapine in the treatment of psychosis in patien
used with caution since it may worsen extrapyramidal side effects (Ellis et al, 2000).

4.6.C.4 Schizophrenia

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in pat
schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-
clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26)

(n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risp
mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 wee
individually (generally increased if response was insufficient, but sometimes reduced because of adverse effe
global neurocognitive score was seen for olanzapine and risperidone. In general executive and perceptual or
speed and attention, improvement was seen with olanzapine. In simple motor function, there was improveme
global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximate
large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive ga
impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits we
in negative symptoms (Bilder et al, 2002b).

b) Clozapine was superior to risperidone for improving positive and negative symptoms of schizophrenia in p
response to treatment. In a prospective, double-blind study, patients meeting DSM-IV criteria for schizophren
to previous treatment underwent a single-blind placebo run-in period when all psychotropic and anticholinergi
They were then randomly assigned to treatment with clozapine (n=138) or risperidone (n=135). Starting with
milligrams (mg) and risperidone 1 mg, dosages were titrated over a period of 4 weeks to a minimum of 300 m
respectively, and possibly to 600 mg/day and 6 mg/day. Patients unable to tolerate the minimum dose were v
the next 8 weeks, doses were adjusted at 2-week intervals within the range of 200 to 900 mg/day for clozapir
risperidone. For patients who completed the 12-week study (n=201), median final daily doses were 600 mg fo
risperidone. Changes in the Positive and Negative Syndrome Scale of the BPRS (Brief Psychiatric Rating Sc
Impression (CBI) scale were significantly greater in the clozapine group than in the risperidone group for the i
who received at least one dose of treatment medication and had one post-dose BPRS evaluation) and in the
who completed the 28-day dose-setting period) (p less than 0.008 for all comparisons). Eighty-six percent of
protocol population and 70% in the risperidone per-protocol population showed 20% or more improvement in
between groups, p less than 0.01). By the end of the study, 94 (76%) patients in the clozapine group and 81
longer met the severity of psychopathology inclusion criteria (p less than 0.05). Extrapyramidal symptoms oc
in the clozapine group than in the risperidone group (13% vs 28%, p=0.008). However, convulsions, dizziness
somnolence occurred significantly more frequently among those receiving clozapine. No case of agranulocyt
study. Granulocytopenia occurred with low incidence in both groups (1% clozapine, 2% risperidone). Low neu
more frequent among risperidone-treated patients (3% vs 11%, p less than 0.01). Hypotension occurred more
treated patients (p less than 0.01). Weight gain was significantly greater for the clozapine group (2.4 kilogram
0.002) (Azorin et al, 2001).

c) In the treatment of refractory schizophrenia, giving a risperidone trial before clozapine was more beneficia
profile. A retrospective review study compared the relative efficacy profiles of clozapine and risperidone in a g
chronically institutionalized patients. The specific goal was to identify superiority (or lack thereof) of either age
well as on specific symptom domains, including positive symptoms, negative symptoms, and aggressive beha
of conventional antipsychotic treatment in a total of 24 patients. Information obtained from systematic retrosp
rated by 2 psychiatrists using the 7-point Clinical Global Impressions Improvement (CGI-I) scale on overall cli
symptom domains as above. The mean dose was 520 +/- 94 mg daily for clozapine and 7.5 +/- 2.2 mg daily f
(58%) were classified as responders to clozapine, while 6 (25%) responded to risperidone. On specific sympt
clozapine were 38% (9/24) on positive symptoms, 29% (7/24) on negative symptoms, and 71% (12/17) on ag
risperidone, response rates were 17% (4/24) on positive symptoms, 8% (2/24) on negative symptoms, and 4
behavior. The results of this study would support the utility of first giving a risperidone trial in patients with trea
because of its better side effect profile compared with clozapine (Sharif et al, 2000).

d) Risperidone and clozapine had similar antipsychotic effects in 59 patients with paranoid schizophrenia. In
study, patients were divided in three groups receiving either 4 milligrams risperidone, 8 milligrams risperidone
daily for 28 days. The antipsychotic effect was highly significant for both risperidone and clozapine. Patients
better tolerated therapy than those patients receiving clozapine. Withdrawals from clozapine treatment were
whereas withdrawals from risperidone treatment occurred from lack of therapeutic response (Heinrich et al, 1

e) Similar effectiveness of risperidone and clozapine was also observed in an 8-week, double-blind trial that
on response in 86 patients with treatment-resistant chronic schizophrenia. The mean effective dose was 6.4
and 291 mg for clozapine. The larger proportion of patients with clinical improvement after 7 and 14 days' trea
suggested earlier onset of effect compared to clozapine treatment (Bondolfi et al, 1998)

f) In a prospective, open-label, 12-week trial, risperidone was found to be a poor substitute for clozapine in th
schizophrenia. Six patients with schizophrenia and 4 with schizoaffective disorder were switched from a mean
milligrams(mg)/day to a mean dose of risperidone 8 mg/day at 12 weeks. No subjects improved after being sw
were switched from clozapine tended to worsen when taking risperidone. Statistically significant increases ov
the Positive and Negative Syndrome Scale occurred at 9 and 12 weeks (P less than 0.05). The Brief Psychia
increased significantly over baseline at weeks 6, 9, and 12 (P less than 0.05). Five subjects failed to complete
patients that completed the 12 weeks, the Clinical Global Impressions Scale indicated that 2 patients were un
worse, and 2 were much worse. The authors concluded that this study does not support replacing clozapine w
treatment-resistant schizophrenia (Still et al, 1996).

4.6.C.5 Adverse Effects

a) Adverse effects and death were more commonly reported as the reasons for the discontinuation of clozap
more often reported as the reason for discontinuation of risperidone (long-acting injection) in a retrospective,
with a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder or other psychotic disorders who
had mean duration of therapy of 12.3 +/- 18.6 months (range, 0.25 to 100 months; median, 3 months) were m
12.6 years (yr); range, 18 to 83 yr) and gender at discontinuation to patients who discontinued risperidone lon
risperidone patients (mean age, 39.9 +/- 13.1 yr , range 18 to 83 yr) were matched without knowledge of the
therapy (mean duration of therapy of 5.9 +/- 8.7 months; range, 0.5 to 46 months; median, 3 months). The re

significantly between clozapine and risperidone injection; additionally, death as reason for discontinuation wa
clozapine (13%) vs risperidone injection (1.9%) (Taylor et al, 2009).

Reasons for Discontinuation: Clozapine vs Risperidone

Reason	Clozapine (n=161) n (%)	Risperidone (n=161) n (%)	OR (95% CI)	p value
Patient's decision	77 (47.8)	64 (39.7)	1.41 (0.89 to 2.21)	0.139
Adverse effects	57 (35.4)	32 (19.9)	2.19 (1.31 to 3.67)	0.0023
Ineffectiveness	3 (1.9)	59 (36.6)	0.034 (0.01 to 0.14)	less than 0.0001
Death	21 (13)	3 (1.9)	7 (2.09 to 23.5)	0.0003
Other	3 (1.9)	3 (1.9)	-	-

The cause of death reported in clozapine patients (mean age, 49.2 +/- 14.5 yr, range 30 to 83 yr) include
carcinoma (n=3), other carcinoma (n=2), myocardial infarction (n=2), cerebrovascular accident (n=2), clo
gastrointestinal hemorrhage (n=1), cardiac arrest (n=1), left ventricular failure (n=1), asphyxia during rest
There was no incidence of neutropenia or agranulocytosis at the time of death in any of the patients. The
risperidone patients included: myocardial infarction (n=1), left ventricular failure (n=1) and sudden unexp
rate for clozapine patients was 8.5 per 1000 patient-years (95% CI, 5.53 to 13.07) vs 5.3 per 1000 patier
(Taylor et al, 2009).

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

c) Clozapine was associated with fewer extrapyramidal side effects (EPS) than was risperidone (Miller et al,
stable doses of clozapine (n=41), risperidone (n=23), or conventional antipsychotics (n=42) were screened fo
Akathisia Scale, akathisia was noted in 7.3% of clozapine patients, 13% of risperidone patients, and 23.8% o
users. From the Simpson-Angus scale, rigidity and cogwheeling were noted in 4.9% and 2.4% of clozapine p
risperidone patients, and 35.7% and 26.2% of conventional antipsychotic users, respectively. However, saliva
clozapine patients, 8.7% of risperidone patients, and 4.8% of conventional antipsychotic users.

d) Insomnia and extrapyramidal side effects were more common with risperidone, and sedation and weight g
clozapine in a single-blind, crossover pilot study of the side effect profiles of the 2 drugs (Daniel et al, 1996).
schizophrenia or schizoaffective disorder were randomized to each drug for 6 weeks separated by a 1-week
crossover. The mean doses at week 6 were 6.1 milligrams/day (range 1 to 10 mg/d) of risperidone and 375 m
mg/d) of clozapine. Three patients dropped out of the study; there was no significant difference in therapeutic
groups. Mean body weight was greater (p less than 0.005) and sleepiness and lack of alertness were reporte
treatment phase. Restlessness and insomnia were more frequent complaints after the risperidone phase. A l
large sample of patients is needed to further elucidate the therapeutic differences and side effect profiles of t

4.6.D Haloperidol

Cognitive function finding

Dementia

Extrapyramidal disease

Mania

Schizophrenia

4.6.D.1 Cognitive function finding

a) Results of a multicenter, randomized, double blind trial assessing cognitive function in patients experienci
episode or a related psychosis demonstrated that overall improvement in cognitive functioning was superior v
haloperidol. Patients (n=533) were randomized to receive either risperidone or haloperidol on a one-to-one ra
2 years or more. There were no significant differences in sex, race or ethnicity, age, diagnosis, or previous ne
group. Dosing strategies were equivalent in both groups where patients were started on 1 milligram per day (
titrated up to 4 mg/day, or in some cases, to a maximum of 8 mg/day. Patients in the risperidone group recei

modal total dose 3.3 mg/day) for an average of 192 days while patients in the haloperidol group received trea
2.9 mg/day) for an average of 218 days. Cognitive assessments, performed at several different follow-up inte
verbal and visuospatial episodic memory, vigilance, executive functioning, processing speed, and verbal fluer
conducted with a focus on the 3-month assessment revealed that there was significant improvement from bas
(n=169) for all measures except category verbal fluency and letter verbal fluency (p less than 0.05). In the ha
statistically significant improvements from baseline were noted in episodic memory, vigilance, and visuomoto
functioning and verbal fluency. Comparison between the two groups showed that, after 3 months of treatmen
significantly more beneficial than the haloperidol group on the composite measure of cognitive functioning. In
as a result of treatment with risperidone was not affected by changes in symptoms. Risperidone therapy also
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 treatment-res
than did haloperidol therapy (Green et al, 1997). In a randomized, double-blind comparison of treatment with
haloperidol (n = 29), verbal working memory was measured at baseline and after 4 weeks of both a fixed dos
Risperidone patients showed a significant improvement in memory using a Digit Span Distractibility Test from
the fixed-dose (p less than 0.0001) and the flexible dose (p less than 0.0003) phases. The haloperidol-treated
significantly. Results suggest that treatment of schizophrenia could be broadened to include the impact on ne

4.6.D.2 Dementia

a) Some Chinese patients with dementia, who were non-responders to haloperidol, responded to risperidone
disturbances and improved mood. Thirty-five Chinese patients who had shown insufficient response to an 8-
having a total score of more than 10 on the Brief Psychiatric Rating Scale (BPRS) at the end of 8 weeks) (typ
switched abruptly from haloperidol to risperidone 0.5 milligrams (mg) at bedtime for weeks 1 to 4 and then (if
weeks 5 to 12. At week 13, the regimen was shifted again to haloperidol at the dose used in the earlier trial. T
the trial. Sixteen patients responded by the end of the risperidone trial (response = a decrease of 25% in the
resumption, the mean BPRS score stayed the same, but the number of responders decreased to 15. Patients
almost 6 times more likely to respond to risperidone than patients with Alzheimer's disease. Mean scores on
Alzheimer's Disease Rating Scale decreased (6.1 at baseline to 1.9 at 12 weeks of risperidone treatment) an
to haloperidol (to 2.4 after 4 weeks of haloperidol). Thirty- four of the 35 patients tolerated both doses of rispe
One patient experienced moderate rigidity with risperidone 1 mg/day, which was relieved by reduction of the
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 psycl
Chinese patients with dementia. Risperidone was associated with less severe exacerbation of extrapyramida
randomized, double-blind trial, 55 elderly Chinese patients (mean age 80 years) with Alzheimer's dementia o
behavioral disturbance, were given either risperidone or haloperidol for 12 weeks after a 2-week washout per
psychotropic and antiparkinsonian drugs. The starting dose for both treatment drugs was 0.5 milligrams (mg)
individually in increments of 0.5 mg no faster than every other day, to a maximum of 2 mg/day. At 12 weeks,
haloperidol was 0.9 mg, and that of risperidone, 0.85 mg. Significant improvements on the Cohen- Mansfield
evident in both groups (haloperidol, p less than 0.001; risperidone, p=0.002). Significant reduction was seen
group and at 4 weeks in the haloperidol group. With risperidone, there were significant improvements in score
disturbances, aggressiveness and diurnal rhythm disturbances, whereas with haloperidol, improvement in on
reached statistical significance. However, none of the measures showed a significant difference between the
haloperidol, there was a significant worsening of EPS (p less than 0.001), whereas, with risperidone, EPS sc
worsened. Final EPS scores were significantly higher for haloperidol (p=0.001) (Chan et al, 2001).

4.6.D.3 Extrapyramidal disease

a) Data from a multicenter comparative study of risperidone, placebo, and haloperidol revealed that risperidc
extrapyramidal symptoms (Simpson & Lindenmayer, 1997). Mean changes in Extrapyramidal Symptom Ratir
baseline to worst score were significantly lower in each risperidone group than the haloperidol group (P less t

4.6.D.4 Mania

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

4.6.D.5 Schizophrenia

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in pat
schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double-
clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26)
(n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risp
mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 weel
individually (generally increased if response was insufficient, but sometimes reduced because of adverse effe
global neurocognitive score was seen for olanzapine and risperidone. In general executive and perceptual or
speed and attention, improvement was seen with olanzapine. In simple motor function, there was improveme
global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximate
large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive ga
impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits we

in negative symptoms (Bilder et al, 2002a).

b) The risk of relapse of schizophrenia was significantly less with long-term treatment with risperidone than v
double-blind study, 365 patients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder and in
flexible doses of either risperidone or haloperidol. The trial was continued until the last enrolled patient had c
Means of modal daily doses were 4.9 milligrams (mg) for risperidone and 11.7 mg for haloperidol. At the end
risperidone group and 40% of the haloperidol group had relapsed. The risk of relapse was significantly higher
haloperidol (risk ratio 1.93, p less than 0.001). The risk of premature discontinuation was greater for the halop
risperidone group (risk ratio 1.52), mainly because of relapse. Median duration of treatment for the risperidon
haloperidol group, 238 days (p=0.02). The subtypes of relapse (psychiatric hospitalization, clinical deteriorati
suicidal or homicidal ideation) were similar in the 2 groups. In the risperidone group, there were improvement
negative symptoms, disorganized thoughts, and anxiety- depression, whereas symptoms were not improved
extrapyramidal symptoms was reduced from baseline in the risperidone group and increased in the haloperid
the groups were significant (p less than 0.02 for total score on the Extrapyramidal Symptom Rating Scale). Th
were somnolence (14% with risperidone and 25% with haloperidol), agitation (10% and 18% respectively), ar
respectively). Those taking risperidone had a mean increase in body weight of 2.3 kilograms (kg) and those t
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 refra
patients. Chinese patients, meeting DSM-III-R criteria for schizophrenia and having a history of treatment fail
neuroleptics given at least 3 months at full dose, were randomly assigned to receive risperidone (n=41) or ha
double-blind trial. The dose of risperidone was increased during the first week to 6 milligrams (mg) per day, a
mg/day. By the end of the study, the average score on the Positive and Negative Syndrome Scale (PANSS) I
risperidone group and by 28.3% for the haloperidol group (p=0.03). The general psychopathology and negati
showed greater improvement with risperidone, but there was no difference between treatments in the positive
patients rated as responders was higher in the risperidone group (31 of 41 vs 20 of 37, p=0.046). Total score
Symptoms Scale (TESS) were significantly lower with risperidone than with haloperidol (2.9 vs 6.9, p=0.01). I
favoring risperidone were those showing symptoms of the nervous system (rigidity, tremor, dystonia, and aka
system (hypotension, dizziness, tachycardia, hypertension and electrocardiogram abnormalities) (p=0.02 and
in the risperidone group required less medication for extrapyramidal symptoms during the study than did patie
authors mentioned that the dose of haloperidol was higher than the dose recommended in the United States
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, paralle
reduction in negative symptoms was significantly better in patients receiving risperidone 16 mg/day than halo
0.05) (Moller et al, 1997). Patients with chronic schizophrenia (n=169) were treated with risperidone 1 mg, 4 r
haloperidol 10 mg/day for 8 weeks. Improvement was noted in each group. Risperidone onset was faster thar
Positive and Negative Syndrome Scale cluster scores revealed significantly greater improvement in the rispe
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 comb
(Chouinard et al, 1993a; Marder & Meibach, 1994) to evaluate five factors of the Positive and Negative Syndr
Data from 513 patients showed that after 6 to 8 weeks of therapy, patients receiving risperidone 6 to 16 millig
adjusted mean changes in total Positive and Negative Syndrome Scale than patients treated with haloperidol
symptom areas that risperidone was significantly superior to haloperidol included: negative symptoms (p less
less than 0.05), disorganized thought (p less than 0.05), uncontrolled hostility/excitement (p less than 0.01), a
than 0.01). One author, however, noted some positive symptoms that reemerged after an initial response to r
1997).

f) In a meta-analysis, risperidone (4 to 8 milligrams(mg)/day) was found to be more effective and produce fe
haloperidol (4 to 20 mg/day). Seven studies done in a double-blind, randomized fashion were included. The p
clinical improvement defined as a 20% reduction in the total scores on the Brief Psychiatric Rating Scale or th
Syndrome Scale. Results showed that patients identified as treatment failures were 50% of those taking rispe
83% on placebo. There was a highly significant need for anticholinergic medication in the haloperidol-treated
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 study (
schizophrenic patients were randomly assigned to receive 4 fixed doses of risperidone (2, 6, 10, and 16 millig
haloperidol 20 milligrams daily or placebo for 8-weeks (Marder and Meibach, 1994). Patients receiving risperi
statistically greater improvement than placebo or haloperidol in Clinical Global Impression (CGI) and total Pos
Scale (PANSS) scores. Of the four doses studied, the 6, 10, and 16 milligram doses were all effective with th
most effective. Similar results have been reported (Chouinard et al, 1993a; Marder, 1992).

h) In an 8-week, double-blind study, 1362 schizophrenic patients were randomly assigned to receive either r
milligrams/day, on a BID schedule, or haloperidol 10 milligrams daily (Muller-Spahn, 1992). Significantly grea
Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) total score, the PANSS Gene
the BPRS Activity and Anxiety/Depression cluster, was observed in the risperidone 4 milligram and 8 milligra
treated patients. In addition, a greater percentage of patients treated with risperidone 4 and 8 milligrams achi
PANSS and BPRS as compared with the haloperidol group.

i) Risperidone was faster acting, more effective, and had fewer side effects than haloperidol in a study to det
negative symptoms of schizophrenia (Claus et al, 1992a). The multicenter double-blind study that took place
included a two-week run-in period and a one-week washout period. The patients (n=42) took one to 5 mg bid
weeks. The Positive and Negative Syndrome Scale for Schizophrenia was the key efficacy parameter. The S
and Schizophrenia Change Conversion was used as a diagnostic aid and symptom severity measure. The Cl
was complete as a global rating. In addition, the occurrence of extrapyramidal side effects was also monitore

was approximately three times greater in the risperidone group, both at week six and at endpoint. In addition, was quicker in the risperidone group. Finally, the risperidone group needed 10 times less anticholinergic med extrapyramidal side effects than did the haloperidol group. According to this study, risperidone showed a grea schizophrenic symptoms than haloperidol.

j) Risperidone was less effective as monotherapy when compared to combination therapy of haloperidol and coexisting psychotic and depressive disorders. In this double-blind multicenter study, 123 patients were rand risperidone (dose titrated to 8 milligrams (mg) by the end of week 1) or the combination of haloperidol and an mg and 200 mg by the end of week 1). For all patients, doses were then adjusted under double blind conditio on response. At endpoint, the mean effective daily dose was 6.9 mg risperidone, and 9 mg haloperidol in con amitriptyline. In the 98 patients who completed at least 3 weeks of treatment, Brief Psychiatric Rating Scale (treatment groups, but the reduction in the combination treatment group was significantly greater than the risp The proportion of patients achieving at least 50% improvement in BPRS scores was also significantly higher 0.002). Greater benefit by combination therapy was still observed in an intent-to-treat analyses of the 123 pat medication for extrapyramidal symptoms was higher in the risperidone group (Muller-Siecheneder et al, 1998

4.6.D.6 Adverse Effects

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

4.6.E Lithium

4.6.E.1 Mania

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

4.6.F Olanzapine

Agitation, acute - Psychotic disorder

Bipolar disorder

Chronic schizophrenia

Dementia - Problem behavior

Extrapyramidal disease

Obsessive-compulsive disorder, Refractory

Schizophrenia

4.6.F.1 Agitation, acute - Psychotic disorder

a) Olanzapine orally disintegrating tablets (ODT) and risperidone oral solution (OS) yielded similar improvem for Positive and Negative Syndrome Scale (PANSS-EC) and the Clinical Global Impression (CGI) scale in 87 psychotic agitation in a psychiatric emergency setting, according to an open-label, flexible-dose study. Patien score of 15 or higher who accepted oral medication were assigned to receive initial doses of either olanzapin or risperidone OS 3 mg (n=53). Treatment group assignments were based on previous effective treatments, olanzapine or risperidone according to the time of study trial entry. Patients who experienced continued agita time, and after 1 hour could receive adjunctive drug therapy. PANSS-EC scores in both groups decreased ov from baseline was similar between the olanzapine and risperidone group (2.8 vs 3.2; p=0.22). Repeated mea score over time ANOVA (at baseline and every 15 minutes for 1 hour) revealed no significant main effect of t treatment over time (F=2.94, p=0.09 and F=0.88, p=0.41, respectively). There was a significant mean change ODT group compared with risperidone OS group (-9.2 vs 1.1 beats/minute, p=0.03). There were no significar treatment groups for adverse effects including extrapyramidal symptoms (Hatta et al, 2008).

4.6.F.2 Bipolar disorder

a) In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic r

improvement of at least 1 point in their Clinical Global Impressions assessment over the 12-week study. Mea
(mg) per day for clozapine, 11.7 mg/day for olanzapine, and 1.7 mg day for risperidone. The only serious adv
study was a seizure in a patient taking clozapine. Extrapyramidal symptoms (EPS) were reported in 12 of 42
occurred in 4 of 25 patients taking risperidone, 1 of 20 taking olanzapine, and 1 of 5 taking clozapine. Weight
patients taking clozapine and olanzapine than in those taking risperidone. Weight gain, which was greater tha
have been affected by concurrent mood enhancing medications (Guille et al, 2000).

4.6.F.3 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp
antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study me
Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/da
mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up
patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%
from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly l
compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than
(HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar betwe
ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due
of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides

4.6.F.4 Dementia - Problem behavior

a) Risperidone and olanzapine were equally effective in the treatment of dementia-related behavioral disturb
term care facilities. In a double-blind, parallel study, patients (mean age, 83 years) with dementia received or
2.5 milligrams (mg)/day, titrated to maximum dose of 10 mg/day) or risperidone (n=19, initial dose 0.5 mg/da
mg/day) at bedtime for two weeks following a 3-day washout period of psychotropic drugs. Antidepressants a
at stable doses and lorazepam was used as a rescue medication at doses of 0.5 to 1 mg as needed for acute
for olanzapine and risperidone were 6.65 mg (range, 2.5 to 10 mg) and 1.47 mg (range, 0.5 to 2 mg), respect
median of 3.5 days (range 1-12 days) and the median dose was 2 mg (range, 0.2 to 21 mg). Primary outcom
Neuropsychiatric Inventory (NPI) and the Clinical Global Impressions Scale (CGI). Both treatments significant
NPI scores from baseline to endpoint (p less than 0.0001, both values), however, there was no difference be
events were frequent in this elderly population, with the most common including drowsiness, falls, and extrap
at, 2003).

4.6.F.5 Extrapyramidal disease

a) Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rate of
than haloperidol, but was similar to rates occurring with risperidone and clozapine therapy. In a pooled analys
clinical trials in 4611 patients with schizophrenia, frequency and severity of EPS associated with olanzapine t
(mg)/day) was compared with that of haloperidol (1 to 20 mg/day), risperidone (4 to 12 mg/day), clozapine (2
Dystonic events (ie, dystonia, oculogyric crisis, opisthotonos, torticollis) occurred in significantly fewer patient
compared with haloperidol (0.5% vs 5.6%, respectively; p less than 0.001) or risperidone (1% vs 3.2%, respe
no significant difference was found between olanzapine- and clozapine-treated patients. As compared with ol
significantly higher percentage of haloperidol-treated patients experienced parkinsonian events (ie, akinesia,
syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively; p less than 0.0
akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no signific
between the olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to th
akathisia events. Overall, EPS occurred in significantly more patients treated with haloperidol as compared w
respectively; p less than 0.001) and in fewer patients treated with clozapine as compared with olanzapine (2.
p=0.047). The overall rate of EPS was similar between the placebo and risperidone groups as compared with
patients received anticholinergic medications in the olanzapine group as compared with the haloperidol (p les
(p=0.018) groups. No difference was found between olanzapine-treated patients as compared with placebo o
percentage of patients given anticholinergic drugs during therapy (Carlson et al, 2003).

4.6.F.6 Obsessive-compulsive disorder, Refractory

a) Adjunctive therapy of risperidone or olanzapine with serotonin-reuptake inhibitors (SRI) were equally effec
compulsive symptoms in SRI monotherapy-resistant outpatients, according to an 8-week, single-blind, randor
conclusion may be limited by the lack of a placebo arm, single-arm design, and underpowered nature of the t
prospective, open-label phase of SRI monotherapy (n=96), patients who were treatment-resistant (defined as
the total score of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and a Clinical Global Impression Seve
entered an 8-week single-blind phase (n=50). Patients in the single-blind phase received SRI daily doses of c
citalopram 50 to 80 mg, fluoxetine 60 mg, fluvoxamine 200 to 300 mg, paroxetine 50 to 60 mg, or sertraline 2
receive either risperidone 1 to 3 mg/day (n=25), or olanzapine 2.5 to 10 mg/day (n=25) in addition to the SRI
personnel and assessor-blinding constituted the single-blind study design; patients were not blinded. In an int
carried forward analysis of the primary endpoints, both treatments significantly improved Y-BOCS and CGI-S
The magnitude of change in mean Y-BOCS total scores, CGI-S scores, and responder rates (35% or greater
versus baseline, and a CGI-I score of 2 or less) was similar between groups.

