DRUGDEX® Evaluations

OLANZAPINE

0.0 Overview

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

2) Dosing Information
- **a)** Adult
  - **1)** Agitation - Bipolar I disorder
    - **a)** initial, 10 mg INTRAMUSCULARLY; lower dose of 5 mg or 7.5 mg may be used if indicated; usual effectiv ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006)
    - **b)** subsequent doses may be given INTRAMUSCULARLY in doses up to 10 mg; maximal dosing, three 10 n orthostatic hypotension prior to the administration of repeated doses) (Prod Info ZYPREXA(R) oral tablets, IM disintegrating tablets, 2006)
  - **2)** Agitation - Schizophrenia
    - **a)** initial, 10 mg INTRAMUSCULARLY; lower dose of 5 mg or 7.5 mg may be used if indicated; usual effectiv ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006)
    - **b)** subsequent doses may be given INTRAMUSCULARLY in doses up to 10 mg; maximal dosing, three 10 n orthostatic hypotension prior to the administration of repeated doses) (Prod Info ZYPREXA(R) oral tablets, IM disintegrating tablets, 2006)
  - **3)** Bipolar I disorder, Acute mixed or manic episodes
    - **a)** monotherapy: 10 to 15 mg/day ORALLY, dose adjustments should be made in 5 mg increments in interva (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006)
    - **b)** combination therapy (with lithium or valproate): 10 mg/day ORALLY, dose adjustments should be made ir hours, MAX dose is 20 mg/day (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) ora
  - **4)** Bipolar I disorder, Maintenance therapy
    - **a)** (monotherapy) 5 to 20 mg ORALLY per day (after achieving a responder status for an average duration o IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006)
  - **5)** Schizophrenia
    - **a)** 5 to 10 mg/day orally with a target dose of 10 mg/day within several days; further dose adjustments shoul MAX dose is 20 mg/day (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disi
- **b)** Pediatric
  - **1)** safety and effectiveness in pediatric patients have not been established

3) Contraindications
- **a)** specific contraindications have not been determined (Prod Info ZYPREXA(R) oral tablets, orally disintegrating table

4) Serious Adverse Effects
- **a)** Cerebrovascular disease
- **b)** Death
- **c)** Diabetic ketoacidosis
- **d)** Status epilepticus
- **e)** Sudden cardiac death

5) Clinical Applications
- **a)** FDA Approved Indications
  - **1)** Agitation - Bipolar I disorder
  - **2)** Agitation - Schizophrenia
  - **3)** Bipolar I disorder, Acute mixed or manic episodes
  - **4)** Bipolar I disorder, Maintenance therapy
  - **5)** 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

Olanzapine

C) Physicochemical Properties

1) Molecular Weight

a) 312.44 (Prod Info Zyprexa(