Primary Efficacy Endpoints at 8 Weeks		

	Risperidone (n=25)	Olanzapine (n=25)
Responder rates*	44% (11/25)	48% (12/25)
Mean end-point Y-BOCS score	22.6 +/- 7.2	22.2 +/- 7.4
Change in mean Y-BOCS score from baseline	-7.5; t=7.588, df=21, p less than 0.001	-8.4; t=7.456, df=20 0.001
Mean end-point CGI-S score	3.2 +/- 1.7	3.1 +/- 1.8
Change in mean CGI-S score from baseline	-1.7; t=7.022, df=21, p less than 0.001	-1.9; t=7.707, df=20 0.001
* p=1; Y-BOCS=Yale-Brown Obsessive Compulsive Scale; CGI-S=Clinical Global Impression Severity s		

b) Adverse effects of risperidone compared with olanzapine-treated patients included tension/inner unrest (2 (16% vs 52%, p=0.016), and amenorrhea (66.7% vs 10%, p=0.02), respectively. The small sample size and t calculation may have contributed to the limitations of this study (Maina et al, 2008).

4.6.F.7 Schizophrenia

a) Olanzapine and risperidone were equally safe and effective therapies in the treatment of schizophrenia in international, multicenter, double-blind study, 175 elderly patients (mean age, 71 years) were randomized to dose, 1.9 milligrams (mg)/day) or olanzapine (mean dose, 11.1 mg/day) for 8 weeks following a 1 week wash medications. Mean duration of illness was 36.5 years and Positive and Negative Syndrome Scale (PANSS) s at baseline. Clinical improvement was defined as a decrease of at least 20% in the total PANSS score. Both significant reductions from baseline in the total PANSS score at all time points (p less than 0.005) and signific observed between groups. Fifty-eight percent of risperidone-treated patients and 59% of olanzapine-treated improvement as defined by the study. Both groups also exhibited significant improvement in four of the five P 0.001). The greatest mean change in the total PANSS score occurred in the 93 patients who had received co medications in the thirty days prior to entering the study (p less than 0.001). The rate of extrapyramidal symp the risperidone and olanzapine treatment groups (9.2% vs 15.9%, respectively, p=ns). The severity of EPS sy groups from baseline to endpoint with no significant difference between groups. A 7% or higher increase in w more olanzapine-treated patients as compared with those who received risperidone (14.8% vs 5.1%, p=0.043 were observed in this patient population and mean QT-c changes were not considered clinically relevant (Jes

b) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in pa schizoaffective disorder that was refractory to treatment with typical antipsychotics. In a randomized, double- clozapine (n=24) 200 to 800 milligrams (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) (n=25) 10 to 30 mg/day. Dose escalation and fixed-dose treatment (target doses: olanzapine 20 mg/day, risp mg/day, clozapine 500 mg/day) occurred during the first 8 weeks of the 14-week study; during the last 6 wee individually (generally increased if response was insufficient, but sometimes reduced because of adverse effe global neurocognitive score was seen for olanzapine and risperidone. In general executive and perceptual or speed and attention, improvement was seen with olanzapine. In simple motor function, there was improveme global neurocognitive performance with olanzapine and risperidone were of medium magnitude (approximate large enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive ga impairments of cognitive ability and social/vocational functioning. Improvements in neurocognitive deficits we in negative symptoms (Bilder et al, 2002).

c) In a prospective, multicenter, double-blind trial, olanzapine was more cost-effective than risperidone in pa schizoaffective disorder, or schizophreniform disorder. One hundred fifty patients were randomized to either per day (mg/d) (n=75) or risperidone (4 to 12 mg/d) (n=75) treatment for a period of 28 weeks. During the stu were significantly more likely to maintain a therapeutic response throughout the course of therapy than risper However, the proportion of patients who responded to treatment was not significantly different between group effects was similar between groups, but significantly more risperidone-treated patients required an anticholine emergent extrapyramidal effects than did those receiving olanzapine (45% versus 25%, p=0.016). Medicatior for olanzapine-treated patients than those treated with risperidone ($2513 versus $1581 US), but this differer in inpatient and outpatient service costs ($3516 vs $7291 US) (Edgell et al, 2000).

d) In an open-label study of patients with DSM-IV schizophrenia, olanzapine (n=21) was shown to be as effe acute treatments. At 6 months, risperidone was more effective for treatment of psychotic symptoms. Howeve less akathisia at the end of 6 months. At discharge the average doses of olanzapine and risperidone were 14 respectively. The reduction of psychotic symptoms with risperidone was significantly greater than with olanaz uncontrolled and adjusted by the treating psychiatrist based on the patient's response, tolerability of side effe recommendations. Measures of effectiveness included the SANS, SAPS, Brief Psychiatric Rating Scale (BPF (GAS) and quality of life measures. (Ho et al, 1999). Larger studies are needed comparing olanzapine and ris

e) Olanzapine (10 to 20 milligrams (mg) daily) was superior to risperidone (4 to 12 mg daily) in the treatment In an international, multicenter, double-blind, parallel-group 28-week prospective study of 339 patients with D schizophreniform disorder, or schizoaffective disorder, the olanzapine group had a significantly better overall decrease in the Positive and Negative syndrome Scale) and was significantly superior to risperidone in the tr

symptomatology. Based on the Kaplan-Meier survival curves, a significantly greater number of the olanzapine response at 28 weeks compared to the risperidone group. Overall adverse reactions were significantly less w extrapyramidal side effects, hyperprolactinemia and sexual dysfunction, with the exception of weight gain; su significantly less in the olanzapine group (Tran et al, 1997). The use of possibly unequivalent doses in this st criticized (Schooler, 1998; Gheuens & Grebb, 1998).

4.6.F.8 Adverse Effects

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

4.6.G Paroxetine

4.6.G.1 Panic attack

a) In an 8-week, randomized, single-blind, comparative trial (n=56) of low-dose risperidone and paroxetine ir both treatments were effective in reducing the occurrence and severity of panic attacks but there was no diffe improve anxiety associated with panic disorders. Thirty-three (8 men, 25 women) subjects were randomized t women) to paroxetine. The average age of the group was 40.36 +/- 12.37 years. Risperidone was initiated at necessary for lack of response or sedation (maximum dose of 16 mg/day). Paroxetine was initiated at 30 mg/ 60 mg/day if needed. The average risperidone dose was 0.53 mg (range 0.125 mg to 1 mg). All subjects in th mg/day except for one who required a dose of 40 mg. Subject assessments were conducted by a clinical rate using the 17-item Hamilton Depression Rating Scales (Ham-D-17), the Hamilton Anxiety Rating Scale (Ham- Scale (PDSS), the Sheehan Panic Anxiety Scale-Patient (SPAS-P) and the Clinical Global Impressions Scale risperidone group and 9 in the paroxetine group completed all study visits. A significant decrease in CGI scor subjects (p less than 0.001), but there was no significant difference between the groups. The CGI score impr to 2.84 +/- 1.02 at final assessment in the risperidone arm. Similarly, paroxetine resulted in a CGI score impr 2.67 +/- 0.71 at final assessment. All subjects, regardless of treatment, demonstrated a significant decrease i total score, PDSS item 1, PDSS item 2, Ham-A and Ham-D. There was no statistical difference between trea study, and there was no significant change in SPAS-p scores over time (Prosser et al, 2009).

4.6.H Perphenazine

Chronic schizophrenia

Schizophrenia

4.6.H.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study me Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/da mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82% from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly l compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar betwe ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides

4.6.H.2 Schizophrenia

a) Risperidone and perphenazine were equally efficacious in a double-blind, multicenter, parallel-group study schizophrenics with acute exacerbation were enrolled (Hoyberg et al, 1993a). No statistically significant differ (defined as a 20% reduction in total Positive and Negative Syndrome Scale score at endpoint) were found be Clinical Global Impression severity scores were also comparable. Patients with predominantly negative symp significantly lower Brief Psychiatric Rating Scale hostility scores compared to patients taking perphenazine.

4.6.I Quetiapine

Chronic schizophrenia

Psychotic disorder

4.6.I.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp
antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study me
Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/da
mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up
patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%
from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly l
compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than
(HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar betwe
ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due
of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides

4.6.I.2 Psychotic disorder

a) Quetiapine and risperidone were similarly efficacious in treating psychotic symptoms and had similar over
treatment resulted in fewer extrapyramidal symptoms (EPS) and was more effective in reducing depression.
patients with schizophrenia, schizoaffective disorder, or other psychotic disorders (including bipolar disorder,
various forms of dementia) were randomized in a ratio of 3:1 to receive quetiapine (n=553) or risperidone (n=
quetiapine was 50 milligrams/day (mg/day), which was increased in 50- or 100- mg increments every 1 to 2 d
mg/day, given in divided doses. Risperidone was started at 1 mg twice daily, with upward titration to a target
3. Dosages were individually titrated to maximize efficacy while minimizing adverse reactions (mean prescrib
risperidone 4.4 mg). At the beginning of the study, approximately half of each group had EPS. There was a s
patients reporting EPS in both groups as the study progressed. The incidence of EPS in the quetiapine group
risperidone group at one month (41.1 vs 47.3) but not at the end of the study (38.6 vs 39.2). The percentage
treatment due to EPS or requiring anti-EPS medication was lower in the quetiapine group than in the risperid
Approximately one third of patients in each group withdrew before completion of the study. A higher percenta
treatment for lack of efficacy (10.3% vs 5.8%) and a higher percentage withdrew from quetiapine treatment b
vs 5.1%). Somnolence was the most common adverse event in both groups, followed by dry mouth and dizzi
significantly more often with quetiapine treatment (p less than 0.05). Occurrence of weight gain was low in bo

4.6.J Ziprasidone

4.6.J.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp
antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study me
Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/da
mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up
patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%
from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly l
compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than
(HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar betwe
ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due
of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides

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DRUGDEX® Evaluations

QUETIAPINE

0.0 Overview

1) Class

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

2) Dosing Information

a) Quetiapine Fumarate

1) Adult

a) Bipolar disorder, depressed phase

1) regular-release tablets, 50 mg ORALLY once a day on day 1, then 100 mg once daily on day 2, then day 3, then 300 mg once daily on day 4 (all doses given at bedtime); patients requiring higher doses sho day 5, increased to 600 mg on day 8 (week 1) (Prod Info SEROQUEL(R) oral tablets, 2008a)

2) re-initiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maint re-initiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed (Prod Info tablets, 2008a)

b) Bipolar disorder, Maintenance

1) regular-release tablets, 400 mg to 800 mg per day ORALLY divided twice daily; generally continuatio or lowest dose to maintain remission; periodically reassess for need and appropriate dose for maintenan Info SEROQUEL(R) oral tablets, 2008a)

c) Manic bipolar I disorder

1) regular-release tablets, initial, 50 mg ORALLY twice daily, may increase dosage by increments up to the second and third day, to a target dose 400 mg per day by the fourth day given in 2 divided doses (Pr (R) oral tablets, 2007b)

2) regular-release tablets, maintenance, dosage adjustments in increments of not more than 200 mg/da day 6; usual effective dosage range is 400 to 800 mg/day; MAX dosage 800 mg/day (Prod Info SEROQU 2007b)

3) re-initiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maint re-initiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed (Prod Info tablets, 2007b)

d) Schizophrenia

1) regular-release tablets, initial, 25 mg ORALLY twice daily, may increase dosage by 25 to 50 mg 2 to second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given doses (Prod Info SEROQUEL(R) oral tablets, 2007b)

2) regular-release tablets, maintenance, dosage adjustments, if indicated, should generally occur at inte days in dose increments/decrements of 25 to 50 mg twice a day; usual effective dosage range is 150 to divided doses), MAX dosage 800 mg/day (Prod Info SEROQUEL(R) oral tablets, 2007b)

3) extended-release tablets, initial, 300 mg ORALLY once daily, preferably in the evening; titrate to a tar to 800 mg daily; dose increases may occur at intervals of at least 1 day in increments of up to 300 mg/da mg/day (Prod Info SEROQUEL XR(TM) extended-release oral tablets, 2007)

4) re-initiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maint re-initiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed (Prod Info extended-release oral tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2007b)

e) Schizophrenia, Maintenance

1) extended-release tablets, 400 to 800 mg ORALLY once daily, preferable in the evening; periodically r appropriate dose for maintenance treatment (Prod Info SEROQUEL(R)XR extended-release oral tablets,

2) Pediatric

a) safety and effectiveness in pediatric patients have not been established (Prod Info SEROQUEL XR(TM) e tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2008a)

3) Contraindications

a) Quetiapine Fumarate

1) hypersensitivity to quetiapine fumarate or any component of the product (Prod Info SEROQUEL(R) oral tablets

4) Serious Adverse Effects

a) Quetiapine Fumarate

1) Agranulocytosis
2) Anaphylaxis
3) Death
4) Leukopenia
5) Neuroleptic malignant syndrome
6) Neutropenia
7) Priapism
8) Seizure

9) Sudden cardiac death
10) Suicidal thoughts
11) Syncope
12) Tardive dyskinesia

5) Clinical Applications
a) Quetiapine Fumarate
1) FDA Approved Indications
a) Bipolar disorder, depressed phase
b) Bipolar disorder, Maintenance
c) Manic bipolar I disorder
d) Schizophrenia
e) Schizophrenia, Maintenance

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In
B) Synonyms
Quetiapine
Quetiapine Fum
Quetiapine Fumarate
C) Physicochemical Properties
1) Molecular Weight
a) Quetiapine fumarate: 883.11 (Prod Info Seroquel, 97)
2) Solubility
a) Systemic: Quetiapine fumarate is moderately soluble in water (Prod Info Seroquel, 97).

1.2 Storage and Stability

A) Quetiapine Fumarate
1) Preparation
a) Oral route
1) Administration
a) Quetiapine extended-release tablets should not be chewed, crushed or split and should be swall
SEROQUEL XR(TM) extended-release oral tablets, 2007).
b) The absorption of extended-release quetiapine tablets is affected by food; give without food or w
approximately 300 calories (Prod Info SEROQUEL XR(TM) extended-release oral tablets, 2007). Re
are only marginally affected by food, and may be given without regards to food (Prod Info SEROQU
2008a).
B) Quetiapine Fumarate
1) Oral route
a) Tablet/Tablet, Extended Release
1) Store at 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 a
(Prod Info SEROQUEL(R) oral tablets, 2008; Prod Info SEROQUEL XR(R) extended-release oral tablets

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage in Other Disease States

1.3.1 Normal Dosage

1.3.1.A Quetiapine Fumarate

1.3.1.A.1 Oral route

Bipolar disorder, depressed phase

Manic bipolar I disorder

Schizophrenia

Schizophrenia, Maintenance

1.3.1.A.1.a Bipolar disorder, depressed phase

1) The recommended quetiapine dosing schedule for the treatment of depressive episodes associa disorder is 50 milligrams (mg), 100 mg, 200 mg, and 300 mg given once a day at bedtime on days 1 respectively. If a higher dose is required, the dose may be increased to 400 mg on day 5 and 600 m In clinical trials, both 300 mg and 600 mg doses demonstrated antidepressant efficacy; however, no seen in the 600 mg group (Prod Info SEROQUEL(R) oral tablets, 2008a).

2) When restarting treatment in patients who have had an interval of less than 1 week off of quetiap dose is not required and the maintenance dose may be re-initiated. The initial titration schedule sho re-initiating therapy in patients who have not taken quetiapine for more than 1 week (Prod Info SER tablets, 2008a).

1.3.1.A.1.b Manic bipolar I disorder

1) As monotherapy or adjunct therapy (with lithium or divalproex) in the treatment of acute bipolar m recommended initial dose of quetiapine is 100 milligrams per day (mg/day) (in two divided doses) or 400 mg/day on day 4 in increments of up to 100 mg/day (in two divided doses). Additional dosage a mg/day by day 6 should be in increments of no more than 200 mg/day. Most patients respond to dos 800 mg/day. The safety of doses greater than 800 mg/day has not been evaluated (Prod Info SERO 2007b).

2) When restarting treatment in patients who have had an interval of less than 1 week off of quetiap dose is not required and the maintenance dose may be re-initiated. The initial titration schedule sho re-initiating therapy in patients who have not taken quetiapine for more than 1 week (Prod Info SER tablets, 2007b).

1.3.1.A.1.c Schizophrenia

1) Regular-Release Tablets

a) For the treatment of schizophrenia, the recommended initial dose of quetiapine regular-relea milligrams (mg) twice daily. On the second or third day, the dose may be increased in incremen or three times daily. By the fourth day a target dose of 300 to 400 mg daily divided in two or thre recommended. Further increases can be made in increments of 25 to 50 mg twice daily at inter days. Antipsychotic efficacy has been demonstrated in the range of 150 to 750 mg usually given The safety of doses greater than 800 mg has not been determined (Prod Info SEROQUEL(R) o

b) For the treatment of schizophrenia, average effective doses of quetiapine in clinical trials ha and 400 milligrams daily, with the dose given in 2 or 3 divided doses; maximum doses have bee (Goren & Levin, 1998; Fulton & Goa, 1995b; Anon, 1995b; Borison et al, 1996b).

c) When restarting treatment in patients who have had an interval of less than 1 week off of qu dose is not required and the maintenance dose may be re-initiated. The initial titration schedule when re-initiating therapy in patients who have not taken quetiapine for more than 1 week (Proc oral tablets, 2008a).

2) Extended-Release Tablets

a) For the treatment of schizophrenia, the recommended initial dose of quetiapine extended-rel milligrams (mg) once daily, preferably given in the evening. Titrate the dose based upon patient tolerance within a range of 400 to 800 mg/day. Doses may be increased in increments of up to intervals as short as 1 day. Doses greater than 800 mg/day have not been evaluated for safety Info SEROQUEL XR(TM) extended-release oral tablets, 2007).

b) When restarting treatment in patients who have had an interval of less than 1 week off of qu the dose is not required and the maintenance dose may be re-initiated. The initial titration sched followed when re-initiating therapy in patients who have not taken quetiapine for more than 1 we

SEROQUEL XR(TM) extended-release oral tablets, 2007).

3) Switching from Regular-Release to Extended-Release

a) Schizophrenic patients currently receiving 2 to 3 divided doses of oral quetiapine fumarate (i formulation) may be switched to the extended-release formulation at the equivalent total daily d orally once daily (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

1.3.1.A.1.d Schizophrenia, Maintenance

1) Doses of 400 to 800 milligrams (mg) per day of extended-release quetiapine were successful in compared to placebo in the double-blind extension phase of a clinical trial in schizophrenic patients open-label treatment for 16 weeks. The dose should be administered once daily in the evening eithe a light meal. The maximum dose evaluated in clinical trials was 800 mg. Periodic reassessments are evaluate the need and appropriate dose for maintenance treatment (Prod Info SEROQUEL(R)XR ex tablets, 2007).

2) When restarting treatment in patients who have had an interval of less than 1 week off of quetiap dose is not required and the maintenance dose may be re-initiated. The initial titration schedule for a be followed when re-initiating therapy in patients who have not taken quetiapine for more than 1 wee SEROQUEL(R)XR extended-release oral tablets, 2007).

1.3.1.A.1.e IMPORTANT NOTE

1) The FDA Safety Information and Adverse Event Reporting Program has reported that there have errors due to the similarity of the names, dosage forms, strengths, and dosing intervals for Seroquel (Anon, 2002).

1.3.2 Dosage in Renal Failure

A) Quetiapine Fumarate

1) Dosage adjustment does not appear necessary in patients with renal insufficiency (Prod Info SEROQUEL release oral tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2008a).

1.3.3 Dosage in Hepatic Insufficiency

A) Quetiapine Fumarate

1) Patients with hepatic impairment should be started on quetiapine therapy using the regular-release tablets (mg)/day then increased daily in increments of 25 to 50 mg/day to an effective dose. In these patients, the me quetiapine is 30% lower than subjects with normal hepatic clearance (Prod Info SEROQUEL XR(TM) extende 2007; Prod Info SEROQUEL(R) oral tablets, 2008a; Green, 1999a).

2) Patients may be switched to an equivalent total daily dose using extended-release tablets once an effectiv reached with the regular-release tablets (Prod Info SEROQUEL XR(TM) extended-release oral tablets, 2007)

1.3.4 Dosage in Geriatric Patients

A) Quetiapine Fumarate

1) Elderly patients should be started on quetiapine therapy using the regular-release tablets at 25 milligrams increased daily in increments of 25 to 50 mg/day to an effective dose. Oral clearance of quetiapine was reduc older than 65 years (Prod Info SEROQUEL XR(TM) extended-release oral tablets, 2007).

2) Patients may be switched to an equivalent total daily dose using extended-release tablets once an effectiv reached with the regular-release tablets (Prod Info SEROQUEL XR(TM) extended-release oral tablets, 2007)

1.3.6 Dosage in Other Disease States

A) Quetiapine Fumarate

1) Debilitated Patients

a) The manufacturer recommends that patients who are debilitated or have a predisposition to hypotens slower dose escalation and lower target dose (Prod Info SEROQUEL(R) oral tablets, 2008a; Prod Info S extended-release oral tablets, 2007).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Quetiapine Fumarate

1.4.1.A.1 Oral route

a) Safety and effectiveness for use in pediatric patients have not been established (Prod Info SEROQUI release oral tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2008a).

b) In a small trial (n=10) of adolescents (mean age of 13.6 years) with selected psychotic disorders, que in a dosage range of 50 to 800 milligrams daily led to satisfactory clinical results and similar pharmacoki profiles to that of adults (McConville et al, 2000).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration
A) Onset
1) Quetiapine Fumarate
a) Initial Response
1) Schizophrenia, oral: 7 to 14 days (Borison et al, 1996; Fulton & Goa, 1995)

2.2 Drug Concentration Levels
A) Quetiapine Fumarate
1) Therapeutic Drug Concentration
a) Schizophrenia, undefined (Fabre et al, 1995)
2) Time to Peak Concentration
a) Oral, regular-release tablets: 1.5 hours (Prod Info SEROQUEL(R) oral tablets, 2007; Fabre et al, 1995; Sh
1) Steady-state concentrations of quetiapine fumarate regular-release tablets occur within 2 days of dos
SEROQUEL(R) oral tablets, 2007).
2) A mean peak level of 278 ng/mL (range, 140 to 365 ng/mL) was observed after a 75-mg oral midday
quetiapine therapy; at this time, patients were receiving total daily doses of up to 250 mg. After a single d
quetiapine in schizophrenic patients, peak serum levels ranged from 18 to 136 ng/mL (mean, 60 ng/mL)
b) Oral, extended-release tablets: 6 h (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007)
1) Steady-state concentrations of quetiapine fumarate extended-release tablets occur within 2 days of d
SEROQUEL(R)XR extended-release oral tablets, 2007).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption
A) Quetiapine Fumarate
1) Bioavailability
a) Oral: 9% (Goren & Levin, 1998).
1) The bioavailability of the extended-release quetiapine fumarate tablets, dosed once daily at stea
comparable to an equivalent dose of the regular-release tablets, dosed twice daily (Prod Info SERO
extended-release oral tablets, 2007).
2) Effects of Food
a) Regular-release tablets: marginally affected (Prod Info SEROQUEL(R) oral tablets, 2007)
1) When regular-release quetiapine fumarate tablets were administered with food, the Cmax and AU
and 15%, respectively (Prod Info SEROQUEL(R) oral tablets, 2007b).
2) Food increases the absorption of quetiapine (Goren & Levin, 1998). In healthy volunteers, admin
with food resulted in an increase in the peak serum concentration and area under the time-concentra
(each by approximately 1.5-fold) compared to the fasting state (Shimada et al, 1994).
b) Extended-release tablets: significant (Prod Info SEROQUEL(R)XR extended-release oral tablets, 200
1) Statistically significant increases in the Cmax and AUC of 44% to 52% and 20% to 22%, respecti
the 50-mg and 300-mg quetiapine fumarate extended-release tablets when given with a high-fat me
to 1000 calories). There was no significant effect on the Cmax or AUC when given with a light meal
calories) (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007; Prod Info SEROQUEL(R

2.3.2 Distribution
A) Distribution Sites
1) Quetiapine Fumarate
a) Protein Binding
1) 83% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-releas

B) Distribution Kinetics
1) Quetiapine Fumarate
a) Volume of Distribution
1) 10 L/kg +/- 4 L/kg (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR ext tablets, 2007)

2.3.3 Metabolism
A) Metabolism Sites and Kinetics
1) Quetiapine Fumarate
a) LIVER, extensive (Goren & Levin, 1998; Green, 1999)
1) Extensive first-pass metabolism occurs with quetiapine (Wetzel et al, 1995a).
2) Quetiapine fumarate is primarily metabolized by sulfoxidation and oxidation via the P450 CYP3A Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets, 2
3) After a single oral dose, less than 1% of quetiapine is excreted unchanged (Prod Info SEROQUE 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).
B) Metabolites
1) Quetiapine Fumarate
a) N-desalkyl quetiapine, (active) (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007)
1) Twenty metabolites of quetiapine have been identified; the 7-hydroxylated metabolite and the N- are pharmacologically active (Goren & Levin, 1998).

2.3.4 Excretion
A) Kidney
1) Quetiapine Fumarate
a) Renal Excretion (%)
1) 70% to 73% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended 2007; Green, 1999; Fulton & Goa, 1995)
a) Following administration of a single oral dose of carbon-labeled quetiapine, approximately 7 recovered in the urine (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)X oral tablets, 2007).
B) Feces
1) Quetiapine Fumarate
a) approximately 20% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extend tablets, 2007)
1) Following administration of a single oral dose of carbon-labeled quetiapine, approximately 20% c recovered in the feces (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR ex tablets, 2007).

2.3.5 Elimination Half-life
A) Parent Compound
1) Quetiapine Fumarate
a) Regular-release tablet, 6 hours (Prod Info SEROQUEL(R) oral tablets, 2007)
b) Extended-release tablet, 7 hours (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007)

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Quetiapine Fumarate
a) Oral (Tablet)
Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk seventeen placebo-controlled trials (modal duration of 10 weeks) largely in patients taking atypical antips revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 times the risk of death in pla Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths a

cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observationa similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mo which the findings of increased mortality in observational studies may be attributed to the antipsychotic d some characteristic(s) of the patients is not clear. Quetiapine fumarate is not approved for the treatment dementia-related psychosis (Prod Info SEROQUEL(R) oral tablets, 2008).

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorde considering the use of quetiapine fumarate or any other antidepressant in a child, adolescent, or young a risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antid to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to plac and older. Depression and certain other psychiatric disorders are themselves associated with increases Patients of all ages who are started on antidepressant therapy should be monitored appropriately and ob clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advise observation and communication with the prescriber. Quetiapine fumarate is not approved for use in pedi Info SEROQUEL(R) oral tablets, 2008).

b) Oral (Tablet, Extended Release)

Increased Mortality in Elderly Patients with Dementia-related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk seventeen placebo-controlled trials (modal duration of 10 weeks) largely in patients taking atypical antips revealed a risk of death in the drug-treated patients of between 1.6 times to 1.7 times the risk of death in patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients w compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in studies suggest that, similar to atypical antipsychotic drugs may increase mortality. The extent to which t increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to so the patients is not clear. Quetiapine fumarate extended-release is not approved for the treatment of patie related psychosis (Prod Info SEROQUEL XR(R) extended-release oral tablets, 2008).

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorde considering the use of quetiapine fumarate or any other antidepressant in a child, adolescent, or young a risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antid to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to plac and older. Depression and certain other psychiatric disorders are themselves associated with increases Patients of all ages who are started on antidepressant therapy should be monitored appropriately and ob clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advise observation and communication with the prescriber. Quetiapine fumarate extended-release tablets are n pediatric patients. Quetiapine fumarate is not approved for use in the treatment of depression, however, form of quetiapine fumarate is approved for the treatment of bipolar depression (Prod Info SEROQUEL X release oral tablets, 2008).

3.1 Contraindications

A) Quetiapine Fumarate

1) hypersensitivity to quetiapine fumarate or any component of the product (Prod Info SEROQUEL(R) oral tablets

3.2 Precautions

A) Quetiapine Fumarate

1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death reported when atyp were used to treat behavorial disorders associated with dementia (Prod Info SEROQUEL XR(R) extended-release Prod Info SEROQUEL(R) oral tablets, 2008)

2) suicidal ideation and behavior or worsening depression; increased risk, particularly in children and adolescents first few months of therapy or during changes in dosing (decreases or increases) (Prod Info SEROQUEL XR(R) e tablets, 2008; Prod Info SEROQUEL(R) oral tablets, 2008)

3) agranulocytosis, including fatal cases, has been reported (Prod Info SEROQUEL(R)XR extended-release oral Info SEROQUEL(R) oral tablets, 2007)

4) aspiration pneumonia, patients at risk for; may cause esophageal dysmotility and aspiration (Prod Info SEROQ release oral tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2007)

5) cardiovascular disease, known; risk of orthostatic hypotension (Prod Info SEROQUEL(R)XR extended-release Prod Info SEROQUEL(R) oral tablets, 2007)

6) cerebrovascular disease; risk of orthostatic hypotension (Prod Info SEROQUEL(R)XR extended-release oral ta SEROQUEL(R) oral tablets, 2007)

7) concomitant use of antihypertensive medications; risk of orthostatic hypotension (Prod Info SEROQUEL(R)XR tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2007)

8) dehydration; risk of orthostatic hypotension (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUE 2007)

9) diabetes mellitus or at risk of diabetes mellitus; occurrence of hyperglycemia, some cases associated with keto hyperosmolar coma or death (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007; Prod Info SEROQ

2007)
10) elderly patients (especially elderly women); increased risk of tardive dyskinesia (Prod Info SEROQUEL(R)XR tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2007)
11) elevated cholesterol and triglyceride levels have been reported (Prod Info SEROQUEL(R)XR extended-relea Prod Info SEROQUEL(R) oral tablets, 2007a)
12) elevated serum transaminases (asymptomatic, transient and reversible) have been reported(Prod Info SERO extended-release oral tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2007)
13) hypovolemia; risk of orthostatic hypotension (Prod Info SEROQUEL(R)XR extended-release oral tablets, 200 SEROQUEL(R) oral tablets, 2007)
14) leukopenia/neutropenia has been reported; increased risk with history of drug-induced leukopenia/neutropeni WBC; if develops, discontinue therapy (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007; Prod In tablets, 2007)
15) neuroleptic malignant syndrome (NMS) has occurred (Prod Info SEROQUEL(R)XR extended-release oral tab SEROQUEL(R) oral tablets, 2007)
16) orthostatic hypotension, with or without syncope, may occur; increased risk during initial dose-titration period, titration, return to previous dose (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007; Prod Info SER tablets, 2007)
17) seizures, history of or predisposing factors for developing (Prod Info SEROQUEL(R)XR extended-release ora Info SEROQUEL(R) oral tablets, 2007)
18) tardive dyskinesia may occur; increased risk with increased duration of treatment and increased total cumula SEROQUEL(R)XR extended-release oral tablets, 2007; Prod Info SEROQUEL(R) oral tablets, 2007)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Quetiapine Fumarate

Orthostatic hypotension

Sudden cardiac death

Syncope

Tachycardia

3.3.1.A.1 Orthostatic hypotension

a) Incidence: 4% to 7% (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007; Prod Info SE tablets, 2007)

b) In monotherapy, placebo-controlled clinical trials for the treatment of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, orthostatic hypotension was reported in 4% of patients receiving quetiapine fuma compared to 1% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUE 2007).

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, hypotension was reported in 7% of patients receiving quetiapine fumarate tablets (n=196) compared to 2 (n=203); doses ranged from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

d) During acute therapy (up to 6 weeks) placebo-controlled clinical trials of adult patients with schizophr hypotension was reported in 7% of patients receiving quetiapine fumarate extended-release tablets (n=9 for placebo (n=319). Use quetiapine fumarate cautiously in patients with cerebrovascular disease, cardio conditions that predispose them to hypotension (i.e., hypovolemia, dehydration, and concomitant antihyp (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

e) The risk of hypotension is greater during dose-titration periods. Should hypotension develop during tit pre-titration dose is appropriate (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)X oral tablets, 2007).

3.3.1.A.2 Sudden cardiac death

a) In a large, retrospective, cohort study that included a primary cohort of 93,300 users of antipsychotic non-users of antipsychotic drugs, there was an increased risk of sudden cardiac death in adult participan age (mean age of 45.7 years) who were using quetiapine compared to those who were not using antipsy (incidence-rate ratio, 1.88; 95% confidence interval (CI), 1.3 to 2.71; p less than 0.001). In participants be atypical antidepressants (clozapine, olanzapine, quetiapine, risperidone), the incidence-rate ratio for sud increased from 1.59 (95% CI, 1.03 to 2.46) for those using low doses to 2.86 (95% CI, 2.25 to 3.65) for th (p=0.01) (Ray et al, 2009).

3.3.1.A.3 Syncope

a) Incidence: tablets, 1% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets, 0.3% SEROQUEL(R)XR extended-release oral tablets, 2007)

b) During clinical trials, syncope was reported in 1% of patients receiving quetiapine fumarate tablets (n= 0.2% for placebo (n=954) and 0.4% for active control (n=527) (Prod Info SEROQUEL(R) oral tablets, 200

c) During clinical trials, syncope was reported in 0.3% of patients receiving quetiapine fumarate extende (n=951) and in 0.3% receiving placebo (n=319) (Prod Info SEROQUEL(R)XR extended-release oral tabl

3.3.1.A.4 Tachycardia

a) Incidence: 0.5% to 6% (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007; Prod Info S tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, tachycardia was reported in 6% of patients receiving quetiapine fumarate tablets 4% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl

c) During clinical trials, tachycardia was reported in 3% of patients receiving quetiapine fumarate extend compared to 1% for placebo. Tachycardia (greater than 120 bpm) was reported in 0.8% of patients recei compared to 0% for placebo at any time during the clinical trials for quetiapine fumarate extended-releas SEROQUEL(R)XR extended-release oral tablets, 2007).

d) In four pooled, placebo controlled clinical trials for the treatment of schizophrenia (3 to 6 weeks in dur tachycardia was reported in 1% of patients receiving quetiapine fumarate tablets (n=399) compared to 0. (n=156) (Prod Info SEROQUEL(R) oral tablets, 2007).

e) In pooled, placebo-controlled clinical trials for the treatment (monotherapy) of acute bipolar mania in a was reported in 0.5% of patients receiving quetiapine fumarate tablets (n=192) compared to 0% for place SEROQUEL(R) oral tablets, 2007).

f) In pooled, placebo-controlled clinical trials for the adjunctive treatment of acute bipolar mania in adults reported in 0.6% of patients receiving quetiapine fumarate tablets (n=166) compared to 0% for placebo (SEROQUEL(R) oral tablets, 2007).

g) Evaluation of ECG's associated a mean increase in heart rate of 7 beats per minute (bpm) for quetiap compared to a mean increase of 1 bpm for placebo (Prod Info SEROQUEL(R) oral tablets, 2007; Prod In extended-release oral tablets, 2007).

h) An increase in heart rate (approximately 9 beats/minute) has been detected during 6 weeks of therap 1996a). Greater than 20 percent of patients receiving 100 to 200 milligrams daily have shown an increas beats per minute or greater or have experienced a decrease in systolic blood pressure of 30 millimeters (Garver, 2000a). The drug has not induced clinically significant arrhythmias in placebo-controlled studies

3.3.2 Dermatologic Effects

3.3.2.A Quetiapine Fumarate

3.3.2.A.1 Rash

a) Incidence: tablets, 4% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets, less th
SEROQUEL(R)XR extended-release oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a
to 12 weeks) in adults, rash was reported in 4% of patients receiving quetiapine fumarate tablets (n=719
placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 20

c) During clinical trials for the treatment of schizophrenia in adults, rash was reported in less than 5% of
quetiapine fumarate extended-release tablets (Prod Info SEROQUEL(R)XR extended-release oral tablet

3.3.3 Endocrine/Metabolic Effects

Quetiapine

Quetiapine Fumarate

3.3.3.A Quetiapine

Diabetes mellitus

Metabolic syndrome

3.3.3.A.1 Diabetes mellitus

See Drug Consult reference: ATYPICAL ANTIPSYCHOTIC AGENTS - EFFECT ON GLUCOSE AND RI

3.3.3.A.2 Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.B Quetiapine Fumarate

Decreased prolactin level

Hyperglycemia

Hypothyroidism

Serum cholesterol raised

Serum triglycerides raised

Weight gain

3.3.3.B.1 Decreased prolactin level

a) In studies of patients with high prolactin levels, serum prolactin was reduced further in patients treate
in those receiving chlorpromazine. Prolactin levels were similar with placebo and quetiapine after 21 and
Quetiapine has minimal effect on the serum prolactin levels of schizophrenic patients. Decreases in prola
cases, were most likely related to discontinuation of the patient's antipsychotic therapy (Borison et al, 19
Fulton & Goa, 1995b).

3.3.3.B.2 Hyperglycemia

a) Incidence: 0.1% to 1% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) Hyperglycemia, including cases associated with ketoacidosis, hyperosmolar coma, or death, has bee
receiving atypical antipsychotics, including quetiapine fumarate. Hyperglycemia has resolved in some ca
discontinuation of the drug, while in other cases, continuation of antidiabetic treatment was required afte
(Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets

c) In two long-term, placebo-controlled clinical trials, blood glucose increases of 126 mg/dL or greater fo than 8 hours since a meal were reported in 10.7% of patients taking quetiapine fumarate tablets (n=646; exposure, 213 days) compared to 4.6% for placebo (n=680; mean duration of exposure, 152 days) (Proc oral tablets, 2007).
d) In placebo-controlled clinical trials of up to 12 weeks, fasting blood glucose levels of 126 mg/dL or gre blood glucose levels of 200 mg/dL or greater were reported for 3.5% of patients taking quetiapine fumara compared to 2.1% for placebo (n=1490) (Prod Info SEROQUEL(R) oral tablets, 2007).
e) In a 24-week trial (n=115), a fasting blood glucose of 126 mg/dL or greater was reported in 2.6% of p nonfasting blood glucose of 200 mg/dL or greater was reported in 1.7% of patients taking quetiapine fum Info SEROQUEL(R) oral tablets, 2007).
f) A 42-year-old man, after one month of quetiapine use, was diagnosed with new-onset diabetes mellitu admitted to the hospital after several days of nausea, vomiting, polyuria, and confusion. His blood glucos admission was 607 milligram/deciliter (mg/dL). Random blood glucose concentrations 4 months prior to t were 126 and 107 mg/dL. He had no prior history of glucose intolerance, hyperglycemia, and no familial The patient's history of bipolar disorder was concurrently treated with lithium carbonate, gabapentin, clor venlafaxine in addition to his quetiapine titration of 200 milligrams at night. He was eventually discharged regimen, and quetiapine was discontinued over the course of 9 days. The patient's insulin dose was wea 5 months after admission (Sobel et al, 1999).

3.3.3.B.3 Hypothyroidism

a) Summary

1) Cases of hypothyroidism have been reported with quetiapine use. Thyroid monitoring is recomm therapy, at least in patients with a history of or a propensity for thyroid disease (Liappas et al, 2006;

b) In placebo-controlled clinical trials, 0.5% and 2.7% of patients receiving quetiapine fumarate extende experienced decreased free thyroxine and increased TSH, respectively, compared to 0% and 1.2% for p (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).
c) In clinical trials using quetiapine fumarate tablets as monotherapy treatment, 0.7% of patients receivi experienced increased TSH levels with six patients requiring thyroid replacement therapy (Prod Info SEF tablets, 2007).
d) In placebo-controlled clinical trials for the adjunctive treatment of mania in adults, elevated TSH level 12% of patients receiving quetiapine fumarate tablets (n=196) compared to 7% for placebo (n=203). Thr treated patients also had concurrent low free T4 levels (Prod Info SEROQUEL(R) oral tablets, 2007).
e) In clinical trials, decreases in total and free thyroxine (T4) appear to be dose-related, with levels drop 20% at the higher end of the therapeutic dose range; maximal decreases were seen during the first two t therapy (Prod Info SEROQUEL(R) oral tablets, 2007).
f) A case of quetiapine-induced hypothyroidism was described in a 49-year-old woman. The patient had dysthymia, with 2 major depressive episodes in the past 14 years, and had been treated over the years v antidepressant and anxiolytic medications to varying degrees of success. Over the last 4 years, she was taking up to 150 mg/day. Six months prior to current presentation, in an attempt to discontinue zolpidem mood, treatment with venlafaxine (300 mg/day), paroxetine (30 mg/day), and quetiapine (800 mg/day) w significant improvement. A routine thyroid screening at the time of current presentation revealed decreas (4.17 mcg/dL; normal range, 6.09 to 12.23 mcg/dL) and free T4 values (0.53 ng/dL; normal range, 0.58 t elevated TSH level (6.78 micro-International Units/mL; normal range, 0.34 to 5.6 micro-International Unit symptoms included a modest weight gain, decrease in appetite, hoarseness of voice, slowing of motor a constipation. Although the patient's past medical record was negative for a thyroid disorder, she had a p for hypothyroidism. Subsequently, quetiapine was tapered and discontinued over a week, while the rest were continued at the same doses. Within the next 2 months, laboratory thyroid tests were within normal displayed a steady mood improvement. It is believed that thyroid autoimmunity may be responsible for th function monitoring is recommended in quetiapine-treated patients with a history of or a propensity for th et al, 2006).
g) A 46-year-old woman developed hypothyroidism 2 months after the addition of quetiapine to her exist Reaching a final titrated total dose of 425 milligrams of quetiapine daily, the patient developed an elevate hormone concentration of 8.45 microunits per liter. Prior medical history included successful radioactive hyperthyroidism but without detection of thyroid abnormalities until 4 years later when quetiapine was init function monitoring is recommended during quetiapine therapy (Feret & Caley, 2000).
h) Decreases in mean total thyroxine and occasionally decreased triiodothyronine levels have occurred schizophrenia with quetiapine (Anon, 1995a; Borison et al, 1996a).

3.3.3.B.4 Serum cholesterol raised

a) Incidence: tablets, 9% to 16% (Prod Info SEROQUEL(R) oral tablets, 2007)
b) During clinical trials for the treatment of schizophrenia in adults, elevations in cholesterol to levels of were reported in 16% of patients receiving quetiapine fumarate tablets compared to 7% for placebo (Pro oral tablets, 2007).
c) During adult bipolar depression clinical trials, elevations in cholesterol to levels of 240 mg/dL or great of patients receiving quetiapine fumarate tablets compared to 6% for placebo (Prod Info SEROQUEL(R)
d) During clinical trials for the treatment of schizophrenia in adults, an increase in mean cholesterol leve were reported in patients receiving quetiapine fumarate extended-release tablets compared to a decreas for placebo (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3.3.3.B.5 Serum triglycerides raised

a) Incidence: tablets, 14% to 23% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) During clinical trials for the treatment of schizophrenia in adults, elevations in triglycerides to levels of were reported in 23% of patients receiving quetiapine fumarate tablets compared to 16% for placebo (Pr (R) oral tablets, 2007).

c) During adult bipolar depression clinical trials, elevations in triglycerides to levels of 200 mg/dL or grea 14% of patients receiving quetiapine fumarate tablets compared to 9% for placebo (Prod Info SEROQUE 2007).

d) During clinical trials for the treatment of schizophrenia in adults, an increase in mean triglyceride leve 15% was reported in patients receiving quetiapine fumarate extended-release tablets compared to a dec 6% for placebo (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3.3.3.B.6 Weight gain

a) Incidence: 5% to 23% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR exte tablets, 2007)

b) Patients receiving quetiapine fumarate tablets demonstrated a greater incidence of weight increase (weight) than placebo in placebo-controlled schizophrenia trials (23% and 6%, respectively); in mania mo and 7%, respectively); in mania adjunct therapy trials (13% and 4%, respectively); and in bipolar depress respectively) (Prod Info SEROQUEL(R) oral tablets, 2007).

c) During adult schizophrenia clinical trials, weight gain of 7% or greater of body weight was reported in receiving quetiapine fumarate extended-release tablets compared to 5% for placebo (Prod Info SEROQU release oral tablets, 2007).

d) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, weight gain was reported in 5% of patients receiving quetiapine fumarate tablets 1% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl

e) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, reported in 6% of patients receiving quetiapine fumarate tablets (n=196) compared to 3% for placebo (n= from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

f) A logistic regression analysis of placebo-controlled clinical study of five fixed-doses of quetiapine fuma patients with schizophrenia revealed a positive correlation between dose and the occurrence of weight g Doses included in these studies included 75 milligrams (mg)/day, 150 mg/day, 300 mg/day, 600 mg/day, (Prod Info SEROQUEL(R) oral tablets, 2007).

g) Adolescent patients taking olanzapine experienced greater weight gain and increased in body mass i patients taking quetiapine in a retrospective study involving 103 patients younger than 18 years of age. F olanzapine (n=50, mean daily dose 13.9 milligrams (mg)) or quetiapine (n=53, mean daily dose 510.9 mg Weight and height were measured at baseline and 14 or more days after baseline. Average weight gain olanzapine group was 3.8 kilograms (kg) (p less than 0.001) compared to 0.03 kg in the quetiapine group and quetiapine groups showed slight, but significant, increases in height from baseline (0.006 meters, p= meters, p less than 0.001, respectively). After controlling for baseline differences, the mean weight chang was significant (3.4 kg, p less than 0.001). BMI increased by an average of 1.3 kg per square meter (m(2 group (p less than 0.001) compared to a decreased of 0.2 kg/m(2) in the quetiapine group. After controlli differences, the mean difference in change in BMI was significant (0.9 kg/m(2), p=0.008) (Patel et al, 200

3.3.4 Gastrointestinal Effects

3.3.4.A Quetiapine Fumarate

Abdominal pain

Constipation

Increased appetite

Indigestion

Vomiting

Xerostomia

3.3.4.A.1 Abdominal pain

a) Incidence: 4% to 7% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, abdominal pain was reported in 4% of patients receiving quetiapine fumarate tabl

to 1% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral t
c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, reported in 7% of patients receiving quetiapine fumarate tablets (n=196) compared to 3% for placebo (n= from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).
d) A logistic regression analysis of placebo-controlled clinical study of five fixed-doses of quetiapine fum patients with schizophrenia revealed a positive correlation between dose and the occurrence of abdomin 0.05). Doses included in these studies included 75 milligrams (mg)/day, 150 mg/day, 300 mg/day, 600 m mg/day (Prod Info SEROQUEL(R) oral tablets, 2007).
e) Anticholinergic adverse effects of quetiapine therapy are dose-related. Dry mouth occurred in 8% to 1 patients in clinical trials. Constipation was also reported. Abdominal pain, dyspepsia, and anorexia occur (Borison et al, 1996a; Wetzel et al, 1995; Fulton & Goa, 1995b).

3.3.4.A.2 Constipation
a) Incidence: tablets, 8% to 10% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets SEROQUEL(R)XR extended-release oral tablets, 2007)
b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, constipation was reported in 8% of patients receiving quetiapine fumarate tablets 3% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tab
c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, reported in 10% of patients receiving quetiapine fumarate tablets (n=196) compared to 5% for placebo (r from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).
d) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, co reported in 10% of patients receiving quetiapine fumarate tablets (n=698) compared to 4% for placebo (r from 300 to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).
e) In placebo-controlled clinical trials for the treatment of schizophrenia (up to 6 weeks) in adults, constip 6% of patients receiving quetiapine fumarate extended-release tablets (n=951) compared to 5% for place ranged from 300 to 800 mg (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).
f) Anticholinergic adverse effects of quetiapine therapy are dose-related. Dry mouth occurred in 8% to 1 patients in clinical trials. Constipation was also reported. Abdominal pain, dyspepsia, and anorexia occur (Borison et al, 1996a; Wetzel et al, 1995; Fulton & Goa, 1995b).

3.3.4.A.3 Increased appetite
a) Incidence: tablets, 5% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets, less th SEROQUEL(R)XR extended-release oral tablets, 2007)
b) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, in reported in 5% of patients receiving quetiapine fumarate tablets (n=698) compared to 3% for placebo (n= from 300 to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).
c) During clinical trials for the treatment of schizophrenia in adults, increased appetite was reported in le taking quetiapine fumarate extended-release tablets (Prod Info SEROQUEL(R)XR extended-release ora

3.3.4.A.4 Indigestion
a) Incidence: 5% to 7% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR exter tablets, 2007)
b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, dyspepsia was reported in 5% of patients receiving quetiapine fumarate tablets (r 1% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl
c) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, dy in 7% of patients receiving quetiapine fumarate tablets (n=698) compared to 4% for placebo (n=347); do to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).
d) In placebo-controlled clinical trials for the treatment of schizophrenia (up to 6 weeks) in adults, dyspe 5% of patients receiving quetiapine fumarate extended-release tablets (n=951) compared to 2% for place ranged from 300 to 800 mg (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).
e) A logistic regression analysis of placebo-controlled clinical study of five fixed-doses of quetiapine fum patients with schizophrenia revealed a positive correlation between dose and the occurrence of dyspeps Doses included in these studies included 75 milligrams (mg)/day, 150 mg/day, 300 mg/day, 600 mg/day, (Prod Info SEROQUEL(R) oral tablets, 2007).
f) Anticholinergic adverse effects of quetiapine therapy are dose-related. Dry mouth occurred in 8% to 1 patients in clinical trials. Constipation was also reported. Abdominal pain, dyspepsia, and anorexia occur (Borison et al, 1996a; Wetzel et al, 1995; Fulton & Goa, 1995b).

3.3.4.A.5 Vomiting
a) Incidence: 5% to 6% (Prod Info SEROQUEL(R) oral tablets, 2007)
b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, vomiting was reported in 6% of patients receiving quetiapine fumarate tablets (n= for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets,
c) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, vo 5% of patients receiving quetiapine fumarate tablets (n=698) compared to 4% for placebo (n=347); dose 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.4.A.6 Xerostomia

a) Incidence: 9% to 44% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR exte tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, dry mouth was reported in 9% of patients receiving quetiapine fumarate tablets (r 3% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, reported in 19% of patients receiving quetiapine fumarate tablets (n=196) compared to 3% for placebo (r from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

d) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, dı in 44% of patients receiving quetiapine fumarate tablets (n=698) compared to 13% for placebo (n=347); 300 to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

e) In placebo-controlled clinical trials for the treatment of schizophrenia (up to 6 weeks) in adults, dry mo 12% of patients receiving quetiapine fumarate extended-release tablets (n=951) compared to 1% for pla ranged from 300 to 800 mg (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

f) Anticholinergic adverse effects of quetiapine therapy are dose-related. Dry mouth occurred in 8% to 1 patients in clinical trials. Constipation was also reported. Abdominal pain, dyspepsia, and anorexia occur (Borison et al, 1996a; Wetzel et al, 1995; Fulton & Goa, 1995b).

3.3.5 Hematologic Effects

3.3.5.A Quetiapine Fumarate

Agranulocytosis

Leukopenia

Neutropenia

Pancytopenia

3.3.5.A.1 Agranulocytosis

a) Agranulocytosis, including fatal incidences, has been reported during clinical trials and post-marketing fumarate (Prod Info SEROQUEL(R) oral tablets, 2008; Prod Info SEROQUEL XR(R) extended-release o

3.3.5.A.2 Leukopenia

a) Incidence: tablets, at least 1% (Prod Info SEROQUEL(R) oral tablets, 2008); extended-release tablet Info SEROQUEL XR(R) extended-release oral tablets, 2008; Prod Info SEROQUEL(R) oral tablets, 200

b) During quetiapine fumarate clinical trials, leukopenia was reported in at least 1% of patients receiving less than 5% of patients receiving extended-release tablets. Leukopenia has also been reported during p quetiapine fumarate. Patients possibly at risk for developing leukopenia include those with a preexisting of drug-induced leukopenia. Should leukopenia develop during quetiapine fumarate therapy, discontinue SEROQUEL(R) oral tablets, 2008; Prod Info SEROQUEL(R) oral tablets, 2008).

3.3.5.A.3 Neutropenia

a) Incidence: 0.3% (Prod Info SEROQUEL(R) oral tablets, 2008; Prod Info SEROQUEL XR(R) extended 2008)

b) During placebo-controlled clinical trials with quetiapine fumarate, neutropenia was reported in 0.3% o quetiapine fumarate monotherapy (n=2967) compared to 0.1% for placebo (n=1349). Neutropenia has al during post-marketing use of quetiapine fumarate. Patients possibly at risk for developing neutropenia in preexisting low WBC or a history of drug-induced neutropenia. Should neutropenia develop, discontinue SEROQUEL(R) oral tablets, 2008; Prod Info SEROQUEL XR(R) extended-release oral tablets, 2008).

3.3.5.A.4 Pancytopenia

a) Pancytopenia developed in a 71-year-old Caucasian male with a history of Parkinson's disease 3 wee quetiapine therapy at a dose of 25 milligrams twice daily for the treatment of drug-induced hallucinations counts improved within 48 hours of withdrawal of the drug and returned to normal in 7 days (Iraqi, 2003).

3.3.6 Hepatic Effects

3.3.6.A Quetiapine Fumarate

3.3.6.A.1 Increased liver enzymes

a) Incidence: tablets, 6% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets, 1% (P
(R)XR extended-release oral tablets, 2007)
b) Transient, asymptomatic and reversible elevations in serum transaminase, primarily alanine aminotra
been reported. Peak elevations are usually seen within the first three weeks of treatment and most retur
with continued therapy (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extenc
tablets, 2007).
c) In pooled, placebo-controlled clinical trials for the treatment of schizophrenia (3 to 6 weeks in duratior
in serum transaminases of greater than 3 times the upper limits of normal was reported in 6% of patients
fumarate tablets compared to 1% for placebo (Prod Info SEROQUEL(R) oral tablets, 2007).
d) In pooled, placebo-controlled 6-week clinical trials for the treatment of schizophrenia in adults, elevati
transaminases of greater than 3 times the upper limits of normal was reported in 1% of patients receiving
extended-release tablets compared to 2% for placebo (Prod Info SEROQUEL(R)XR extended-release or

3.3.7 Immunologic Effects

3.3.7.A Quetiapine Fumarate

3.3.7.A.1 Anaphylaxis
a) Anaphylactic reactions, temporally related to quetiapine therapy, have been reported during post-mar
SEROQUEL(R) oral tablets, 2008a).

3.3.8 Musculoskeletal Effects

3.3.8.A Quetiapine Fumarate

3.3.8.A.1 Backache
a) Incidence: 3% to 5% (Prod Info SEROQUEL(R) oral tablets, 2007)
b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a
to 12 weeks) in adults, back pain was reported in 3% of patients receiving quetiapine fumarate tablets (n
1% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl
c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults,
reported in 5% of patients receiving quetiapine fumarate tablets (n=196) compared to 3% for placebo (n=
from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.9 Neurologic Effects

3.3.9.A Quetiapine Fumarate

Akathisia

Altered mental status

Asthenia

Dizziness

Dystonia

Extrapyramidal disease

Headache

Insomnia

Lethargy

Parkinsonism

Restless legs syndrome

Sedated

Seizure

Somnolence

Tardive dyskinesia

Tremor

3.3.9.A.1 Akathisia

a) Incidence: less than 5% (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007)

b) During clinical trials for the treatment of schizophrenia in adults, akathisia was reported in less than 5 quetiapine fumarate extended-release tablets (Prod Info SEROQUEL(R)XR extended-release oral tablet

c) Akathisia developed in a male patient with Parkinson's disease following the administration of quetiap of dopamimetic psychosis. The 62-year-old man was taking levodopa at a daily dose of 400 milligrams (r a dose of 12.5 to 25 mg daily for approximately 5 days, when he developed severe motor restlessness, a pacing. His score on the Barnes Akathisia Scale (range, 0= no symptoms to 14=severe akathisia) reache withdrawn and symptoms of akathisia completely resolved within 2 days (Prueter et al, 2003).

3.3.9.A.2 Altered mental status

a) A 62-year-old man experienced acute mental status changes within 3 days of increasing his quetiapir milligrams daily while symptoms resolved within 48 hours of discontinuing quetiapine. There was no clini serotonin syndrome, or alcohol intoxication or withdrawal. Quetiapine is believed to be associated with th changes due to the close temporal relationship between the onset and resolution of symptoms (Sim et al

3.3.9.A.3 Asthenia

a) Incidence: 5% to 10% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, asthenia was reported in 5% of patients receiving quetiapine fumarate tablets (n= for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets,

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, in 10% of patients receiving quetiapine fumarate tablets (n=196) compared to 4% for placebo (n=203); d to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.9.A.4 Dizziness

a) Incidence: 9% to 18% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR exte tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, dizziness was reported in 11% of patients receiving quetiapine fumarate tablets (r 5% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, reported in 9% of patients receiving quetiapine fumarate tablets (n=196) compared to 6% for placebo (n= from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

d) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, di in 18% of patients receiving quetiapine fumarate tablets (n=698) compared to 7% for placebo (n=347); d to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

e) In placebo-controlled clinical trials for the treatment of schizophrenia (up to 6 weeks) in adults, dizzine 10% of patients receiving quetiapine fumarate extended-release tablets (n=951) compared to 4% for pla ranged from 300 to 800 mg (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3.3.9.A.5 Dystonia

a) Incidence: less than 5% (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007)

b) During the first few days after initiating treatment with an antipsychotic medication, symptoms of dyst susceptible individuals. Symptoms may include spasm of neck muscles, which may progress to tightenin swallowing difficulty, breathing difficulty, and/or protrusion of the tongue. These symptoms can occur at l often occur (and occur with a greater severity) with high potency and at higher doses of first generation a medications. Males and younger age groups appear to be at greater risk for developing acute dystonia (I (R) oral tablets, 2008a).

c) During clinical trials for the treatment of schizophrenia in adults, dystonia was reported in less than 5% quetiapine fumarate extended-release tablets (Prod Info SEROQUEL(R)XR extended-release oral tablet

d) A 43-year-old Caucasian woman developed acute dystonia after receiving four weeks of quetiapine tl dose of 400 milligrams (mg) daily. The woman experienced slow movement of her head to the right side, increased incidence of involuntary movement when under stress. Dystonic movement of her head to the observed. The patient was cross-tapered to ziprasidone (80 mg/day) and symptoms of dystonia resolved dose was reduced to 100 mg/day (Kropp et al, 2004).

3.3.9.A.6 Extrapyramidal disease

a) Incidence: 4% to 12% (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR exte tablets, 2007)

b) In two placebo-controlled clinical trials of adult bipolar depression patients, extrapyramidal symptoms included akathisia, tremor, dyskinesia, dystonia, extrapyramidal disorder, involuntary muscle contraction muscle rigidity and psychomotor hyperactivity) were reported in 12% of patients receiving quetiapine fum or 600 mg) compared to 6% for placebo. Individual adverse events in these studies did not exceed 4% fo (Prod Info SEROQUEL(R) oral tablets, 2007).

c) There were no differences in the incidence of extrapyramidal symptoms between groups receiving qu tablets and placebo in three adult acute mania and three adult schizophrenia placebo-controlled clinical t SEROQUEL(R) oral tablets, 2007)

d) In a 6-week, fixed-dose clinical trial of adult schizophrenia patients, extrapyramidal symptoms (which akathisia, akinesia, extrapyramidal syndrome, hypertonia, neck rigidity, hypokinesia, tremor and cogwhe reported in 6%, 6%, 4%, 8% and 6% of patients receiving quetiapine fumarate tablets (75 milligrams (mg 300 mg/day, 600 mg/day, and 750 mg/day, respectively) compared to 16% for placebo (Prod Info SERO 2007).

e) In placebo-controlled clinical trials of adult schizophrenic patients, adverse reactions potentially relate symptoms (akathisia, extrapyramidal disorder, dyskinesia, restlessness, dystonia, muscle rigidity, and tre for 8% of patients receiving quetiapine fumarate extended-release tablets, 8% for patients receiving quet tablets, and 5% for placebo; quetiapine doses ranged from 300 to 800 milligrams. Individual adverse eve did not exceed 3% for any treatment group (Prod Info SEROQUEL(R)XR extended-release oral tablets,

f) The severity of extrapyramidal symptoms (EPS) with quetiapine therapy has not differed from that of p trials (Garver, 2000a; Green, 1999a; Borison et al, 1996a; Fulton & Goa, 1995b; Anon, 1995a; Fabre et a

3.3.9.A.7 Headache

a) Incidence: tablets, 17% to 21% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release table SEROQUEL(R)XR extended-release oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, headache was reported in 21% of patients receiving quetiapine fumarate tablets (14% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tal

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, reported in 17% of patients receiving quetiapine fumarate tablets (n=196) compared to 13% for placebo from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

d) Headache was reported 7.4% of adult schizophrenic patients taking quetiapine fumarate extended-re a randomized, placebo-controlled, long-term trial (up to 12 months). After completion of an initial open la with quetiapine fumarate extended-release tablets, stabilized patients were randomized to either continu or switch to placebo (n=103) to determine the possibility of relapse (Prod Info SEROQUEL(R)XR extend tablets, 2007).

3.3.9.A.8 Insomnia

a) Incidence: tablets, 12% (Masand, 2000a; Green, 1999a; Borison et al, 1996a; Anon, 1995a; Fulton & al, 1995a); extended-release tablets, 8.5% (Prod Info SEROQUEL(R)XR extended-release oral tablets,

b) Insomnia was reported 8.5% of adult schizophrenic patients taking quetiapine fumarate extended-rele a randomized, placebo-controlled, long-term trial (up to 12 months). At the completion of the initial open patients who were stabilized on quetiapine fumarate extended-release tablets were randomized to either therapy or switch to placebo (n=103) to determine the possibility of relapse (Prod Info SEROQUEL(R)XR oral tablets, 2007).

c) The adverse effect of insomnia has a 12% frequency with quetiapine use (Masand, 2000a; Green, 19 1996a; Anon, 1995a; Fulton & Goa, 1995b; Fabre et al, 1995a).

3.3.9.A.9 Lethargy

a) Incidence: 5% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, le 5% of patients receiving quetiapine fumarate tablets (n=698) compared to 2% for placebo (n=347); dose 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.9.A.10 Parkinsonism

a) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar ris of parkinsonism as does typical antipsychotic therapy. In a population-based, retrospective cohort study, and older) with evidence of dementia were followed for up to 1 year for the development of parkinsonism with typical or atypical antipsychotic use. As compared with older adults receiving atypical antipsychotic olanzapine, risperidone, quetiapine), incident parkinsonism was 30% more likely to occur in those taking (i.e., chlorpromazine, haloperidol, perphenazine) (adjusted HR, 1.3; 95% CI, 1.04 to 1.58), and 60% less patient who did not receive either therapy (HR, 0.4; 95% CI, 0.29 to 0.43). Older adults using higher pote antipsychotics had almost a 50% greater risk of experiencing parkinsonism as compared with patients pr antipsychotics (all were considered lower potency) (HR, 1.44; 95% CI, 1.13 to 1.84); however, in patients potency typical antipsychotics, the risk of developing parkinsonism was no different from that in adults ta antipsychotics (HR, 0.75; 95% CI. 0.48 to 1.15). In addition, a positive dose-related relationship was obs

occurrence of incident parkinsonism and the use of atypical antipsychotics. The risk for developing parki
than twice as great in patients using a high-dose atypical antipsychotic agent as compared with those pr
atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patients taking a typical antip
to have a similar risk for the development of parkinsonism as patients receiving high-dose atypical antips
(p=ns). The authors conclude that atypical antipsychotics may not be safer than typical antipsychotics wh
are considered (Rochon et al, 2005).

3.3.9.A.11 Restless legs syndrome

a) Restless legs, temporally related to quetiapine therapy, have been reported during post-marketing us
SEROQUEL(R) oral tablets, 2008a).

3.3.9.A.12 Sedated

a) Incidence: tablets, 30% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets, 13%
SEROQUEL(R)XR extended-release oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, se
in 30% of patients receiving quetiapine fumarate tablets (n=698) compared to 8% for placebo (n=347); d
to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

c) In placebo-controlled clinical trials for the treatment of schizophrenia (up to 6 weeks) in adults, sedati
13% of patients receiving quetiapine fumarate extended-release tablets (n=951) compared to 7% for pla
ranged from 300 to 800 mg (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3.3.9.A.13 Seizure

a) Incidence: tablets, 0.5% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets, 0.1%
SEROQUEL(R)XR extended-release oral tablets, 2007)

b) Seizures were reported in 0.5% of patients treated with quetiapine fumarate tablets (n=3490) compar
with active control drugs (n=527) and 0.2% for placebo (n=954) in clinical trials (Prod Info SEROQUEL(R

c) During clinical trials, seizures were reported in 0.1% of patients treated with quetiapine fumarate exte
(n=951) compared to 0.9% for placebo (n=319) (Prod Info SEROQUEL(R)XR extended-release oral tabl

d) Quetiapine fumarate should be used cautiously in patients with a history of seizures (Prod Info SERO
2007; Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3.3.9.A.14 Somnolence

a) Summary

1) Somnolence was commonly reported during quetiapine fumarate clinical trials, especially during
periods (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release

b) Incidence: tablets, 16% to 34% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release table
SEROQUEL(R)XR extended-release oral tablets, 2007)

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults,
reported in 34% of patients receiving quetiapine fumarate tablets (n=196) compared to 9% for placebo (r
from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

d) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, so
reported in 28% of patients receiving quetiapine fumarate tablets (n=698) compared to 7% for placebo (r
from 300 to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

e) Somnolence was reported in 18% of patients treated with quetiapine fumarate tablets compared to 11
schizophrenia trials (Prod Info SEROQUEL(R) oral tablets, 2007).

f) In clinical trials for the treatment of acute bipolar mania using quetiapine fumarate as monotherapy, so
reported in 16% of patients taking quetiapine fumarate tablets compared to 4% for placebo (Prod Info SE
tablets, 2007).

g) In placebo-controlled clinical trials for the treatment of schizophrenia (up to 6 weeks) in adults, somno
12% of patients receiving quetiapine fumarate extended-release tablets (n=951) compared to 4% for pla
ranged from 300 to 800 mg (Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3.3.9.A.15 Tardive dyskinesia

a) Incidence: tablets, 0.1% to 1% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablet
Info SEROQUEL(R)XR extended-release oral tablets, 2007)

b) A potentially irreversible tardive dyskinesia may develop in patients receiving antipsychotic drugs; this
duration of treatment and the cumulative dose. Less commonly, the syndrome can develop after brief tre
doses. Antipsychotics may mask the underlying process by suppressing the signs and symptoms of the s
prevalence of the syndrome appears to be highest among the elderly, especially elderly women; howeve
rely upon prevalence to estimate which patients are likely to develop the syndrome. The syndrome may
completely upon discontinuation of the antipsychotic medication (Prod Info SEROQUEL(R) oral tablets, 2
SEROQUEL(R)XR extended-release oral tablets, 2007).

c) During clinical trials for the treatment of schizophrenia in adults, tardive dyskinesia was reported 0.1%
taking quetiapine fumarate tablets (Prod Info SEROQUEL(R) oral tablets, 2007).

d) During clinical trials for the treatment of schizophrenia in adults, tardive dyskinesia was reported in le
taking quetiapine fumarate extended-release tablets (Prod Info SEROQUEL(R)XR extended-release ora

e) A 44-year-old woman with schizophrenia resistant to typical neuroleptic agents developed tardive dys
of quetiapine therapy. While receiving 150 milligrams of quetiapine daily she developed involuntary chor

the tongue and jaw. Later, she also developed finger involvement. Quetiapine was discontinued and she therapy which improved the tardive dyskinesia symptoms (Ghelber & Belmaker, 1999).

3.3.9.A.16 Tremor

a) Incidence: tablets, 8% (Prod Info SEROQUEL(R) oral tablets, 2007); extended-release tablets, less th SEROQUEL(R)XR extended-release oral tablets, 2007)

b) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, 8% of patients receiving quetiapine fumarate tablets (n=196) compared to 7% for placebo (n=203); dose 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

c) During clinical trials for the treatment of schizophrenia in adults, tremor was reported in less than 5% quetiapine fumarate extended-release tablets (Prod Info SEROQUEL(R)XR extended-release oral tablet

3.3.10 Ophthalmic Effects

3.3.10.A Quetiapine Fumarate

Amblyopia

Disorder of lens

3.3.10.A.1 Amblyopia

a) Incidence: 2% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, amblyopia was reported in 2% of patients receiving quetiapine fumarate tablets (r 1% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl

3.3.10.A.2 Disorder of lens

a) Although a causal relationship has not been substantiated, lens changes in patients during long-term fumarate have been reported. Examination to detect cataract formation is recommended at initiation of tr after beginning treatment, and every 6 months during the course of treatment (Prod Info SEROQUEL(R) Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).

3.3.12 Psychiatric Effects

3.3.12.A Quetiapine Fumarate

Agitation

Anxiety

Suicidal thoughts

3.3.12.A.1 Agitation

a) Incidence: 6% to 20% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, agitation was reported in 20% of patients receiving quetiapine fumarate tablets (n 17% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tal

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, in 6% of patients receiving quetiapine fumarate tablets (n=196) compared to 4% for placebo (n=203); do to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.12.A.2 Anxiety

a) Incidence: 4% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, anxiety was reported in 4% of patients receiving quetiapine fumarate tablets (n=7 for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets,

3.3.12.A.3 Suicidal thoughts

a) In two clinical studies involving patients with bipolar depression, the incidence of treatment emergent attempt during eight weeks of treatment was 1.7% and 2.6% in patients treated with quetiapine fumarate (mg)/day (n=350) and 600 mg/day (n=348), respectively, and 2.0% in patients receiving placebo (Prod Ir oral tablets, 2007).

3.3.14 Reproductive Effects

3.3.14.A Quetiapine Fumarate

3.3.14.A.1 Priapism

a) Priapism was reported in one patient taking quetiapine fumarate tablets; a causal relationship has not (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.15 Respiratory Effects

3.3.15.A Quetiapine Fumarate

Cough

Hyperventilation

Nasal congestion

Pharyngitis

Rhinitis

3.3.15.A.1 Cough

a) Incidence: at least 1% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) During clinical trials for the treatment of schizophrenia in adults, increased cough was reported in at l taking quetiapine fumarate tablets (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.15.A.2 Hyperventilation

a) A 69-year-old African-American female, admitted for major depression with psychotic features, develo acute respiratory alkalosis 3 days after being discharged from the hospital. At the time of the occurrence dose of quetiapine was 50 milligrams twice daily with concurrent treatments with metronidazole and micc etiologies include a comorbid hypersensitivity to quetiapine or to the concomitant administration of metro inhibit metabolism of quetiapine. Symptoms improved after discontinuation of quetiapine (Shelton et al, 2

3.3.15.A.3 Nasal congestion

a) Incidence: 5% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, na reported in 5% of patients receiving quetiapine fumarate tablets (n=698) compared to 3% for placebo (n= from 300 to 600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.15.A.4 Pharyngitis

a) Incidence: 4% to 6% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, pharyngitis was reported in 4% of patients receiving quetiapine fumarate tablets (3% for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tabl

c) In placebo-controlled clinical trials for the adjunct treatment of acute mania (up to 3 weeks) in adults, reported in 6% of patients receiving quetiapine fumarate tablets (n=196) compared to 3% for placebo (n= from 100 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.15.A.5 Rhinitis

a) Incidence: 3% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a to 12 weeks) in adults, rhinitis was reported in 3% of patients receiving quetiapine fumarate tablets (n=71 for placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets,

3.3.16 Other

Quetiapine

Quetiapine Fumarate

3.3.16.A Quetiapine

3.3.16.A.1 Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.B Quetiapine Fumarate

Death

Fatigue

Fever

Neuroleptic malignant syndrome

Pain

3.3.16.B.1 Death

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

b) Results of a population-based, retrospective cohort study demonstrated comparable to possibly great
associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and olde
atypical antipsychotic medications. The analysis excluded patients with cancer and included only new us
medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders
on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37
identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively
the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug
mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which cont
confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus aty
1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were
risperidone, the mortality ratio associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine
1.19 to 1.40), while there was no difference associated with olanzapine. The increased mortality risk for
atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio
1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory a
multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the resu
(Schneeweiss et al, 2007).

c) The findings of one meta-analysis suggest that there may be a small increased risk of death associat
atypical antipsychotic agents for the treatment of dementia in elderly patients. The study analysis (n=511
randomized, double-blind, placebo-controlled, parallel group trials of antipsychotic use (i.e., aripiprazole
(n=5), quetiapine (n=3), risperidone (n=5)) in elderly patients (weighted mean age, 81.2 years) with dem
occurred more often in patients receiving atypical antipsychotic therapy as compared with placebo (118
respectively). The overall odds ratio, as assessed by meta-analysis, for death in elderly patients receivin
antipsychotics as compared with placebo was 1.54 (95% CI, 1.06 to 2.23; p=0.02), and the risk differenc
0.004 to 0.02; p=0.01). Overall, the relative risk associated with atypical antipsychotic use was 1.65 (95%
p=0.003); however this increased risk was only identified when all drugs were pooled for analysis; meta-
drugs did not show a statistically significant increased risk. A similar dropout rate was observed between
placebo-treated patients (32.2% vs 31.4%, respectively), with no significant difference in dropouts found
(Schneider et al, 2005).

d) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at leas
antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The st
new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mea

higher adjusted relative risk of death was associated with the use of conventional antipsychotics as comp
antipsychotics at all time points studied after beginning therapy (within 180 days: RR, 1.37; 95% CI, 1.27
days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.59; 80 to 180 days: RR
1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI, 1.15
dementia (RR, 1.45; 95% CI, 1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in
1.42; 95% CI, 1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as comp
antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (i.e
median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Additional studies which specifica
optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance
intervention can be provided (Wang et al, 2005).

3.3.16.B.2 Fatigue

a) Incidence: 10% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment of bipolar depression (up to 8 weeks) in adults, fa
10% of patients receiving quetiapine fumarate tablets (n=698) compared to 8% for placebo (n=347); dos
600 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 2007).

3.3.16.B.3 Fever

a) Incidence: 2% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a
to 12 weeks) in adults, fever was reported in 2% of patients receiving quetiapine fumarate tablets (n=719
placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 20

3.3.16.B.4 Neuroleptic malignant syndrome

a) Incidence: rare (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-r
2007)

b) A 20-year-old man developed neuroleptic malignant syndrome (NMS) within 8 to 9 weeks of starting
treatment of unprovoked aggression. The patient's medical history included severe mental retardation (IQ
of frequent unprovoked episodes of aggression, and treatment with haloperidol 5 mg/day for 14 months
symptoms. Quetiapine (100 mg/day) was added to the haloperidol therapy to help control the aggression
developed increased salivation, profuse perspiration, daytime drowsiness, decreased psychomotor activ
emotional reactivity within 4 to 5 days of starting the quetiapine. The symptoms persisted for 5 weeks an
haloperidol was decreased to 2.5 mg/day and the quetiapine was increased to 200 mg/day. Additionally,
started on lorazepam up to 5 mg/day. Within 3 weeks, the symptoms worsened and the patient develope
grade fever and later developed difficulty in walking with stiffness of the entire body, coarse tremors, high
sensorium, and difficulty in swallowing with regurgitation of both liquids and solids. Upon physical examir
muscular rigidity, profuse perspiration and elevated blood pressure. Laboratory analyses revealed leuko
creatinine phosphokinase (greater than ten fold increase), myoglobinuria, and mild renal impairment. The
a recent history of strenuous physical exercise, exposure to high ambient temperatures or any concomita
counter medications. Computed tomography of the brain and cerebrospinal fluid analysis did not reveal a
patient was diagnosed with NMS and all psychotropic medications were discontinued. Bromocriptine 7.5
consequently started along with supportive management. Within 48 hours the patient experienced a dec
perspiration, and his blood pressure stabilized. By the 4th day of treatment with bromocriptine his muscu
however, he developed patchy pneumonitis and was treated with antibiotics. Despite the treatment with a
respiratory status continued to decline and he died on the 10th day. Authors concluded a temporal relatio
initiation of quetiapine and the onset of NMS symptoms (Dan et al, 2009).

c) Based on a retrospective medication review, quetiapine was a probable cause of neuroleptic maligna
a 34-year-old male. His past medical history included a childhood accident resulting in severe brain dam
mental retardation, and seizures was hospitalized for mental status changes, tremors, temperature of 39
(C), and was subsequently diagnosed with (NMS) accompanied by extrapyramidal effects (EPS). During
patient experienced lead pipe rigidity, tachycardia, and high creatine kinase (CK) level. His medications i
200 mg three times per day, guanfacine 2 mg/day, carbamazepine 400 mg every 12 hours, valproic acid
and lorazepam 2 mg (frequency unknown). Quetiapine was discontinued on hospital day 2, and the patie
traditional treatment for NMS, which included bromocriptine 2.5 mg via a gastric feeding tube every 8 ho
dantrolene 1 mg/kg. On day 3, the patient continues to have high fever (41 degrees C), became hypoxic
intubated. Midazolam drip was started and titrated per hospital protocol to sedate the patient, bromocript
mg every 8 hours, and an infusion of 0.45% NaCl with sodium bicarbonate was started due to a high CK
international units per liter (L) and serum creatine levels up to 1.4 mcg/mL. Further, IV norepinephrine dr
because the patient was not hemodynamically stable. On day 6, his blood cell counts remained stable, t
NaCl with sodium bicarbonate was discontinued and bromocriptine was decreased to 2.5 mg every 6 ho
level and temperature have decreased (4450 international units/L and 39.3 degrees C, respectively). On
of NMS had resolved. The Naranjo probability scale suggested that quetiapine was the probable cause o
is not common for atypical antipsychotic drugs to cause NMS with associated EPS as reported in this ca
cases of NMS due to quetiapine identified in the literature and 75% of these cases had reactions that inc
et al, 2009).

d) Neuroleptic malignant syndrome (NMS), which can manifest clinically with hyperpyrexia, muscle rigid
instability, altered mental status, elevated CPK levels, myoglobinuria, and acute renal failure has been re
antipsychotic substances, including quetiapine fumarate. If neuroleptic malignant syndrome does occur,

medications and other drugs not essential to concurrent therapy should be discontinued, intensive sympt
monitoring should be initiated, and treatment of any concomitant serious medical problems should occur
of reintroduction of antipsychotics after a patient has experienced NMS should be taken; recurrences ha
(Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets
e) A 44-year-old woman with a history of schizoaffective disorder and 3 earlier episodes of neuroleptic n
(NMS) presented with fever, decreased level of consciousness, rigidity, and urinary incontinence. Her me
quetiapine 200 milligrams/day (mg/day), clozapine 400 mg/day, divalproex sodium 750 mg/day, lamotrig
clonazepam 4 mg/day. She was found to have bilateral pneumonia and highly elevated creatine phospho
Antibiotics and oral bromocriptine 1.25 mg twice daily were started; antipsychotics were withheld. When
day 3, she showed paranoid delusions. Clozapine, divalproex sodium, lamotrigine, and clonazepam were
hospital day 4, her temperature was normal and her CPK level reduced. Ten days later her CPK level wa
returned to her baseline mental status. Although some of the findings could be attributable to pneumonia
symptoms and the previous history of NMS supported the diagnosis of NMS in this instance (Bourgeois e

3.3.16.B.5 Pain

a) Incidence: 7% (Prod Info SEROQUEL(R) oral tablets, 2007)

b) In placebo-controlled clinical trials for the treatment (monotherapy) of schizophrenia (up to 6 weeks) a
to 12 weeks) in adults, pain was reported in 7% of patients receiving quetiapine fumarate tablets (n=719)
placebo (n=404); doses ranged from 75 to 800 milligrams/day (Prod Info SEROQUEL(R) oral tablets, 20

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 SEROQUEL(R) oral tablets,

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other)
controlled studies in women or studies in women and animals are not available. Drugs should be given only if
justifies the potential risk to the fetus.

2) Australian Drug Evaluation Committee's (ADEC) Category: B3(Australian Government Department of Health a
Therapeutic Goods Administration, 2006)

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing ag
in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been ob
animals have shown evidence of an increased occurrence of fetal damage, the significance of which is consid
humans.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) There are no adequate and well-controlled studies in pregnant women. Two cases of quetiapine use durin
produced no abnormalities in the infants (Gentile, 2006; Tenyi et al, 2003). Until more information is available
quetiapine during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus (P
(R) oral tablets, 2007).

5) Literature Reports

a) A prospective, observational study of 54 women (mean age, 30.7 years) recruited from the Emory Women
program exposed to antipsychotic medication during pregnant showed permeability of the placental barrier. C
determined by maternal and umbilical cord blood samples taken at delivery and though data collected from m
medical records. Placental passage showed a significant difference between antipsychotic medications, olan
CI, 46.8%-97.5%) being the highest, followed by haloperidol 65.5% (95% CI, 40.3%-90.7%), risperidone 49.2
84.8%), and quetiapine 24.1% (95% CI, 18.7%-29.5%), showing the lowest placental passage. In the quetiap
there was one case of preterm labor (< less than 37 weeks gestation) and 2 infants that required neonatal int
admission. Seven neonates developed respiratory complications and 2 developed cardiovascular events. Lo
2500 g) occurred in one infant (Newport et al, 2007).

b) Treatment of a 33-year-old woman with fluvoxamine 200 mg/day and quetiapine 400 mg/day during her s
resulted in an uneventful pregnancy and the birth of a healthy female infant. The patient was being treated wi
quetiapine when she was diagnosed with a severe postpartum psychotic depression after the birth of her first
attempts at reducing her medication led to relapse. After being informed of the risk-benefit of fluvoxamine/que
during pregnancy, the patient decided to go forward with a second pregnancy while maintaining her drug regi
and quetiapine with the addition of folate 5 mg/day throughout the pregnancy. The patient gained 9 kg with no
psychiatric instability. Routine biochemical tests were within the normal range and 5 echographic reports four
abnormalities. The presence of an intrauterine myoma led to an elective caesarean-section. A healthy female
g and measuring 49 cm in length was delivered, with Apgar scores of 9 and 10 at 1 minute and 5 minutes, re
2006).

c) One case report describes the maternal use of quetiapine 300 to 400 mg throughout gestation, and the su
healthy male infant without abnormality. At 6 months of age, the infant was developing normally (Tenyi et al,

d) In pregnant rats and rabbits treated with quetiapine 0.3 to 2.4 times the maximum recommended human d
to 2.4 times the MRHD, no teratogenicity was observed. However, embryo/fetal toxicity was observed in rats
0.6 to 2.4 times the MRHD and 1.2 to 2.4 times the MRHD, respectively. The high quetiapine dose in rats and
produced maternal toxicity. In a perio/postnatal reproductive study in rats, no quetiapine-related effects were
0.12, and 0.24 the MRHD. There were, however, increased fetal and pup death and decreased mean litter we
MRHD (Prod Info SEROQUEL(R) oral tablets, 2007).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.
a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk wh breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this dr breastfeeding.
2) Clinical Management
a) Limited data on the safety of quetiapine in nursing infants demonstrates no evidence of toxicity (Rampono 2006). It is recommended that nursing woman who are receiving quetiapine should not breast-feed (Prod Info tablets, 2007). If quetiapine treatment is required in a nursing mother, monitor infant progress and periodically in the infant's plasma (Rampono et al, 2007).
3) Literature Reports
a) A case report of a 26-year-old woman prescribed quetiapine while breast-feeding her 3-month-old infant d plasma (M:P) ratio of 0.29 (an estimated relative infant dose of 0.09% of the maternal weight-adjusted dose) of exposure generally acceptable for breast-feeding. The woman was prescribed quetiapine 400 mg at night f treatment of nonresponsive depression with concomitant chronic pain. At 16 months prior to the study, she w quetiapine 300 mg with an increase to 400 mg during month 4 of her pregnancy and continuing to the study d treated with oxycodone 20 mg 3 times daily and fluoxetine 40 mg daily during gestation and up to the study d weighing 3.4 kg (50th percentile) was delivered at week 37. On the study day, the 3-month-old infant weighed percentile). During the study, the infant was receiving oral morphine 120 mcg 3 times daily for opioid depende fed 6 to 7 times daily. Blood samples were collected immediately prior to the mother's quetiapine dose and 5 elimination phase (between 12.8 and 23.1 hours after the dose). Due to limited plasma concentration measur quetiapine dosing, the M:P ratio, calculated using the milk and average plasma concentration during the elim 0.29 (0.09% of the maternal weight-adjusted dose). The infant's plasma contained quetiapine 1.4 mcg/L equi maternal plasma concentration. Upon clinical examination, the infant was healthy and his Denver age was th chronological age (Rampono et al, 2007).
b) Treatment with fluvoxamine 200 mg/day and quetiapine 400 mg/day in a 33-year-old woman during her se resulted in an uneventful pregnancy and the birth of a healthy female infant weighing 2600 g and measuring 4 Apgar scores of 9 and 10 at 1 minute and 5 minutes, respectively. The patient chose to breast-feed; however to supplement her breast milk due to insufficient milk production. In the 3 months that the infant received brea with formula, no adverse effects were detected and the infant continues to develop normally (Gentile, 2006).

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

Drug-Lab Modifications

3.5.1 Drug-Drug Combinations

Acecainide

Ajmaline

Amiodarone

Amitriptyline

Amobarbital

Amoxapine

Amprenavir

Aprindine

Aprobarbital

Arsenic Trioxide

Astemizole

Atazanavir

Azimilide

Bepridil

Betamethasone

Bretylium

Butabarbital

Butalbital

Carbamazepine

Chloral Hydrate

Chloroquine

Chlorpromazine

Cisapride

Clarithromycin

Cortisone

Darunavir

Deflazacort

Dehydroepiandrosterone

Desipramine

Dexamethasone

Dibenzepin

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Encainide

Enflurane

Erythromycin

Eterobarb

Flecainide

Fluconazole

Fluoxetine

Fosamprenavir

Foscarnet

Fosphenytoin

Gemifloxacin

Halofantrine

Haloperidol

Halothane

Hydrocortisone

Hydroquinidine

Ibutilide

Imipramine

Indinavir

Isoflurane

Isradipine

Itraconazole

Ketoconazole

Lidoflazine

Lopinavir

Lorcainide

Mefloquine

Mephobarbital

Mesoridazine

Methohexital

Methylprednisolone

Nelfinavir

Nortriptyline

Octreotide

Paramethasone

Pentamidine

Pentobarbital

Phenobarbital

Phenylalanine

Phenytoin

Pirmenol

Prajmaline

Prednisolone

Prednisone

Primidone

Probucol

Procainamide

Prochlorperazine

Propafenone

Protriptyline

Rifampin

Risperidone

Ritonavir

Saquinavir

Secobarbital

Sematilide

Sotalol

Spiramycin

Sulfamethoxazole

Tedisamil

Telithromycin

Terfenadine

Thiopental

Thioridazine

Tipranavir

Triamcinolone

Trifluoperazine

Trimethoprim

Trimipramine

Vasopressin

Warfarin

Zolmitriptan

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 quetiapine is not recommended due to the risk of additive ef interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreud
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of acecainide and quetiapine is not recommended du inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
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 ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as acecainide and 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, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999x; O'Brien et al, 1999p; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Duenas-Laita et al, 1999x; Agelink et al, 2001v; Lande et al, 1992w; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
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), iloperic 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 ther
Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip
studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th
significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine
treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL
to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1
haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we
changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo
changes than an elimination 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 quetiapine is not recommended due to the risk of additive e
interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreud
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of amiodarone and quetiapine is not recommended c
inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
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
ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol
quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as amiodarone and
additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.D 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
haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c
2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac
been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod
2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr
corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves.
studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m
mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhytl
(R), 1999b).

3.5.1.E Amobarbital

1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer
receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu
P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien
and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

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
haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c
2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac
been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod
2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhytl (R), 1999b).

3.5.1.G Amprenavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine 335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) c
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.H Aprindine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of quetiapine with other drugs that potentially prolong the QTc interval, such a be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring 2001o; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of aprindine and quetiapine is not recommended due inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.I Aprobarbital
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.J Arsenic Trioxide
1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricular ta fibrillation, and torsades de pointes and should not be administered with other drugs that may prolong the QT Trisenox(R), 2001a). Several antipsychotic agents have demonstrated QT prolongation including amisulpride 1999m), haloperidol (O'Brien et al, 1999i), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets (Duenas-Laita et al, 1999p), sertindole (Agelink et al, 2001m), quetiapine (Owens, 2001s), sultopride (Lande ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and antipsychotics is not recomme
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 pointe heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL t trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic triox returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Inf

3.5.1.K 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 I haloperidol (O'Brien et al, 1999h), quetiapine (Owens, 2001q), risperidone (Duenas-Laita et al, 1999n; Prod I risperidone, 2002a), sertindole (Agelink et al, 2001l), sultopride (Lande et al, 1992k), and zotepine (Sweetma no formal drug interaction studies have been done, the coadministration of astemizole and other drugs known 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 interva 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 doses (I 1993e; Wilt et al, 1993c). Three patients developed the dysrhythmia after administration of 211 to 825 m 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subseque arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) or respirator patients recovered with no adverse sequelae.

3.5.1.L Atazanavir

1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine 335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) c
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.M Azimilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of azimilide and quetiapine is not recommended due to the risk of additive effe If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of azimilide and quetiapine is not recommended due inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
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 ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as azimilide and qu additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

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 other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002a; Agelink et al, 2001c; Owens, 20 1999d; Prod Info Haldol(R), 1998a). In U.S. clinical trials, bepridil increased QT and QTc intervals which was torsades de pointes in approximately 1% of patients. Other drugs that increase the QT interval may exaggera the QT interval observed with bepridil (Prod Info Vascor(R), 1997). Pimozide is contraindicated in patients tak may prolong the QT interval (Prod Info Orap(R), 1999d).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT inte is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patie cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhytl (R), 1999c).

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

3.5.1.O Betamethasone

1) Interaction Effect: decreased serum quetiapine concentrations

2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir P450 3A.

7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

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 quetiapine is not recommended due to the risk of additive effe If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of bretylium and quetiapine is not recommended due inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo

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 ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as bretylium and qu additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.Q Butabarbital

1) Interaction Effect: decreased serum quetiapine concentrations

2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.

7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.R Butalbital

1) Interaction Effect: decreased serum quetiapine concentrations

2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.

7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.S Carbamazepine

1) Interaction Effect: decreased serum quetiapine concentrations

2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving carbamazepine, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001a).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is indicated when quetiapine is administered with carbamazepine or other i

cytochrome P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic sympto
receiving quetiapine and carbamazepine.
7) Probable Mechanism: unknown

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 therapeutic d
1986). Even though no formal drug interaction studies have been done, the administration of drugs known to
interval, such as antipsychotics and chloral hydrate is not recommended. Several antipsychotic agents have
prolongation including amisulpride (Prod Info Solian(R), 1999k), haloperidol (O'Brien et al, 1999g), quetiapine
risperidone (Duenas-Laita et al, 1999m), sertindole (Agelink et al, 2001k), sultopride (Lande et al, 1992j), and
2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of chloral hydrate and antipsychotics is not recomme
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
developing torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998a). Periodic
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 doses (
1993d; Wilt et al, 1993b). Three patients developed the dysrhythmia after administration of 211 to 825 m
2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subseque
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 dos
effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Aralen
antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999v),
et al, 1999o), quetiapine (Owens, 2001ab), risperidone (Duenas-Laita et al, 1999w), sertindole (Agelink et al,
(Lande et al, 1992u), 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 inte
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 rispe
(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 on the
recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co
Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects,
available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info
haloperidol (O'Brien et al, 1999f), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006),
2001n), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001j), sultopride (Lande et al, 1992
Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen
antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.W Cisapride
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated
other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002; Owens, 2001a; Prod Info Orap(R)
pointes and QT prolongation have been reported with cisapride (Prod Info Propulsid(R), 2000).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT inte

cisapride, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndr history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhytl (R), 1999).
b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone (Due 1999a; Ravin & Levenson, 1997).

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 haloperidol (O'Brien et al, 1999b), quetiapine (Owens, 2001g), risperidone (Duenas-Laita et al, 1999e), sertin 2001d), sultopride (Lande et al, 1992c), and zotepine (Sweetman, 2004). Even though no formal drug interac been done, concomitant use of clarithromycin and antipsychotic agents may cause additive effects on the QT 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 inte 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 significant in concentration following administration of quetiapine. The patient, hospitalized for acute psychotic sympto 50 mg quetiapine daily, with a gradual increase in dosage to 700 mg over 10 days. Psychotic symptoms weeks. On day 28, the patient developed a lower airway infection, and was orally treated with 750 mg su clarithromycin along with his evening dose of quetiapine 400 mg. The following morning, 750 mg sultami clarithromycin, and the morning 300-mg quetiapine dose were given. Within hours the patient became so sample testing resulted in 826.8 microgram/L (normal range, 70 to 170 microgram/L). The patient develo consciousness and respiratory depression. Quetiapine overdose was suspected and treatment was disc levels were continually measured over the course of a week until complete recovery was achieved (Schu 2008).
b) A total of 7 patients developed torsade de pointes after therapeutic use of haloperidol in high doses (1993a; Wilt et al, 1993). Three patients developed the dysrhythmia after administration of 211 to 825 mg 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subseque arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) or respirator patients recovered with no adverse sequelae.
c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info Risperdal

3.5.1.Y Cortisone
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other i P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.Z Darunavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine 335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) c
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri

protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.AA Deflazacort
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.AB Dehydroepiandrosterone
1) Interaction Effect: reduced effectiveness of quetiapine
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/decil conducive for optimal treatment of patients with psychosis (Howard, 1992a). In case reports, patients have be antipsychotics when DHEA levels were elevated (Howard, 1992a). Patients being treated with quetiapine sho supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and quetiapine. If DHEA 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
8) Literature Reports
a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 mill fluphenazine 40 mg, lithium carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg Cushinoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resulted in substantial improvement within one w appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were assc psychosis resistant to conventional antipsychotic therapy (Howard, 1992).
b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accom of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional t visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He w chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizoaffective disorde was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipramine 100 mg. H to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1000 mg, perph lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at bedtime resulted in a normal l mcg/dL. By day 5, psychosis improved and the patient was well-oriented, conversational, and was makir Once dexamethasone was discontinued, rapid decompensation and florid psychosis ensued despite "sul psychotropic medications". DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA l with florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

3.5.1.AC 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 haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c 2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhyt (R), 1999b).

3.5.1.AD Dexamethasone

1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.AE 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 haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c 2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhyt (R), 1999b).

3.5.1.AF 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, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999x; O'Brien et al, 1999p; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Duenas-Laita et al, 1999x; Agelink et al, 2001v; Lande et al, 1992w; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
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), iloperic 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 ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.AG Dofetilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of dofetilide and quetiapine is not recommended due to the risk of additive effe If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised. Dofetilide should l 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 quetiapine is not recommended due inducing life-threatening arrhythmias. Dofetilide should be stopped for at least 2 days before any interacting d 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 ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have also demonstrated QT including quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as dofetili have additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.AH 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 haloperidol (O'Brien et al, 1999e), quetiapine (Owens, 2001l), risperidone (Duenas-Laita et al, 1999j), sertind 2001h), sultopride (Lande et al, 1992g), and zotepine (Sweetman, 2003). Even though no formal drug interac been done, the coadministration of dolasetron and other drugs known to prolong the QTc interval, including a 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 interva 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, and Q to baseline values. Measured changes in ECG parameters were transient, reversible, and asymptomatic QRS intervals may be due to prolongation of maximum upstroke velocity (Vmax) due to binding of dolase channels. The cause of QTc interval prolongation appears to be due to prolongation of the QRS interval, 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 doses (1993c; Wilt et al, 1993a). Three patients developed the dysrhythmia after administration of 211 to 825 m 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subseque arrest upon readministration of haloperidol. Four patients developed the dysrhythmia after administration over 1 to 4 days for delirium associated with bacterial meningitis (1), status asthmaticus (2) or respirator patients recovered with no adverse sequelae.
c) Prolongation of the QTc interval was reported in 8 patients receiving risperidone (Prod Info Risperdal

3.5.1.AI 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 haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c 2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhytl (R), 1999b).

3.5.1.AJ 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 haloperidol (O'Brien et al, 1999l), quetiapine (Owens, 2001y), risperidone (Duenas-Laita et al, 1999s), sertinc 2001q), sultopride (Lande et al, 1992r), and zotepine (Sweetman, 2003). Droperidol has been shown to prolo the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coa droperidol and other drugs known to prolong the QTc interval, including antipsychotics is not recommended (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.AK Encainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of quetiapine with other drugs that potentially prolong the QTc interval, such a be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring 2001o; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of encainide and quetiapine is not recommended due inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AL 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 other agents which lengthen the QT interval (Agelink et al, 2001y; Owens, 2001ah; Prod Info Haldol(R), 1998 1992z). Even though no formal drug interaction studies have been done, antipsychotic agents should not be other drugs which are also known to prolong the QTc interval, including enflurane (Owens, 2001ah).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of enflurane and agents that prolong the QT interval, 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 rispe (Duenas-Laita et al, 1999aa; Ravin & Levenson, 1997h).

3.5.1.AM Erythromycin

1) Interaction Effect: increased quetiapine serum concentrations
2) Summary: Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of CYP3A, clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapin studied, a similar interaction could be expected with other inhibitors of CYP3A (e.g., itraconazole, fluconazole Therefore, use caution and a reduced quetiapine dosage when it is administered concomitantly with a potent including erythromycin (Prod Info SEROQUEL(R) oral tablets, 2008a). There may also be some potential for prolongation with the concomitant administration of erythromycin and quetiapine. Erythromycin significantly ir QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995). Erythromycin h prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 2000). Although QT interval prolongation has been reported with quetiapine during postmarketing use (Prod Info SEROQUEL 2008a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Use caution and a reduced quetiapine dose if it is administered concomitantly with Info SEROQUEL(R) oral tablets, 2008a). Monitor the patient for quetiapine adverse events (tardive dyskinesi hypotension) as well as for QTc interval prolongation.
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism by erythromycin

3.5.1.AN Eterobarb

1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.AO Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of quetiapine with other drugs that potentially prolong the QTc interval, such a be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring 2001o; 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 quetiapine is not recommended due inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AP Fluconazole
1) Interaction Effect: increased quetiapine serum concentrations
2) Summary: Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of CYP3A, clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapin studied, a similar interaction could be expected with other inhibitors of CYP3A (e.g., itraconazole, fluconazole Therefore, use caution and a reduced quetiapine dosage when it is administered concomitantly with a potent including fluconazole (Prod Info SEROQUEL(R) oral tablets, 2008a). There may also be some potential for a prolongation with the concomitant administration of fluconazole and quetiapine. Case reports have described prolongation and torsades de points associated with fluconazole (Khazan & Mathis, 2002; Wassmann et al, 1 result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Although data are conflicting, prolongation has been reported with quetiapine during postmarketing use (Prod Info SEROQUEL(R) oral tabl
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Use caution and a reduced quetiapine dose if it is administered concomitantly with SEROQUEL(R) oral tablets, 2008a). Monitor the patient for quetiapine adverse events (tardive dyskinesia, sc hypotension) as well as for QTc interval prolongation.
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism by fluconazole

3.5.1.AQ Fluoxetine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Fluoxetine has been shown to prolong the QTc interval at the recommended therapeutic dose 2001). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics known to prolong the QTc interval, including fluoxetine, is not recommended. Several antipsychotic agents ha prolongation including amisulpride (Prod Info Solian(R), 1999o), quetiapine (Owens, 2001u), sertindole (Agel sultopride (Lande et al, 1992n), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of fluoxetine and antipsychotics is not recommended
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AR Fosamprenavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine 335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) o
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.AS Foscarnet
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest
2) Summary: Foscarnet can prolong the QT interval in some patients, which may result in ventricular tachyca fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prolongation includi Info Solian(R), 1999z), haloperidol (O'Brien et al, 1999q), quetiapine (Owens, 2001ag), risperidone (Duenas- sertindole (Agelink et al, 2001x), sultopride (Lande et al, 1992y), and zotepine (Sweetman, 2003). Because a prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of foscarnet and a 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.AT Fosphenytoin
1) Interaction Effect: decreased quetiapine efficacy
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are

with fosphenytoin (Prod Info Cerebyx(R), 1999). Coadministration of quetiapine 250 mg three times daily and three times daily increased the mean oral clearance of quetiapine by 5-fold. Quetiapine is metabolized by cyt isoenzymes, which are induced by the administration of phenytoin (Prod Info Seroquel(R), 1997).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Increased doses of quetiapine may be required to maintain control of psychotic sym receiving quetiapine and fosphenytoin. Caution should be taken if fosphenytoin is withdrawn from therapy or inducing anticonvulsant.
7) Probable Mechanism: induction of quetiapine metabolism by phenytoin

3.5.1.AU 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 interva antipsychotics, have not been performed, gemifloxacin should be used cautiously in patients receiving antips (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 as ge antipsychotics, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.AV Halofantrine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachy fibrillation, and torsades de pointes. Some antipsychotic agents prolong the QT interval and an additive effec if administered with other agents which lengthen the QT interval (Agelink et al, 2001a; Owens, 2001d; Prod In Prod Info Haldol(R), 1998; Lande et al, 1992a). The concurrent administration of halofantrine with antipsycho recommended (Prod 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 recommer
7) Probable Mechanism: additive cardiac effects

3.5.1.AW Haloperidol
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 & Balk, 20 (R), 2001a). Quetiapine may prolong the QT interval at therapeutic and toxic doses. Coadministration of halo daily with quetiapine 300 mg twice daily did not alter the steady-state pharmacokinetics of quetiapine (Prod In 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. Screen pa that may predispose to QT prolongation and torsade de pointes (i.e. cardiomyopathy, alcohol abuse, hypothy 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 (TdP) a haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, a reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral a The risk increases with doses greater than 35 milligrams (mg) over 24 hours, though TdP has been assc low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, screen patie dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electro and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Disc the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves c Balk, 2003).

3.5.1.AX 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 other agents which lengthen the QT interval (Agelink et al, 2001i; Owens, 2001m; Prod Info Solian(R), 1999i; 1998c; Lande et al, 1992h). Even though no formal drug interaction studies have been done, antipsychotic ag coadministered with other drugs which may also prolong the QTc interval, including halothane (Owens, 2001
3) Severity: major

4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of halothane and agents that prolong the QT interval antispsychotics, 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 rispe (Duenas-Laita et al, 1999k; Ravin & Levenson, 1997c).

3.5.1.AY Hydrocortisone
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other i P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.AZ 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, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999x; O'Brien et al, 1999p; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Duenas-Laita et al, 1999x; Agelink et al, 2001v; Lande et al, 1992w; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
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), iloperic 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 ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.BA Ibutilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of ibutilide and quetiapine is not recommended due to the risk of additive effect concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ibutilide and quetiapine is not recommended due t inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
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 ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as ibutilide and que additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.BB 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 haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c

2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac
been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod
2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr
corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves.
studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m
mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhytl
(R), 1999b).

3.5.1.BC Indinavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co
ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine
335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co
other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are
quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) o
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as
elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri
protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.BD 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
other agents which lengthen the QT interval (Agelink et al, 2001w; Owens, 2001ae; Prod Info Solian(R), 1999
(R), 1998g; Lande et al, 1992x). Even though no formal drug interaction studies have been done, antipsychot
be coadministered with other drugs which are also known to prolong the QTc interval, including isoflurane (O
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of isoflurane and agents that prolong the QT interval,
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 risper
(Duenas-Laita et al, 1999y; Ravin & Levenson, 1997f).

3.5.1.BE Isradipine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Isradipine can prolong the QT interval in some patients, which may result in ventricular tachyca
fibrillation, and torsades de pointes, and its use with other drugs known to cause QT prolongation is not recor
DynaCirc(R), 2000). Several antipsychotic agents have demonstrated QT prolongation including amisulpride
1999f), haloperidol (O'Brien et al, 1999c), quetiapine (Owens, 2001i), risperidone (Duenas-Laita et al, 1999g)
al, 2001a), 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 recommende
7) Probable Mechanism: additive cardiac effects

3.5.1.BF Itraconazole
1) Interaction Effect: increased quetiapine serum concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co
ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine
335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co
other CYP3A inhibitors such as itraconazole. Therefore, caution and a reduced quetiapine dosage are recom
quetiapine is administered to patients receiving itraconazole concomitantly (Prod Info SEROQUEL(R) oral tab
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take itraconazole as this r quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administering conco itraconazole (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A4-mediated quetiapine metabolism

3.5.1.BG Ketoconazole
1) Interaction Effect: increased quetiapine serum concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent inhibitor of CYP3A, reduced oral clearance of quetiapi a 335% increase in maximum plasma concentration of quetiapine. Therefore, caution and a reduced quetiapi recommended when quetiapine is administered to patients receiving ketoconazole concomitantly (Prod Info S tablets, 2008a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for an increased incidence of quetiapine adverse effects and toxici somnolence, hypotension). A reduced quetiapine dosage is recommended when administering concomitantly (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A4-mediated quetiapine metabolism by ketoconazole

3.5.1.BH 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 1983). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics known to prolong the QTc interval is not recommended. Several antipsychotic agents have demonstrated QT amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), quetiapine (Owens, 2001), risperid 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.BI Lopinavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine 335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) c
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.BJ Lorcainide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of quetiapine with other drugs that potentially prolong the QTc interval, such a be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring 2001o; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of lorcainide and quetiapine is not recommended due inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BK 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 mefloquin drugs which can prolong the QTc interval (Prod Info Lariam(R), 1999). Mefloquine was associated with signifi in a study of 46 healthy subjects (Davis et al, 1996). Antipsychotics including haloperidol (Prod Info Haldol(R) (Owens, 2001w), risperidone (Prod Info Risperdal(R) risperidone, 2000a), amisulpride (Prod Info Solian(R), 1 (Agelink et al, 2001p); sultopride (Lande et al, 1992p), and zotepine (Sweetman, 2004) have been shown to p

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.BL Mephobarbital
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.BM Mesoridazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with oth prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Several antipsychotic agents have de prolongation including amisulpride (Prod Info Solian(R), 1999r), haloperidol (O'Brien et al, 1999k), paliperidor (TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001x), risperidone (Duenas-Laita et al, 1999 et al, 2001o), sultopride (Lande et al, 1992q), ziprasidone (Prod Info GEODON(R) intramuscular injection, ora 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 antips mesoridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.BN Methohexital
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.BO Methylprednisolone
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.BP Nelfinavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine 335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) c
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as

elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri
protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.BQ 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 I
haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c
2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac
been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod
2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr
corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves.
studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m
mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhyt
(R), 1999b).

3.5.1.BR 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
(R), 1999). Even though no formal drug interaction studies have been done, the coadministration of antipsych
known to prolong the QTc interval, including octreotide, is not recommended. Several antipsychotic agents ha
prolongation including amisulpride (Prod Info Solian(R), 1999t), haloperidol (O'Brien et al, 1999m), risperidon
1999t), sertindole (Agelink et al, 2001r), quetiapine (Owens, 2001z), sultopride (Lande et al, 1992s), and zote
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.BS Paramethasone
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer
receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir
P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.BT 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 dos
1990). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics
known to prolong the QTc interval, including pentamidine, is not recommended (Agelink et al, 2001e; Owens,
Haldol(R), 2001; Prod Info Solian(R), 1999e; Duenas-Laita et al, 1999f; Duenas-Laita et al, 1999f; Prod Info M
Metzger & Friedman, 1993b; 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 recommend
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.BU Pentobarbital
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer
receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu
P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien
and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.BV Phenobarbital
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer
receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu
P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien
and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

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

3.5.1.BX Phenytoin
1) Interaction Effect: decreased quetiapine efficacy
2) Summary: Coadministration of quetiapine 250 mg three times daily and phenytoin 100 mg three times dai
oral clearance of quetiapine by 5-fold. Quetiapine is metabolized by cytochrome P450 3A4 isoenzymes, whic
administration of phenytoin (Prod Info Seroquel(R), 2003b; Wong et al, 2001a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Increased doses of quetiapine may be required to maintain control of psychotic sym
receiving quetiapine and phenytoin. Caution should be taken if phenytoin is withdrawn from therapy or replac
anticonvulsant.
7) Probable Mechanism: induction of quetiapine metabolism by phenytoin
8) Literature Reports
a) Coadministration of phenytoin with quetiapine significantly decreased the plasma concentration-time
resulting in a 5-fold increase in oral clearance in patients with DSM-IV-diagnosed schizophrenia, schizoa
bipolar disorder. Seventeen patients participated in an open-label, nonrandomized, multiple-dose study t
pharmacokinetics and tolerability of quetiapine when administered alone or in combination with phenytoi
escalating doses of quetiapine from 25 to 250 mg three times daily on days 3 to 10. Maintenance doses
administered on days 11 to 22. Phenytoin 100 mg three times daily was administered between days 13 a
under the concentration-time curve (AUC) from 0 to 8 hours after dosing at steady-state with quetiapine

phenytoin was 3642 ng hr/mL and 728 ng hr/mL , respectively (P equal 0.0001). The maximum plasma c steady-state (Cmax, ss) for quetiapine versus quetiapine plus phenytoin was 1,048 ng/mL and 359 ng/m Clearance over bioavailability (CL/F) for quetiapine alone versus quetiapine plus phenytoin was 80.3 L/h respectively. The induction of cytochrome P450 3A4 by phenytoin is the most likely mechanism for the a quetiapine metabolism (Wong et al, 2001).

3.5.1.BY 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, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999x; O'Brien et al, 1999p; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Duenas-Laita et al, 1999x; Agelink et al, 2001v; Lande et al, 1992w; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
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), iloperic 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 ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.BZ 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, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999x; O'Brien et al, 1999p; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Duenas-Laita et al, 1999x; Agelink et al, 2001v; Lande et al, 1992w; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
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), iloperic 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 ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.CA Prednisolone

1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified

5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.CB Prednisone
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.CC Primidone
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.CD 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 QTc interval is not recommended. Probucol has been shown to prolong the QTc interval (Gohn & Simmons, 1 Lorelco(R), 1991). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998d), quetiapine (Owens, 200 Info Risperdal(R) risperidone, 2000), amisulpride (Prod Info Solian(R), 1999n), sertindole (Brown & Levin, 19 (Lande et al, 1992m), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therape
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.CE 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, halop paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM Prod Info Solian(R), 1999x; O'Brien et al, 1999p; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Duenas-Laita et al, 1999x; Agelink et al, 2001v; Lande et al, 1992w; Prod Info GEODON(R) intramuscular inj 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and incre arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended ((TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is r
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), iloperic 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 ther Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antip studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. Th significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1 haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) we changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible fo changes than an elimination alteration (Young et al, 1993).

3.5.1.CF Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info haloperidol (O'Brien et al, 1999f), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), 2001n), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001j), sultopride (Lande et al, 1992 Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.CG Propafenone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Coadministration of quetiapine with other drugs that potentially prolong the QTc interval, such a should be approached with caution. If concurrent use cannot be avoided, cautious dosing and telemetric mon (Owens, 2001o; Larochelle et al, 1984).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of propafenone and quetiapine is not recommended inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CH 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 haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c 2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pro corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhyth (R), 1999b).

3.5.1.CI Rifampin

1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving rifampin, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with rifampin or other inducers 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by rifampin

3.5.1.CJ Risperidone

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Risperidone can prolong the QT interval in some patients, which may result in ventricular tachy fibrillation, and torsades de pointes, and its use with other agents that may prolong the QT interval, such as q recommended (Prod Info Risperdal(R), 2002; Owens, 2001r). Coadministration of risperidone 3 mg twice dail mg twice daily did not alter the steady-state pharmacokinetics of quetiapine (Prod Info Seroquel(R), 2003a).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: Because of the potential additive effects on the QT interval, the concurrent administ
and risperidone is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking rispe
(Duenas-Laita et al, 1999o; Ravin & Levenson, 1997d; Gesell & Stephen, 1997; Lo Vecchio et al, 1996;

3.5.1.CK Ritonavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co
ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine
335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co
other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are
quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) c
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as
elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri
protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.CL Saquinavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co
ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine
335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co
other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are
quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) c
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as
elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri
protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.CM Secobarbital
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer
receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu
P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien
and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.CN Sematilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of sematilide and quetiapine is not recommended due to the risk of additive eff
interval. If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreud
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of sematilide and quetiapine is not recommended du
inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
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
ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol
quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as sematilide and q
additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CO Sotalol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of sotalol and quetiapine is not recommended due to the risk of additive effects

concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong et
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of sotalol and quetiapine is not recommended due to inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
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 ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as sotalol and queti additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CP 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 al, 1997). Even though no formal drug interaction studies have been done, the coadministration of antipsycho known to prolong the QTc interval, including spiramycin, is not recommended. Several antipsychotic agents h prolongation including amisulpride (Prod Info Solian(R), 1999u), haloperidol (O'Brien et al, 1999n), quetiapine risperidone (Duenas-Laita et al, 1999u), sertindole (Agelink et al, 2001s), sultopride (Lande et al, 1992t), and 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of spiramycin and antipsychotics is not recommende
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CQ Sulfamethoxazole
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic do 1987). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics known to prolong the QTc interval, including cotrimoxazole, is not recommended. Several antipsychotic agen QT prolongation including amisulpride (Prod Info Solian(R), 1999g), haloperidol (O'Brien et al, 1999d), quetia risperidone (Duenas-Laita et al, 1999h), sertindole (Agelink et al, 2001f), sultopride (Lande et al, 1992e), and 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and antipsychotics is not recommer
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.CR Tedisamil
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concurrent use of tedisamil and quetiapine is not recommended due to the risk of additive effe If concurrent use cannot be avoided, cautious dosing and telemetric monitoring is advised (Yamreudeewong
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of tedisamil and quetiapine is not recommended due inducing life-threatening arrhythmias. If concurrent use cannot be avoided, cautious dosing and telemetric mo
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 ventricular fibrillation, and torsades de pointes. Several antipsychotic agents have demonstrated QT prol quetiapine (Owens, 2001c). Concomitant use of Class III antiarrhythmic agents such as tedisamil and qu additive effects on the QT interval and is not recommended (Yamreudeewong et al, 2003).

3.5.1.CS 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 other agents which lengthen the QT interval (Agelink et al, 2001g; Owens, 2001k; Prod Info Haldol(R), 1998b Even though no formal drug interaction studies have been done, antipsychotic agents should not be coadmin drugs which are also known to prolong the QTc interval, including telithromycin (Owens, 2001k).
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 administra 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 thera Laita et al, 1999i; Ravin & Levenson, 1997b).

3.5.1.CT 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 therap Geodon(TM), 2002b; Owens, 2001af; Prod Info Orap(R), 1999f). Even though no formal drug interaction stud the coadministration of terfenadine and other drugs known to prolong the QTc interval, including antipsychoti (Anon, 1997).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT int antipsychotic agents, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhyt (R), 1999e).

3.5.1.CU Thiopental
1) Interaction Effect: decreased serum quetiapine concentrations
2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a barbiturate, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001c).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with barbiturates or other indu P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patien and barbiturates.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by barbiturates

3.5.1.CV 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 the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstra including amisulpride (Prod Info Solian(R), 1999p), haloperidol (O'Brien et al, 1999j), pimozide (Prod Info Ora quetiapine (Owens, 2001v), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risper et al, 1999q), sertindole (Agelink et al, 2001o), sultopride (Lande et al, 1992o), ziprasidone (Prod Info GEOD 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 antips thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CW Tipranavir
1) Interaction Effect: increased quetiapine plasma concentrations
2) Summary: In vitro studies indicated that quetiapine is metabolized by the CYP3A4 isozyme in the liver. Co ketoconazole (200 mg once daily for 4 days), a potent CYP3A inhibitor, reduced oral clearance of quetiapine 335% increase in maximum plasma concentration of quetiapine. Although not studied, a similar interaction co other CYP3A inhibitors such as protease inhibitors. Therefore, caution and a reduced quetiapine dosage are quetiapine is administered to patients receiving protease inhibitors concomitantly (Prod Info SEROQUEL(R) c
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing quetiapine to patients who take protease inhibitors as elevated quetiapine plasma concentrations. A reduced quetiapine dosage is recommended when administeri protease inhibitors (Prod Info SEROQUEL(R) oral tablets, 2008a).
7) Probable Mechanism: inhibition of CYP3A-mediated quetiapine metabolism

3.5.1.CX Triamcinolone
1) Interaction Effect: decreased serum quetiapine concentrations

2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving a glucocorticoid, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001b).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Caution is indicated when quetiapine is administered with glucocorticoids or other ir P450 3A.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of quetiapine by glucocorticoid

3.5.1.CY Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Co Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info haloperidol (O'Brien et al, 1999f), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), 2001n), risperidone (Duenas-Laita et al, 1999l), sertindole (Agelink et al, 2001j), sultopride (Lande et al, 1992 Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phen antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.CZ Trimethoprim
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic do 1987). Even though no formal drug interaction studies have been done, the coadministration of antipsychotics known to prolong the QTc interval, including cotrimoxazole, is not recommended. Several antipsychotic agen QT prolongation including amisulpride (Prod Info Solian(R), 1999g), haloperidol (O'Brien et al, 1999d), quetia risperidone (Duenas-Laita et al, 1999h), sertindole (Agelink et al, 2001f), sultopride (Lande et al, 1992e), and 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of cotrimoxazole and antipsychotics is not recommer
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DA 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 haloperidol (O'Brien et al, 1999a), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), c 2001e), sultopride (Lande et al, 1992b), and zotepine (Sweetman, 2003). Even though no formal drug interac been done, the coadministration of a tricyclic antidepressant and an antipsychotic is not recommended (Prod 2001; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a tricyclic antidepressant and an antipsychotic is n
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included pr corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 m mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhytl (R), 1999b).

3.5.1.DB 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 recommen (Owens, 2001b; Prod Info Solian(R), 1999a; Duenas-Laita et al, 1999b; Brown & Levin, 1998; Harry, 1997; P 1996; Metzger & Friedman, 1993; Mauro et al, 1988). Even though no formal drug interaction studies have be 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 antipsy

vasopressin, is not recommended.
7) Probable Mechanism: additive effects on QT prolongation

3.5.1.DC Warfarin
1) Interaction Effect: potentiation of anticoagulant effects
2) Summary: A 71-year-old female experienced enhanced anticoagulant effects from warfarin when quetiapi drug regimen. Her medications included phenytoin 300 mg daily with a serum concentration of 9.87 mg/L, wa with an international normalized ratio (INR) of 2.6, benztropine 0.5 mg daily, and olanzapine 20 mg daily. Ola discontinued, and quetiapine therapy was initiated at 200 mg daily. Five days later, the INR was 2.7. After tw treatment, the INR increased to 9.2. Quetiapine was discontinued and two doses of vitamin K 10 mg were ad clinical signs observed in the patient were a small amount of bleeding at the site of the vitamin K injection an The INR decreased back to baseline with the discontinuation of quetiapine (Rogers et al, 1999).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Closely monitor the international normalized ratio (INR) in patients receiving concur quetiapine therapy.
7) Probable Mechanism: competitive inhibition of cytochrome P450 3A4 and 2C9 by quetiapine

3.5.1.DD 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 2001). Antipsychotics including haloperidol (Prod Info Haldol(R), 1998f), quetiapine (Owens, 2001ac), risperi Risperdal(R) risperidone, 2000b), amisulpride (Prod Info Solian(R), 1999w), sertindole (Agelink et al, 2001u); al, 1992v), and zotepine (Sweetman, 2004) have been shown to prolong the QT interval at therapeutic doses formal drug interaction studies have been done, the coadministration of drugs known to prolong the QT interv recommended.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of zolmitriptan and antipsychotics is not recommende
7) Probable Mechanism: additive effect on QT interval

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol
1) Interaction Effect: potentiation of the cognitive and motor effects of alcohol
2) Summary: Quetiapine potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects wi disorders. Alcoholic beverages should be avoided while taking quetiapine (Prod Info Seroquel(R), 2001d).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients should be instructed to avoid ethanol ingestion while taking quetiapine.
7) Probable Mechanism: additive CNS depression

3.5.3 Drug-Lab Modifications

Methadone measurement, urine

Tricyclic antidepressant measurement

3.5.3.A Methadone measurement, urine
1) Interaction Effect: false-positive urine drug screen for methadone
2) Summary: There have been cases of false-positive methadone urine drug screens with the use of assays Methadone II testkit(R) in patients treated with quetiapine. Clinicians should consider confirming positive met more specific methods, such as gas chromatography/mass spectrometry, or other quantitative methods parti whose results do not coincide with medical history, or current behaviors and observations (Cherwinski et al, 2 et al, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Clinicians should be aware that there have been cases of false-positive urine meth patients receiving quetiapine. Consider confirming a positive urine methadone screen with more specific met chromatography/mass spectrometry, or other quantitative methods, particularly in patients whose results do n medical history, or current behaviors and observations (Cherwinski et al, 2007; Widschwendter et al, 2007).

7) Probable Mechanism: mechanism unknown
8) Literature Reports
a) In a retrospective chart review, 12 pediatric patients (mean age of 15.5 years) admitted to a behavior treated with quetiapine from 125 to 160 mg daily had false methadone-positive urine drug screens with t (R) by Roche. Although 5 of these patients had positive substance abuse history, none were admitted fo issues. All patients denied current methadone use, and final clinical impressions were that they had not u substances. Results of confirmatory testing using gas chromatography/mass spectroscopy, performed in were negative for methadone (Cherwinski et al, 2007).
b) Three schizophrenic patients, being treated with quetiapine monotherapy, had false-positive urinalysi methadone using the Cobas Integra Methadone II testkit(R) by Roche. This method, used for semiquanti detection of methadone in urine, has a threshold of 300 ng/mL for methadone positivity. Blood samples t day after quetiapine administration ended also tested positive for methadone with mass spectrometry. H medical histories of the patients, these results were unexpected. Further screening of the patient's plasm quantitative assay did not reveal methadone positivity (Widschwendter et al, 2007).

3.5.3.B Tricyclic antidepressant measurement
1) Interaction Effect: a false-positive urine tricyclic antidepressant assay
2) Summary: A 34-year-old male patient receiving quetiapine 600 mg daily showed a positive toxicology scre antidepressants despite his denial of tricyclic use. Quetiapine is structurally similar to tricyclic antidepressants as the cause of this assay abnormality. A laboratory test confirmed that quetiapine is capable of causing a fal screen for tricyclic antidepressants (Sloan et al, 2000).
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clinicians should be aware that quetiapine may cause false-positive test results in a tricyclic antidepressants. This possibility should be considered in patients receiving quetiapine who deny tricy use but have a positive urine screen for tricyclics.
7) Probable Mechanism: assay interference

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) Quetiapine Fumarate
1) Therapeutic
a) Physical Findings
1) In schizophrenic patients, improvements of positive symptoms (eg, delusions, hallucinations, paranoi negative symptoms (eg, blunted affect, poverty of speech, amotivation) are indicative of a therapeutic res
2) Reassess the need for maintenance treatment and appropriate dose periodically (Prod Info SEROQU release oral tablets, 2007).
2) Toxic
a) Laboratory Parameters
1) Quetiapine use has been associated with exacerbation of pre-existing diabetes, hyperglycemia, diabe diabetic coma, and death. For patients with diabetes mellitus risk factors (eg, obesity, family history), per glucose testing at the beginning of and periodically during quetiapine therapy. For patients with pre-exist monitor fasting blood glucose regularly during quetiapine therapy to detect worsening of glucose control. SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).
2) Quetiapine use has been associated with leukopenia, neutropenia, and agranulocytosis, which has in Perform CBC frequently during the first few months of therapy in patients with a pre-existing low WBC or induced leukopenia/neutropenia. Monitor patients for severe neutropenia (absolute neutrophil count less which will necessitate discontinuing quetiapine therapy (Prod Info SEROQUEL(R) oral tablets, 2007; Pro XR extended-release oral tablets, 2007).
b) Physical Findings

1) Patients should be carefully monitored for clinical worsening of depression, suicidality, and unusual cl
which make be precursors to suicidality, especially if symptoms are severe, abrupt or unusual. This is es
the initial few months of antidepressant therapy or during dose changes. Adult and pediatric patients with
disorder may experience unusual changes in behavior and onset of suicidal behavior (suicidality). Antide
be associated with the emergence of suicidality and inducing worsening of depression in patients, espec
treatment phase and in children, adolescents, and young adults ages 18 to 24 years. It is important that
to patients with major depressive disorder or other psychiatric and nonpsychiatric disorders be vigilant in
emergent anxiety, agitation, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania, irritability
changes in behavior (Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended
2007).
2) In patients with neutropenia, carefully monitor for fever or other signs or symptoms of infection (Prod
oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).
3) Quetiapine use has been associated with exacerbation of pre-existing diabetes, hyperglycemia, diabe
diabetic coma, and death. Monitor all patients receiving quetiapine for symptoms of hyperglycemia (eg, p
polyphagia, weakness). For patients with diabetes mellitus risk factors (eg, obesity, family history), perfo
glucose testing at the beginning of and periodically during quetiapine therapy. Patients with pre-existing
regularly monitor fasting blood glucose during quetiapine therapy to detect worsening of glucose control
SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).
4) Quetiapine use has been rarely associated with the development of neuroleptic malignant syndrome
should be monitored for signs and symptoms of NMS, such as hyperpyrexia, muscle rigidity, altered mer
autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythm
SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007).
5) Due to the risk of developing irreversible, involuntary, dyskinetic movements, patients should be obse
symptoms of extrapyramidal effects and tardive dyskinesia. Monitoring is especially critical in elderly pati
longer duration of treatment, and higher total cumulative doses, but has occurred after relatively brief du
(Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets
6) Although a causal relationship has not been established, long-term quetiapine therapy has been impl
changes. Ocular examination (eg, slit lamp exam) to detect cataract formation is recommended at treatm
every 6 months during chronic quetiapine treatment (Prod Info SEROQUEL(R) oral tablets, 2007; Prod I
extended-release oral tablets, 2007).
7) Quetiapine use may induce postural hypotension, dizziness, tachycardia, and syncope has been repo
(Prod Info SEROQUEL(R) oral tablets, 2007; Prod Info SEROQUEL(R)XR extended-release oral tablets
pressure and heart rate during quetiapine therapy. Perform ECG at baseline and periodically during ther
Kecskemeti, 2004).

4.2 Patient Instructions

A) Quetiapine (By mouth)

Quetiapine

Treats schizophrenia and symptoms of bipolar disorder (manic-depressive illness).

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

How to Use This Medicine:
Long Acting Tablet, Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed
order to find out what works best for you. Do not use more medicine or use it more often than your doctor tell
start with a low dose, even if you have used this medicine before.
Your doctor may tell you to take the medicine at bedtime, because quetiapine can make you sleepy.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your d
you have any questions. Ask your pharmacist for the Medication Guide if you do not have one. Your doctor m
some forms to show that you understand this information.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next
use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine 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
your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

Make sure your doctor knows if you are also using levodopa, Sinemet®, erythromycin (Ery-Tab®), lorazepam
(Rifadin®, Rifamate®), or a steroid medicine (such as dexamethasone, prednisolone, prednisone, or Medrol®

Tell your doctor if you are also using medicine for seizures (such as carbamazepine, divalproex, phenytoin, p
Depakote®, Dilantin®, Luminal®, or Tegretol®), medicine to treat a fungus infection (such as fluconazole, itra
ketoconazole, Diflucan®, Nizoral®, or Sporanox®), or other antipsychotic medicine such as thioridazine (Mell
Make sure your doctor knows if you are also using medicine to lower blood pressure. Some blood pressure m
hydrochlorothiazide (HCTZ), lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®
Zestril®.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a
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, Alzheimer's d
problems, or a history of seizures or breast cancer. Tell your doctor if you have diabetes or a family history of
Make sure your doctor knows if you have heart disease or circulation problems, such as heart failure, low blo
problems, blood problems, high cholesterol, or a history of heart attack or stroke. Also tell your doctor if you h
condition called neuroleptic malignant syndrome (NMS) in the past.
For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your do
doctor right away if you or your child start to feel more depressed and have thoughts about hurting yourselves
thoughts or behaviors that trouble you or your child, especially if they are new or are getting worse quickly. M
knows if you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to ac
the doctor if you or your child have sudden or strong feelings, such as feeling nervous, angry, restless, violen
doctor know if you, your child, or anyone in your family has bipolar disorder (manic-depressive) or has tried to
This medicine is not approved to treat behavior disorders in older people who have dementia. Using this med
problem could increase the risk of death. This risk has not been shown for the approved uses of this medicine
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine
you are having signs of tardive dyskinesia such as rapid, worm-like movements of the tongue, or other uncon
the mouth, tongue, cheeks, jaw, or arms and legs.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
are not alert. You may also feel lightheaded when getting up suddenly from a lying or sitting position, so get u
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to ke
appointments.You may also need to have your eyes tested on a regular basis.
Tell your doctor about any other medicine you have used to treat a mental disorder, especially if the medicine
You might get overheated more easily while using this medicine. Be aware of this if you are exercising or the
Drinking water might help. If you get too hot and feel dizzy, weak, tired, confused, or sick to your stomach, yo

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, d
breathing.
Agitation, anxiety, or restlessness.
Changes in behavior, or thoughts of hurting yourself or others.
Constant muscle movement that you cannot control (often in your lips, tongue, jaw, arms, or legs).
Decrease in how much or how often you urinate, increased thirst, increased hunger, or weakness.
Fast heartbeat.
Fever, sweating, confusion, uneven heartbeat, muscle stiffness.
Lightheadedness or fainting (more common at the beginning or when changing doses).
Painful, prolonged erection of the penis.
Seizures or tremors.
Severe drowsiness, dizziness, or sleepiness.
Trouble seeing, or bright light bothering your eyes.
Trouble swallowing.
Unusual tiredness.

If you notice these less serious side effects, talk with your doctor:
Back pain.
Changes in menstrual periods.
Headache, sore throat.
Increased appetite.
Nausea, vomiting, constipation, dry mouth, upset stomach, or stomach pain.
Stuffy or runny nose.
Weight gain.

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

4.3 Place In Therapy

A) Current users of atypical antipsychotic drugs (including quetiapine) and typical antipsychotic drugs had a similar do
sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 m
study included patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who

prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as occurrin
and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or cause
ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescription was filled and th
supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine, and dose
chlorpromazine 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in cu
antipsychotic drugs in 79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the
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 ris
death in current quetiapine users in 17,355 person-years was 1.88 (95% CI, 1.3 to 2.71, p less than 0.001). The risk o
death significantly increased with increasing dose in both the typical and atypical antipsychotic drug groups. In atypica
the incidence rate ratio increased from 1.59 (95% CI, 1.03 to 2.46) in low-dose use to 2.86 (95% CI, 2.25 to 3.65) in hi
the effects of confounding of the study results, there was a secondary analysis performed in a cohort of patients match
score, which resulted in a similar risk of sudden death as the primary cohort analysis (Ray et al, 2009). In an editorial i
Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence
vulnerable populations with cardiac risk profiles (eg, elderly patients), there should be an age-dependent justification r
administration. It has also been suggested (although not formally tested) that ECGs be performed before and shortly a
antipsychotic therapy to screen for existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).
B) Quetiapine is indicated for the treatment of depressive episodes associated with bipolar disorder and acute manic
with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex. Quetiapine is also indicated fo
schizophrenia (Prod Info SEROQUEL(R) oral tablets, 2006).
See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHREN

4.4 Mechanism of Action / Pharmacology

A) Quetiapine Fumarate

1) PHARMACOLOGY

a) Quetiapine is a dibenzothiazepine antipsychotic agent bearing structural similarity to clozapine and olanza
1998; Fabre et al, 1995; Anon, 1995; Green, 1999).

b) Quetiapine has been shown to have affinity for multiple neurotransmitter receptors in in vitro binding studi
high affinity for serotonergic type 2 (5-HT2) receptors and moderate affinity for dopamine type 2 (D2) recepto
antagonism of D1 and 5-HT1A receptors is relatively weak. Appreciable affinity for alpha-1 adrenergic, alpha-
histamine H1 receptors has also been observed (Saller & Salama, 1993; Fulton & Goa, 1995; Anon, 1995). C
clozapine, affinities of quetiapine for all receptor types are lower; notably, the binding affinities of quetiapine f
adrenergic receptors are 11 times and 7 times lower, respectively, than affinities for clozapine (Saller & Salar
clozapine, quetiapine has essentially no affinity for benzodiazepine receptors; unlike clozapine, quetiapine de
affinity for muscarinic receptor types (Anon, 1995; Saller & Salama, 1993; Fulton & Goa, 1995). Despite relat
receptor binding, these collectively suggest the similarity of clozapine and quetiapine with respect to mixed 5-
(which may contribute to lower EPS potential), and that quetiapine may be less likely than clozapine to induce
antiadrenergic effects.

c) Quetiapine's D2/5-HT2a affinity profile has not yet been established with certainty. Affinity for 5-HT2 recep
reported as greater than for D2 receptors with both quetiapine and risperidone, another atypical agent, althou
the D2 receptor is relatively weak with quetiapine and very high with risperidone (similar to haloperidol) (Boris
However, others report higher D2-receptor affinity for quetiapine (Caley & Rosenbaum, 1998). Atypical antips
generally share higher affinity for 5-HT2 receptors.

d) Platelet serotonin-2 (5-HT(2)) receptor density in schizophrenic patients appears to have increased with s
quetiapine therapy in a small (n=9), double-blind, placebo-controlled study, (Faustman et al, 1996). Two patie
maximum dose of 250 milligrams/day; one of these patients dropped out after 2 weeks. Two patients receive
mg/d and one patient received 750 mg/d for the final 12 days before he dropped out at day 38 of the study. T
platelet 5-HT(2) receptor density increased over the mean baseline value for the quetiapine-treated patients b
group (n=4). Similar increases have been seen during clozapine therapy. The clinical significance of these re
addressed by the authors.

2) REVIEW ARTICLES

a) The use of atypical antipsychotics for the treatment of drug- induced psychosis in Parkinson's disease has
(Friedman & Factor, 2000).

b) The pharmacology and clinical efficacy of quetiapine have been reviewed (Green, 1999; Goren & Levin, 1
1995).

c) The new antipsychotic medications including quetiapine have been reviewed (Keck et al, 2000; Glazer, 20

d) The use of atypical antipsychotic medications in adults (Markowitz et al, 1999; Brown et al, 1999), older a
1999), and children (Malone et al, 1999; Lewis, 1998; Toren et al, 1998) has been reviewed.

e) The side effects of antipsychotics, including quetiapine, in adults and the elderly were reviewed (Garver, 2

4.5 Therapeutic Uses

Quetiapine

Quetiapine Fumarate

4.5.A Quetiapine

4.5.A.1 Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.B Quetiapine Fumarate

Bipolar disorder

Bipolar disorder, depressed phase

Bipolar disorder, Maintenance

Bipolar disorder - Cocaine dependence

Delirium

Delirium, Refractory

Dementia

Gilles de la Tourette's syndrome

Manic bipolar I disorder

Obsessive-compulsive disorder, Refractory

Parkinson's disease - Psychotic disorder

Posttraumatic stress disorder

Schizophrenia

Schizophrenia, Maintenance

Tardive dyskinesia

4.5.B.1 Bipolar disorder

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:

Add-on quetiapine therapy may be effective for patients with rapid cycling bipolar disorder, as demo
open-label study (n=14; average treatment cycle=112 days) (Vieta et al, 2002)

c) Adult:

1) The results of a small, open-label study suggest that add-on quetiapine therapy may be an effective t
with rapid cycling bipolar disorder. In this prospective study, fourteen patients with rapid cycling bipolar d
quetiapine (initial, 50 milligrams (mg)/day, then titrated according to clinical response and tolerability) in a
ongoing psychotropic treatment for an average of 112 days. Response was evaluated using the Global C
Bipolar Disorder Scale (CGI-BP), the Young Mania Rating Scale (YMRS), and the Hamilton Depression
The general and manic sub-scales of the CGI-BP showed significant score reductions following the addit
therapy (p=0.013 and p=0.016, respectively). A significant reduction in manic symptoms was also seen v
YMRS scores (p=0.025). While there were reductions in depressive symptoms, they were not significant
during the first fifteen days of quetiapine treatment varied according to the initial episode treated (manic,
depressive, 183 mg/day). Additionally, there were significant reductions in maximum average dose as co
dose for the entire sample group (443 mg/day vs 268 mg/day, respectively; p=0.008). Quetiapine was ge
with drowsiness (43%) and weight gain (29%) as the most commonly reported side effects (Vieta et al, 2

4.5.B.2 Bipolar disorder, depressed phase

FDA Labeled Indication

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Quetiapine is indicated for the treatment of depressive episodes associated with bipolar disorder (Pr
(R) oral tablets, 2008a)

Quetiapine monotherapy was well-tolerated and more effective than placebo in the treatment of bipo
(Calabrese et al, 2005)

c) Adult:

1) Quetiapine was more effective than placebo in the treatment of depressive episodes associated with
identical 8-week, randomized, double-blind, placebo-controlled studies (n=1045), patients with either bip
those with or without a rapid cycling course received quetiapine fixed doses of either 300 milligrams (mg
daily. The change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) score at wee
endpoint for both studies. Quetiapine was superior to placebo in reducing the MADRS score. In both stu
symptoms as measured by the change in MADRS score relative to placebo was observed on day 8 (We
The Quality of Life Satisfaction Scale Questionnaire (Q-LES-Q(SF)) measurement showed statistically si
improvements in overall quality of life and satisfaction, related to various areas of functioning, for the 300
the placebo; however, no additional benefit was observed with the 600 mg dose (Prod Info SEROQUEL(
2007b).

2) Quetiapine monotherapy was well-tolerated and more effective than placebo in the treatment of bipol
a double-blind, randomized, fixed-dose, placebo-controlled, parallel-group study, patients with bipolar I (
with a major depressive episode (DSM-IV) were assigned to 8 weeks of quetiapine 600 (n=180) or 300 n
(n=181) or placebo (n=181). An initial dose of 50 mg was given on day 1 and titrated up to 300 mg by da
8, and all doses were given at bedtime. In this study, effects of treatment were evaluated by Montgomery
Rating Scale (MADRS) total score (primary end-point, mean change from baseline to week 8), Clinical G
severity and improvement, Hamilton Anxiety Rating Scale, Pittsburgh Sleep Quality Index, and Quality of
Satisfaction Questionnaire. Statistically significant improvement in MADRS total score from week 1 onwa
both quetiapine groups compared with placebo. The mean change in MADRS total score from baseline t
(intent-to-treat) was -16.73, -16.39, and -10.26 for the 600 mg, 300 mg and placebo groups, respectively
both quetiapine doses vs placebo). At the final assessment, both quetiapine groups had significantly high
(defined as at least 50% MADRS score improvement) when compared with placebo (58.2% in 600 mg/da
300 mg/day group vs 36.1% in placebo; p less than 0.001). In addition, 52.9% of patients in both quetiap
remission criteria (MADRS score of 12 or less) compared to 28.4% of patients in the placebo group (p les
Significant improvements from baseline were observed in 9 of 10 and 8 of 10 MADRS items in the quetia
mg/day groups, respectively, compared with placebo (p less than 0.05). Quetiapine and placebo groups
rates of treatment-emergent mania (3.2% and 3.9%, respectively). The rates of serious adverse events w
different across treatment groups, and none were treatment related (5% in the 600 mg/day group and 3.4
group compared with 8.9% in the placebo group). The overall rates of study discontinuation due to adver
(n=47), 16% (n=29), and 8.8% (n=16) for the 600 mg/day group, 300 mg/day group, and placebo group,
(Calabrese et al, 2005).

4.5.B.3 Bipolar disorder, Maintenance

FDA Labeled Indication

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the maintenance treatment of bipolar I disorder as adjunctive therapy to lithium or dival
SEROQUEL(R) oral tablets, 2008a)

As adjunct therapy to lithium or divalproex, quetiapine was more effective than placebo in maintenar
bipolar I disorder in 2 double-blind, randomized, placebo-controlled studies (n=1326) (Prod Info SEF
tablets, 2008a)

c) Adult:

1) As adjunct therapy to either lithium or divalproex, quetiapine was more effective than placebo in main
bipolar I disorder. Two identical, randomized, double-blind studies evaluated patients (n=1326), with bipo
defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Patients m
could be manic, depressed, or mixed, with or without psychotic characteristics. Once in the open-label pl
required to be stabilized on quetiapine plus lithium or divalproex for a minimum of 12 weeks, (mean was
were to continue either lithium or divalproex, and were randomized to quetiapine twice daily for a total da

milligrams (mg) to 800 mg or to placebo. The primary outcome was time to recurrence of a mood event. defined as medication intervention, or requirement of hospitalization for a mood occurrence, a Young Ma (YMRS) score, or a Montgomery-Asberg Depression Rating Scale (MADRS) score greater than or equal discontinuation of study due to a mood event. During the double-blind phase, by day 280, approximately quetiapine group discontinued, and by day 117, approximately 50% of patients in the placebo group disc revealed quetiapine as superior to placebo at improving length of time before recurrence of any mood ev was independent of subgroup specifics, such as concomitant mood stabilizers, gender, age, race, or mo episode, or rapid cycling episode (Prod Info SEROQUEL(R) oral tablets, 2008a)

4.5.B.4 Bipolar disorder - Cocaine dependence

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:

A small, 12-week, open-label, add-on study (n=17) demonstrated that quetiapine may be effective ir symptoms and drug cravings in patients with bipolar disorder and comorbid cocaine dependence (B

c) Adult:

1) The results of an open-label study indicate that quetiapine therapy may be effective in decreasing psy and drug cravings in patients with bipolar disorder and cocaine dependence. In this small, 12-week, ope patients with bipolar I or II disorder with comorbid cocaine dependence received quetiapine at initial dose milligrams (mg) daily with weekly titrations as indicated for symptoms (mean dose at exit, 229 mg/day)(n was an add-on therapy, patients continued to take their current psychiatric medications and those enrolle treatment programs continued with that therapy as well. Psychiatric symptoms were measured at baselir intervals using the Hamilton Depression Rating Scale (HDRS), and Young Mania Rating Scale (YMRS). were assessed at baseline and at weekly intervals using a version of the Cocaine Craving Questionnaire report of dollar amount spent on cocaine was used to assess weekly drug use. In the intent to treat grou HDRS, YMRS, and BPRS were significantly decreased from baseline to exit (p less than 0.01). In additic significantly reduced from baseline to exit in this group (p=0.05). Money spent on cocaine, days of drug u positive urine drug screens were reduced; however, this change was not significant (Brown et al, 2002).

4.5.B.5 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 the treatment of delirium in two small, prospective, open-label studies (Pae et al, 2004; Sasa

c) Adult:

1) Low-dose quetiapine therapy may be effective in the treatment of delirium. In a prospective, open-lab Korean patients (mean age, 69 years; age range, 48 to 85 years) with delirium secondary to a medical c lung cancer, intra- cranial hemorrhage, cerebrovascular attack, femur neck fracture, or acquired immune received quetiapine for the treatment of delirious symptoms. Patients received quetiapine at a mean dail milligrams (mg) (initial mean dose, 37.5 mg/day; maximum mean dose, 177.3 mg/day) for an average of reductions in the mean severity scores for the Delirium Rating Scale-revised-98 (DRS-R-98) and Clinical Severity (CGI-S) scale were observed from baseline to post-treatment (21.8 vs 9.3 and 4.9 vs 2.1, respe 0.0001, both values). A reduction in the DRS-R-98 and CGI-S scores of at least 50% was observed in 19 (77.3%) patients, respectively. Sedation was the most common adverse event and no extrapyramidal sy observed. Controlled trials are needed to confirm these findings (Pae et al, 2004).

2) Symptoms of delirium resolved in twelve patients (mean age 67.3 years) following treatment with que prospective, open-label study, patients with delirium received oral quetiapine (mean dose, 44.9 milligram mean dose, 63.5 mg/day) at flexible dosing schedules for a time period lasting at least until remission of was defined as a Delirium Rating Scale-Japanese version (DRS-J) score of less than 12 points in additic assessment that symptoms of delirium had remitted clinically. Remission of delirium was achieved in all following a mean treatment duration of 4.8 days. From baseline to time of remission, the mean DRS-J sc 18.1 to 9.3. In an assessment of 8 of the 12 patients, the mean score for the Mini Mental Health State Ex version significantly improved from 19.6 at baseline to 24 after remission (p=0.0256). No adverse events quetiapine was generally well tolerated. Randomized, controlled studies are needed to substantiate thes al, 2003).

4.5.B.6 Delirium, Refractory

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:
Improved symptoms of treatment-refractory delirium in two hospitalized patients (52-year-old male and 5
Samarrai et al, 2003)

c) Adult:
1) Quetiapine therapy improved symptoms of agitation and aggression in two hospitalized patients with
delirium. A 52 year-old male and a 50-year-old female patient with delirium refractory to treatment with ri
haloperidol responded to quetiapine therapy. Trials of quetiapine in the male and female patient (initial 5
titrated to 400 mg/day and 200 mg/day, respectively) effectively controlled aggression and agitation in bo
improved cognitive ability (Al-Samarrai et al, 2003).

4.5.B.7 Dementia
See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.B.8 Gilles de la Tourette's syndrome

a) Overview
FDA Approval: Adult, no; Pediatric, no
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:
In a small, 8-week, prospective, open-label study (n=12) of pediatric patients with Tourette's disorder, pa
reduction in motor and phonic tics with quetiapine therapy (Mukaddes & Abali, 2003)

c) Pediatric:
1) Quetiapine therapy was effective in the reduction of motor and phonic tics in pediatric patients with To
prospective, open-label study (n=12) patients 8 to 16 years of age (11 boys, 1 girl) with Tourette's disord
quetiapine therapy at an initial dose of 25 milligrams (mg) daily, titrated to maximum doses of 75 mg/day
100 mg/day (12 years and older). The mean dose of quetiapine was 72.9 mg/day with a range of 50 to 1
total tic score of the Yale Global Tic Severity Scale was significantly reduced from baseline to 4 weeks (6
respectively; p less than 0.01), and from baseline to 8 weeks (61.17 vs 24.17, respectively; p less than 0
patients demonstrated a 30% to 100% improvement in tic severity (mean change, 61.91; 95% CI=50.03
Mild, transient sedation was reported in three patients; however, extrapyramidal adverse effects and stat
weight gain were not observed. Larger, randomized, controlled studies are needed to confirm the safety
quetiapine for the treatment of Tourette's disorder in children (Mukaddes & Abali, 2003).

4.5.B.9 Manic bipolar I disorder
FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes (regular-release oral tablets); 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:
Indicated for the treatment of acute manic episodes associated with bipolar I disorder as either mon
therapy to lithium or divalproex (Prod Info SEROQUEL(R) oral tablets, 2008a)
As monotherapy, two studies revealed that quetiapine was more effective than placebo in the treatm
patients with bipolar I disorder (McIntyre et al, 2005; Bowden et al, 2005)
As adjunct therapy, quetiapine was more effective than placebo in the treatment of acute manic sym
bipolar I mania(Sachs et al, 2004; Yatham et al, 2004)

c) Adult:
1) Monotherapy
a) Quetiapine monotherapy was more effective than placebo in the treatment of acute mania in pati
disorder. This international, 12 week, multicenter, double-blind, parallel-group study randomized pat
quetiapine (n=107), lithium (n=98), or placebo (n=95). Primary inclusion criteria allowed for adult pat
hospitalized for less than 3 weeks, with diagnosis of bipolar I disorder, and who were presently expe
manic episode based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (
were required to have at least 1 previously, well documented manic or mixed episode, however, pat
and mixed episodes, based on DSM-IV criteria were excluded. Patients required a score of at least
Young Mania Rating Scale (YMRS), items of irritability, speech, content, and disruptive/aggressive b
baseline YMRS scores for the quetiapine group was (32.7) and (34) for the placebo group. Quetiapi
as a flexible, twice daily dose, starting at 100 milligrams (mg) on day 1, 200 mg on day 2, 300 mg or
on day 4. By day 5, the patients' dose could be increased to 600 mg/day, and up to 800 mg/day from
84. The average dose of quetiapine in the responders was 586 mg/day in the week prior to day 21.
was the change from baseline of the YMRS score at day 21. The parallel group evaluated lithium ve

and secondary outcomes were analyzed on the intent to treat (ITT) groups and included all randomi
at least 1 dose of study treatment and who had at least 1 set of post-baseline YMRS scores. The av
was 38 years and 56.1% of them were male. At day 21, change in YMRS score from baseline was s
in the quetiapine groups versus placebo (-14.62 vs -6.71; p less than 0.001). Change in YMRS scor
versus placebo group was also statistically significant (-15.20 vs -6.71; p less than 0.001); however,
between quetiapine and lithium groups was not significant. Secondary outcomes of note include sig
in the change in YRMS score from baseline through treatment day 84 (-20.28 vs -9; p less than 0.0
defined as 50% or greater reduction in YMRS score from baseline at day 21 were significant (53.3%
0.001). YMRS remission rates, defined as a YMRS score of 12 or less at day 21 were also significar
less than 0.001). Adverse effects were considered mild to moderate. The most common, occurring a
included dry mouth, somnolence, weight gain, dizziness, insomnia, headache, asthenia, depression
(Bowden et al, 2005).

b) Quetiapine monotherapy was more effective than placebo in the treatment of acute mania in pati
disorder. This international, 12 week, multicenter, double-blind, parallel-group study randomized pat
quetiapine (n=101), haloperidol (n=98), or placebo (n=100). Primary inclusion criteria allowed for ad
age of 42.8 years, 36.6% male, who were hospitalized for less than 3 weeks, with diagnosis of bipol
without psychotic characteristics, and who were presently experiencing an acute manic episode bas
and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Patients were required to have
well documented manic or mixed episode, however, patients with rapid cycling and mixed episodes
criteria were excluded. Patients required a score of at least 4, on 2 of the core Young Mania Rating
of irritability, speech, content, and disruptive/aggressive behavior. Mean baseline YMRS scores for t
was (34) and (33.1) for the placebo group. Quetiapine was administered twice daily, starting at 100 r
1, 200 mg on day 2, 300 mg on day 3, and 400 mg on day 4. By day 5, the patients' dose could be i
mg/day based on efficacy and tolerability, and up to 800 mg/day thereafter from treatment days 6 to
recommended target dose was 600 mg/day. The average dose of quetiapine in the responders was
primary outcome was the change from baseline of the YMRS score at day 21. The parallel group ev
versus placebo. Primary and secondary outcomes were analyzed on the intent to treat (ITT) groups
randomized patients who took at least 1 dose of study treatment and who had at least 1 set of post-
scores. At day 21, change in YMRS score from baseline was statistically significant in the quetiapine
placebo (-12.29 vs -8.32; p less than 0.01). Change in YMRS scores for the haloperidol versus plac
statistically significant (-15.71 vs -8.32; p less than 0.001). Secondary outcome of change from base
day 84 revealed quetiapine and haloperidol treated patients continued to experience statistically sig
17.52 and -18.92 vs -9.48, respectively; p less than 0.001 for both comparisons to placebo). The mo
effects occurring greater than 10% included insomnia, somnolence, and extrapyramidal-related effe
and extrapyramidal syndromes were significantly more frequent with haloperidol compared to quetia
less than 0.001) (McIntyre et al, 2005).

2) Adjunct Therapy

a) Quetiapine with lithium or divalproex was more effective than lithium or divalproex monotherapy
acute mania in patients with bipolar I disorder. This 3-week, double blind, placebo controlled, paralle
patients to receive quetiapine (n=81) as add on therapy to lithium or divalproex versus placebo (n=8
divalproex. Inclusion criteria allowed for adult patients, average age of 39.6 years, 49 patients were
of bipolar I disorder based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edit
required hospitalization for less than 3 weeks for a current manic episode and treatment with lithium
least 7 days of the immediately preceding 28 days prior to randomization. Patients were also require
previously, well documented manic or mixed episode prior to the current episode, and a score of at l
core YMRS items of irritability, speech, content, and disruptive/aggressive behavior. Patients with ra
were excluded. Eligible patients either began or continued lithium or divalproex on day 1 of study. Q
administered twice daily, morning and evening, starting at 100 milligram (mg) on day 1, 200 mg on d
3, and 400 mg on day 4. By day 5, the patients' dose could range from 200 milligram per day (mg/da
based on efficacy and tolerability, and up to 800 mg/day on days 6 to 21. Study guidelines encourag
quetiapine dosage to at least 600 mg/day prior to patients withdrawing from the study due to lack of
last-week quetiapine dose among the responders was 584 mg/day. The primary outcome was the ch
the YMRS score at final assessment. Mean baseline YMRS scores for the quetiapine with lithium or
(31.5) and (31.1) for the placebo group. Outcomes were analyzed on the intent to treat (ITT) groups
YMRS score from baseline was statistically significant in the quetiapine group versus placebo (-13.7
Secondary outcomes, also statistically significant were YRMS response rates, defined as 50% or gr
YMRS score from baseline at day 21, (54.3% vs 32.6%; p=0.005). As well as, YMRS remission rate
score of 12 or less at day 21, (45.7% vs 25.8%; p=0.007). The most common adverse effects occur
were somnolence, headache, dry mouth, asthenia, postural hypotension, and dizziness (Sachs et al

b) Quetiapine with lithium or divalproex was more effective than lithium or divalproex monotherapy
acute mania in patients with bipolar I disorder. This double blind, placebo controlled study randomiz
quetiapine (n=185) as add on therapy to lithium or divalproex versus placebo (n=185) with lithium or
weeks or 6 weeks duration. Eligible patients were adult patients, average age of 39.2 years, 54.1% r
bipolar I disorder, with or without psychotic features, based on the Diagnostic and Statistical Manual
Fourth Edition (DSM-IV). Patients required hospitalization for less than 3 weeks for a current manic
with lithium or divalproex for at least 7 days prior to randomization, and a history of at least 1 manic
the last 5 years. Patients with rapidly cycling or mixed episodes were excluded. Patients required a s
on 2 of the core Young Mania Rating Scale (YMRS) items of irritability, speech, content, and disrupt

behavior, and a score of 4 or greater on the Clinical Global Impression-Bipolar (CGI-BP) Severity of randomization, patients were to continue lithium or divalproex treatment. Clinicians could adjust lithi doses for efficacy, for reduction of adverse effects, and for established, therapeutic range (0.7 to 1.0 liter, (mEq/L) lithium, or 50 to 100 microgram per milliliter (mcg/mL) divalproex). Quetiapine was adn starting at 100 milligram per day (mg/day) on day 1, 200 mg/day on day 2, 300 mg/day on day 3, an 4. By day 5, quetiapine could be administered up to 600 mg/day, and up to 800 mg/day from day 6 t treatment. By day 21, the average dose of quetiapine in the responders was 492 mg/day. The prima change from baseline of the YMRS score at day 21. Because the protocol was identical for the 3 we treatment group, the results were combined for analysis to increase the power of the study to identif important effects. Mean baseline YMRS scores for the quetiapine with lithium or divalproex group wa the placebo group. Outcomes were analyzed on the intent to treat (ITT) groups. At day 21, change i baseline was statistically significant in the quetiapine group versus placebo (-15.29 vs -12.19; p less statistically significant secondary outcomes were change in response rate, defined as 50% or greate score from baseline at day 21, (55.7% vs 41.6%; p less than 0.01). YMRS remission rates, defined a or less at day 21, was statistically significant (48.7% vs 33%; p less than 0.01). Common adverse ef or greater, and at least twice that of placebo were somnolence, dry mouth, asthenia, postural hypote and pharyngitis (Yatham et al, 2004).

4.5.B.10 Obsessive-compulsive disorder, Refractory

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:

Obsessive-compulsive disorder (OCD) symptoms were reduced when quetiapine was added to SSRI (se reuptake inhibitor) treatment (Denys et al, 2002; Mohr et al, 2002)

c) Adult:

1) The addition of quetiapine to selective serotonin reuptake inhibitor (SSRI) therapy was effective in pro of symptom activity in patients with treatment-refractory obsessive-compulsive disorder (OCD). In a sma patients with at least a 5-year history of OCD symptoms who failed a minimum of 3 adequate treatments scored at least 18 on the Yale-Brown Obsessive Compulsive Scale (YBOCS) received quetiapine for 8 w their current SSRI (n=10). Using a fixed dosing schedule, quetiapine was given at an initial dose of 75 m titrated to 200 mg/day (100 mg/day in week 2, 150 mg/day in week 3, 200 mg/day in week 4). Overall, th reduction (35.4%) in patients' mean YBOCS score from baseline to endpoint (p=0.002). Quetiapine was sedation being the most common adverse event (Denys et al, 2002).

2) Symptoms of obsessive-compulsive disorder (OCD) were reduced by treatment with quetiapine, in co selective serotonin reuptake inhibitor (SSRI). The charts of 8 patients who had been treated for OCD by tolerated dose of an SSRI for at least 12 weeks and who were then given add- on treatment of quetiapin Quetiapine doses were started at 25 milligrams (mg) daily and increased to a maximum of 300 mg daily. Brown Obsessive-Compulsive Scale improved for 4 of the patients, at doses of 50, 75 (2 patients), and 3 patient was unable to tolerate quetiapine (Mohr et al, 2002).

4.5.B.11 Parkinson's disease - Psychotic disorder

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

In several studies and case reports, quetiapine therapy controlled psychotic symptoms in patients with P (Fernandez et al, 2000; Weiner et al, 2000; Fernandez et al, 1999; Friedman & Factor, 2000a)(Parsa & E

c) Adult:

1) A study designed to measure the effectiveness of clozapine replacement by quetiapine in 15 patients induced psychosis in Parkinson's disease concluded that quetiapine is an effective alternative to clozapi assessed at baseline, and 4 and 8 weeks after discontinuation of clozapine. At baseline, the starting cloz reduced by 6.25 milligrams (mg) per week for 2 weeks, 12.5 mg per week for 2 weeks, and 25 mg per w was discontinued. The baseline initiation dose of quetiapine was 12.5 mg daily for 1 week and was incre mg per day until the patient was no longer receiving clozapine. Quetiapine dosage adjustments were per titration period, which ranged from 1 to 10 weeks. The average quetiapine ending dose was 62.5 mg. An standardized weekly telephone interview was performed on all patients and their caregivers. Twelve of th transition without a worsening of cognition or loss of antipsychotic effect at the 4 and 8-week visits. All 12 quetiapine. Side-effects noted were mild and transient. Only 1 patient had increased dyskinesia and 4 pa transient worsening of tremor. At the end of 12 months, 9 of 12 patients were stable on quetiapine. Two experienced a decline in motor function switched back to clozapine (Fernandez et al, 2000).

2) An 81-year-old man with a 14-year history of Parkinson's disease who developed levodopa-induced p

successfully treated with quetiapine after olanzapine was discontinued due to worsened parkinsonism. Q
6 weeks after the discontinuation of olanzapine and was titrated to a dose of 25 milligrams at bedtime. T
complete resolution of hallucinations, complete resolution of belligerent behavior, and no worsening of pa
al, 2000).
3) Quetiapine was shown to be beneficial and well tolerated in the treatment of drug-induced psychosis
Parkinson's disease (PD) (Fernandez et al, 1999). Thirty-five patients received a mean daily dose of que
milligrams. Of 24 neuroleptic-naive patients, 20 reported marked improvement of psychosis without a co
motor function. There was a clinically and statistically significant (p=0.024) improvement in Brief Psychia
(BPRS) in the patients that had a baseline and 4-week follow-up assessment. Five patients were able to
a transition from clozapine or olanzapine to quetiapine, while 6 could not due to confusion, erratic behavi
hallucinations. The data suggests quetiapine may be beneficial to treat DIP in PD but it should be used v
replacing other atypical antipsychotic drugs.
4) In a review of several smaller studies (n= 10 to 40), quetiapine (25 to 300 milligrams/day) was succes
Psychiatric Rating Scale (BPRS) scores and improving or not worsening motor functions (Friedman & Fa
5) A 52-week open-label pilot study reported successful use of quetiapine in treating psychosis in two ne
patients with Parkinson's disease (1 with and 1 without dementia) (Parsa & Bastani, 1998). For each pati
introduced at 25 milligrams (mg) per day; it was increased to a maximum dose of 200 mg/day over 16 we
without dementia (a 74-year-old man) and 400 mg/day over 12 weeks for the patient with dementia (a 74
Severity of psychiatric symptoms was measured by the Brief Psychiatric Rating Scale and a Clinical Glob
Severity of Illness scale. Treatment successfully controlled psychotic symptoms without worsening motor
patients, although improvement was not as pronounced in the patient with dementia.

4.5.B.12 Posttraumatic stress disorder

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:

Adjunctive quetiapine therapy reduced the posttraumatic stress disorder (PTSD) symptoms of a 49-year-
with severe PTSD (Sattar et al, 2002)

c) Adult:

1) Adjunctive quetiapine therapy reduced symptoms in one patient suffering from posttraumatic stress d
year-old Caucasian male with severe PTSD received adjunctive treatment with quetiapine after therapy w
of paroxetine (titrated to 40 milligrams (mg)/day) failed to control his symptoms. Initially, he received que
bedtime for 2 days, but continued to be irritable and anxious. The dose was then increased to 100 mg at
following 3 days his symptoms eased, however periodic episodes of severe anxiety persisted during the
dose was increased to 25 mg twice daily and 100 mg at bedtime and he showed continued improvement
His scores on the Hamilton-D rating scale for Depression (HAM-D) and clinician-administered PTSD scre
from 40 and 98 (on admission) to 11 and 60, respectively. His symptoms remained controlled at this dos
months. No adverse events were reported (Sattar et al, 2002).

4.5.B.13 Schizophrenia

FDA Labeled Indication

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Quetiapine is indicated for the treatment of schizophrenia (Prod Info SEROQUEL(R) oral tablets, 20
SEROQUEL XR(TM) extended-release oral tablets, 2007)
In 3 short-term (6-week) controlled-trials of patients with schizophrenia who met DSM III-R criteria fo
higher quetiapine doses were generally more effective than lower doses in treating patients with sch
DSM III-R criteria for schizophrenia (Prod Info SEROQUEL(R) oral tablets, 2007b)
Moderate degree of efficacy for treating positive and negative symptoms in schizophrenic patients ir
studies (Wetzel et al, 1995b; Fulton & Goa, 1995b; Fabre et al, 1995b; Borison et al, 1996b; Anon, 1
In one 6-week placebo-controlled trial (n=109), the efficacy of quetiapine was not sustained beyond
(Borison et al, 1996b)
In an open-label, 12-week, prospective study (n=56), oral quetiapine, at doses ranging from 200 to 8
was well tolerated and yielded clinical benefit in symptoms of early-onset schizopreniform-spectrum
adolescents (Schimmelmann et al, 2007)
In a small, open-label study (n=10) of adolescents, quetiapine was well tolerated and effective in the
schizoaffective disorder or bipolar disorder with psychotic features (McConville et al, 2000; McConvi

c) Adult:

1) In 3 short-term (6-week) controlled-trials of patients with schizophrenia who met DSM III-R criteria for

quetiapine doses were generally more effective than lower doses in treating patients with schizophrenia
criteria for schizophrenia. One of the trials used a single fixed dose haloperidol arm as a comparative tre
single group was inadequate to provide a reliable and valid comparison of quetiapine and haloperidol (Pr
(R) oral tablets, 2007b).

a) A placebo-controlled trial (n=361) that involved 5 fixed doses of quetiapine 75, 150, 300, 600 and
day (mg/day) in 3 divided doses reported that the 4 highest doses were superior to placebo on the B
Scale (BPRS) total score, the BPRS psychosis cluster and the Clinical Global Impression (CGI) sev
maximal effect was observed at 300 mg/day, and this dose was superior to placebo on the Scale for
Symptoms (SANS). The observed effects of 150 to 750 mg/day were generally identical (Prod Info S
tablets, 2007b).

b) Another placebo-controlled trial (n=286) that involved the titration of quetiapine in high (up to 750
(mg/day) in 3 divided doses) and low (up to 250 mg/day in 3 divided doses) doses reported that only
quetiapine group was superior to placebo on the Brief Psychiatric Rating Scale (BPRS) total score, t
cluster, the Clinical Global Impression (CGI) severity score, and the Scale for Assessing Negative S
(Prod Info SEROQUEL(R) oral tablets, 2007b).

c) A dose regimen comparison trial (n=618) that compared two fixed doses of quetiapine (450 millig
3 divided doses and 50 mg/day in 2 divided doses) reported that only the 450 mg/day (225 mg twice
was superior to the 50 mg/day (25 mg twice daily) quetiapine dose group on the Brief Psychiatric Ra
total score, the BPRS psychosis cluster, the Clinical Global Impression (CGI) severity score, and on
Assessing Negative Symptoms (SANS) (Prod Info SEROQUEL(R) oral tablets, 2007b).

2) A 6-week, fixed-dose, placebo-controlled trial of patients who met DSM IV criteria for schizophrenia (r
that 400 milligram (mg), 600 mg, and 800 mg once daily doses of extended-release quetiapine were sup
Therapy was initiated with extended-release tablets at 300 mg/day (once daily) on Day 1. The dose was
400 mg or 600 mg on Day 2 or to 800 mg by Day 3. Change between baseline and endpoint (Day 42) fo
Negative Syndrome Scall (PANSS) was used as the primary efficacy measure. Analysis of PANSS total
quetiapine extended-release doses of 400 mg, 600 mg and 800 mg were all superior to placebo (Prod In
(TM) extended-release oral tablets, 2007).

3) Several open (Wetzel et al, 1995b; Fulton & Goa, 1995b) and placebo-controlled studies (Fabre et al,
1996b; Anon, 1995b; Fulton & Goa, 1995b) of short duration (6 weeks or less) have suggested the effica
for treating both positive and negative symptoms of schizophrenia (mostly patients with acute exacerbati
chronic illness). In these trials, effects of treatment were mainly evaluated by the Brief Psychiatric Rating
Clinical Global Impression (CGI) Severity of Illness score, and the modified Scale for Assessment of Neg
(SANS). Clinical responses were observed within 2 weeks of starting quetiapine therapy and were best v
300 milligrams daily; in one study, doses of up to 750 milligrams daily (mean, 360 milligrams daily) were
to lower doses (up to 250 milligrams daily; mean, 209 milligrams daily) and placebo at week 6 of treatme
and SANS (Anon, 1995b). The severity of extrapyramidal symptoms (EPS) was similar in patients treate
quetiapine.

4) Quetiapine therapy in 145 patients diagnosed with psychotic mood disorders was reviewed. All patier
with quetiapine, and 20% received quetiapine alone while 80% received other psychoactive drugs with q
was associated with more substantial clinical effects in patients with affective psychoses and in patients
chronically ill. The response rate for the majority of psychiatric diagnoses studied was equal or superior t
schizophrenia. These preliminary findings suggest that quetiapine may be useful as an alternative or adj
patients with affective psychosis when used with mood stabilizers. Controlled studies are needed (Zarate

5) An uncontrolled trial in elderly patients with psychotic disorders found quetiapine to be associated wit
improvement and to be well tolerated (McManus et al, 1999). An interim statistical analysis was performe
week 12. The median total daily dose of quetiapine was 100 milligrams/day. The most common adverse
the central nervous system (somnolence, dizziness, agitation) and cardiovascular system (postural hypo
Extrapyramidal symptoms occurred in 6% of patients. Mean Simpson-Angus Scale total score showed si
(p less than 0.0001) at endpoint. In addition, Brief Psychiatric Rating Scale (BPRS) and Clinical Global Ir
scores showed significant (p less than 0.0001 and p less than 0.01, respectively) improvement. This non
supports the need for further controlled clinical trials of quetiapine use in the elderly.

6) Considerable interindividual differences in the response to quetiapine have been reported (Wetzel et
Goa, 1995b), and in larger placebo-controlled trials, differences in favor of quetiapine have not always re
significance or were marginally significant and beneficial changes from baseline scores were at times sm
questionable clinical significance; up to one-third of patients receiving quetiapine have dropped out of tre
efficacy (Fulton & Goa, 1995b; Borison et al, 1996b; Anon, 1995b). One 6-week placebo-controlled trial (
1996b) reported a significant reduction in BPRS and CGI scores with oral quetiapine for three of the first
there was no significant difference in scores between placebo and quetiapine at week 6. Improvement in
sustained with quetiapine on days 21 to 42, although statistical significance was barely achieved. Thirty
treated patients discontinued therapy due to lack of benefit in this study.

d) Pediatric:

1) In an open-label, 12-week, prospective study (n=56), treatment with oral quetiapine, at doses ranging
milligrams (mg) per day, was well tolerated and led to significant improvement in symptoms of early-onse
spectrum disorders in adolescents. Following a 1- to 9-day washout period of prior psychoactive medicat
age, 15.9 years; range, 12-17.9 years; 67.9% male) meeting the DSM-IV criteria for schizophrenia, schiz
schizophreniform disorder and had a Positive and Negative Syndrome Scale (PANSS) total score of 60 o
with quetiapine for 12 weeks. Following a fixed titration protocol during week 1 (50 mg at day 1 increased
7), the quetiapine dose was adjusted based on clinical response and tolerability to a range of 200 to 800

dose, 605.6 mg/day (week 6) and 584.2 mg/day (week 12)). The use of benztropine (1 to 6 mg/day) to tr
symptoms (EPS) and benzodiazepines (diazepam or lorazepam; up to 40 mg/day of diazepam equivaler
agitation, or sleep disturbances were allowed during the study. Assessments occurred at weekly visits ur
visits every other week during weeks 6-12. The majority of study patients (76.8%) were antipsychotic-nai
week 12, 51.8% (n=25/52) of study participants had dropped out, with 30.4% discontinuing due to lack o
modified intent-to-treat (ie, patients with at least 1 post-baseline efficacy measurement) revealed a signif
mean +/- standard deviation PANSS total score (primary endpoint) from baseline (91.5 +/- 17.2) to week
less than 0.0001), yielding a difference of 24.9 points (95% confidence interval (CI), 17.3 to 32.4; effect s
difference was evident as early as week 1 and was maintained throughout the study. A 50% reduction in
occurred in 34.6% (n=18/52) at a median of 85 days while 51.9% (n=27/52) had a 40% reduction in PAN
median of 57 days. Among the PANSS sub-scales, the effect size at week 12 was greater for the positive
5.2 at baseline to 14.9 +/- 6.9; 95% CI, 4.8 to 9.1; effect size=0.91) than the negative sub-scale (22.8 +/-
18.2 +/- 8.7; 95% CI, 2 to 7.1; effect size=0.5). Additionally, significant improvements occurred among th
impulsivity/hostility, and anxiety/depression sub-scales of the PANSS, along with the Clinical Global Impr
Illness scale (5.2 +/- 0.9 at baseline to 3.7 +/- 1.8 at week 12) and the Subjective Well-being under Neuro
Scale (75.5 +/- 17.6 at baseline to 7.5 +/- 17.1 at week 12). Adverse events occurred in 78.6% of patient
(21.4%), fatigue (17.9%), and headache (17.9%) being the most common. Five (8.9%) and 2 (3.6%) pati
least 1 moderate EPS (at doses of 400 to 600 mg/day) and mild-to-moderate akithisia (at doses of 500 to
respectively; however, none required treatment or resulted in study discontinuation. Compared to baselir
significant increase in weight and BMI at week 12 (mean increase, 6.2 kilograms (weight), 2.1 kilograms/
with 60.7% of patients gaining more than 7% of their baseline weight (Schimmelmann et al, 2007).

2) A small study (n=10) of adolescents ranging in age from 12.3 through 15.9 years concluded quetiapir
and effective in the treatment of schizoaffective disorder or bipolar disorder with psychotic features. Quet
open-label, rising-dose trial was initiated at 25 milligrams (mg) twice daily and reached 400 mg twice dail
concluded on day 23. Quetiapine improved both positive and negative symptoms significantly (p less tha
and endpoint symptoms were compared and there were no unexpected side effects (McConville et al, 20
of this trial, all ten patients continued open-label treatment with quetiapine (initial, 800 mg/day titrated ov
optimal dose; mean dose, 600 mg/day) for up to 88 weeks. Significant improvements in mean scores fro
were seen at all time points through week 64 for the Brief Psychiatric Rating Scale (BPRS) and Clinical G
(CGI) Severity of Illness scale (p less than 0.05). Improvements in mean scores on the Scale for Assessi
Symptoms (SANS) were significant through week 52 (p less than 0.05). Quetiapine was well tolerated ar
were mild to moderate, with somnolence (60%), headache (50%), and pharyngitis (40%) being reported
Extrapyramidal symptoms were not observed during the trial, however, 30% of patients reported increas
body mass index as a "mild" adverse event. Larger, controlled studies are needed to further establish lor
efficacy and safety in this patient population (McConville et al, 2003).

4.5.B.14 Schizophrenia, Maintenance

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended release only); 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:

The extended-release formulation of quetiapine fumarate is indicated for the maintenance treatment
(Prod Info SEROQUEL(R)XR extended-release oral tablets, 2007)
In a randomized, double-blind, extension study (n=171), continued treatment with extended-release
400 to 800 milligrams per day led to a longer time to relapse compared to placebo in adult patients v
stabilized during 16 weeks of an open-label trial (Prod Info SEROQUEL(R)XR extended-release ora

c) Adult:

1) Maintenance treatment with extended-release quetiapine fumarate (quetiapine XR), at doses of 400 t
per day, led to a statistically significant delay in relapse compared to placebo in the double-blind, random
of an open-label trial. Clinically stable adult outpatients (n=171) who met the Diagnostic and Statistical M
Disorders (4th edition) criteria for schizophrenia and who remained stable following 16 weeks of open-lal
quetiapine XR 400 to 800 mg/day were included. Patients who had a Clinical Global Impression (CGI)-S
less and a Positive and Negative Syndrome Scale (PANSS) total score of 60 or less beginning to end of
(not exceeding a 10- or greater point increase in PANSS total score) were considered to be stabilized. In
extension phase, patients were randomized to continue receiving quetiapine XR at their current dose or
observed for possible relapse, which was defined as a 30% or greater increase in the PANSS total score
score of 6 or greater, hospitalization due to worsening of schizophrenia, or need for any other antipsycho
Treatment with quetiapine XR led to a significantly longer time to relapse than placebo (Prod Info SERO
release oral tablets, 2007).

4.5.B.15 Tardive dyskinesia

a) Overview

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

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

b) Summary:
Quetiapine treatment improved symptoms in three women with tardive dyskinesia (Chari et al, 2002)

c) Adult:

1) Treatment with quetiapine reduced persistent symptoms of tardive dyskinesia in three women receivi therapy. A 42-year-old Caucasian woman with a 25-year history of schizophrenia and scoring a 22 on th Involuntary Movement Scale (AIMS) was prescribed quetiapine for tardive dyskinesia. Within a year and treatment she no longer scored on the scale. The tardive dyskinesia symptoms of a 63-year-old Caucasi year history of schizoaffective disorder were also successfully treated with quetiapine. After a year of the was reduced from 19 to 3. In addition, a 52-year-old Asian woman with a 5-year history of psychotic illne quetiapine for tardive dyskinesia and after 24 weeks of treatment her AIMS score dropped from 17 to 10 are needed to substantiate these findings (Chari et al, 2002).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Chlorpromazine

Haloperidol

Olanzapine

Paliperidone

Perphenazine

Risperidone

Ziprasidone

4.6.A Chlorpromazine

4.6.A.1 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo- controlled, fixed-dose and f drug development trials, the minimum effective dose of quetiapine was 150 milligrams/day (equivalent to chlo milligrams/day) (Woods SW, 2003).

b) Quetiapine 75 to 750 milligrams daily (mean, 407 mg daily) offered no significant advantage over chlorpro milligrams daily (mean, 384 mg daily) in a double-blind, parallel-group trial involving patients with acute exace subchronic schizophrenia, or schizophreniform disorder (n=201). Both drugs were associated with similar red Psychiatric Rating Scale (BPRS) scores, Clinical Global Impression (CGI) scores, and negative scale scores Negative Syndrome Scale (PANSS) (negative symptom assessment). The severity of extrapyramidal sympto comparable (assessed by Simpson scale) (Fulton & Goa, 1995a).

4.6.B Haloperidol

4.6.B.1 Schizophrenia

a) In a study involving 361 patients, quetiapine (across 5 fixed doses) was found to be superior to placebo in symptoms in schizophrenic patients, while haloperidol (12 milligrams/day) was not. Additionally, depressive s improved in a greater proportion of patients treated with quetiapine versus haloperidol or placebo. None of th withdrew from the study due to extrapyramidal symptoms, while 4 haloperidol and 1 placebo patient withdrew Glazer, 2000).

b) A 6-week, multicenter, double-blind trial comparing quetiapine and haloperidol (mean total daily doses of milligrams, respectively) in the treatment of acute exacerbation of schizophrenia concluded that quetiapine in better tolerated than haloperidol. Both agents produced clear reductions in the Positive and Negative Syndro Clinical Global Impression Severity of Illness and Global Improvement scores. Quetiapine was better tolerate extrapyramidal symptoms. In addition, mean serum prolactin concentration decreased in quetiapine patients haloperidol patients (Copolov et al, 2000).

4.6.C Olanzapine

4.6.C.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp

generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychoti
before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 t
(mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or zipr
mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months
ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with o
discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard rati
confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.9
discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risp
olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilogr
greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.D Paliperidone

4.6.D.1 Schizophrenia, Recent exacerbation, in hospitalized patients

a) In a randomized, double-blind, placebo- and active-controlled clinical trial (n=394), treatment with paliperic
(ER) produced significantly improved Positive and Negative Syndrome Scale (PANSS) total scores compared
hospitalized patients with a recent exacerbation of schizophrenia. Hospitalized patients 18 to 65 years of age
(defined as lasting less than 4 weeks but more than 4 days) of schizophrenia (paranoid, disorganized, or und
diagnosed using Diagnostic and Statistical Manual of Mental Disorders Fourth edition (DSM-IV)), a Clinical G
Severity (CGI-S) scale score of 5 or greater, and symptom scores of 4 or greater on 2 or more of the following
hostility, excitement, tension, uncooperativeness, and poor impulse control (with a combined score of these it
were eligible for enrollment. Following the discontinuation of all psychotropic agents, patients were randomize
paliperidone ER (n=157; baseline mean PANSS total score, 102.8 +/- 13.1 points), quetiapine (n=157; baseli
score, 101.3 +/- 13.3 points), or placebo (n=80; baseline mean PANSS total score, 103.8 +/- 15.7 points). In a
phase, paliperidone ER was initiated at 6 milligrams (mg)/day on days 1 to 3 and then increased to 9 mg/day
an optional dose increase to 12 mg/day starting on day 8 if necessary (mean dose, 10.4 +/- 1.7 mg/day) and
at 50 mg/day on day 1, 100 mg/day on day 2, 200 mg/day on day 3, 400 mg/day on day 4, 600 mg/day on da
dose increase to 800 mg/day on day 8 (mean dose, 690.9 +/- 134.3 mg/day). Psychotropic medications (excl
additional paliperidone ER or quetiapine) could be added following the 14-day monotherapy phase (one or m
agents: paliperidone ER, 52.9%; quetiapine, 55.4%; placebo, 66.7%). The least-squares mean PANSS total s
baseline to day 14 was significantly decreased in the paliperidone ER arm (-23.4 +/- 1.8 (standard error (SE))
with the quetiapine arm (-17.1 +/- 1.8 (SE) points; p less than 0.001) (primary endpoint) and the placebo arm
between group analyses (using a least-squares mean differences in change scores with the last observation
patients in the paliperidone ER arm had significantly improved PANSS total score, PANSS scale negative sy
PANSS scale disorganized thoughts scores, PANSS scale uncontrolled hostility/excitement scores, and CGI-
with patients in the quetiapine and placebo arms at day 14 and at the end of 6 weeks of treatment (day 42) (T
the PANSS scale positive symptoms score (PANSS-P) and Clinical Global Impression of Change (CGI-C) sc
improved in the paliperidone ER arm compared with the quetiapine and placebo arms at day 14 and paliperic
improved PANSS-P and CGI-C compared with placebo at day 42 (Table 1). Serious adverse events were rep
and 2.5% of patients in the paliperidone ER, quetiapine, and placebo arms, respectively. Extrapyramidal sym
significantly (p less than 0.001) higher in the paliperidone ER arm following the 14-day monotherapy phase c
quetiapine using the Simpson-Angus Rating Scale (total score). The incidence of movement disorders at day
significantly different between the 3 arms using the Barnes Akathisia Rating Scale and the Abnormal Involunt
(Canuso et al, 2009).

Table 1: Between Group Analyses

Outcome measures	Day 14			Day 42	
PANSS score Mean (SE)	Paliperidone ER versus Quetiapine	Paliperidone ER versus Placebo	Quetiapine versus Placebo	Paliperidone ER versus Quetiapine	Paliperido ER versus Placebo
Total	-6.3* (1.8)	-8.4* (2.2)	-2.1 (2.2)	-4.7* (2)	-7.8* (2.
Positive symptoms	-1.6* (0.6)	-2.1* (0.7)	-0.5 (0.7)	-1.1 (0.6)	-1.9* (0.
Negative symptoms	-1.3* (0.5)	-2.2* (0.6)	-0.9 (0.6)	-1.2* (0.5)	-2.1* (0.
Anxiety/depression	-0.5 (0.3)	-0.6 (0.4)	-0.1 (0.4)	-0.4 (0.3)	-0.5 (0.4
Disorganized thoughts	-1.3* (0.4)	-2.1* (0.5)	-0.8 (0.5)	-1* (0.5)	-2* (0.6
Uncontrolled hostility/excitement	-1.5* (0.4)	-1.6* (0.5)	-0.1 (0.5)	-1* (0.4)	-1.3* (0.
CGI-S (Mean SE)	-0.3* (0.1)	-0.4* (0.1)	-0.1 (0.1)	-0.3* (0.1)	-0.5* (0.
CGI-C (Mean SE)	-0.4* (0.1)	-0.5* (0.1)	-0.2 (0.1)	-0.1 (0.1)	-0.4* (0.

*p less than 0.05
PANSS, Positive and Negative Syndrome Scale; SE, standard error; CGI-S, Clinical Global Impression Clinical Global Impression of Change

4.6.E Perphenazine

4.6.E.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychoti before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 t (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or zipr mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with o discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard rati confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.9 discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risp olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilogr greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.F Risperidone

Chronic schizophrenia

Psychotic disorder

4.6.F.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychoti before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 t (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or zipr mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with o discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard rati confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.9 discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risp olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilogr greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.F.2 Psychotic disorder

a) Quetiapine and risperidone were similarly efficacious in treating psychotic symptoms and had similar over quetiapine treatment resulted in fewer extrapyramidal symptoms (EPS) and was more effective in reducing d month, open-label study, patients with schizophrenia, schizoaffective disorder, or other psychotic disorders (i disorder, major depressive disorder and various forms of dementia) were randomized in a ratio of 3:1 to recei or risperidone (n=175). The starting dosage of quetiapine was 50 milligrams/day (mg/day), which was increas increments every 1 to 2 days, to a maximum of 800 mg/day, given in divided doses. Risperidone was started with upward titration to a target dose of 3 mg twice daily by day 3. Dosages were individually titrated to maxin minimizing adverse reactions (mean prescribed dose: quetiapine 253.9 mg, risperidone 4.4 mg). At the begin approximately half of each group had EPS. There was a steady decline in the number of patients reporting EI the study progressed. The incidence of EPS in the quetiapine group was lower than in the risperidone group 47.3) but not at the end of the study (38.6 vs 39.2). The percentage of patients requiring a change of treatme requiring anti-EPS medication was lower in the quetiapine group than in the risperidone group (7% vs 20.5%) third of patients in each group withdrew before completion of the study. A higher percentage withdrew from ri for lack of efficacy (10.3% vs 5.8%) and a higher percentage withdrew from quetiapine treatment because of vs 5.1%). Somnolence was the most common adverse event in both groups, followed by dry mouth and dizzi occurred significantly more often with quetiapine treatment (p less than 0.05). Occurrence of weight gain was (Mullen et al, 2001).

4.6.G Ziprasidone

4.6.G.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychoti before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 t

(mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or zipr
mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months
ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with o
discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard rati
confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.9
discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for ris
olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilogr
greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

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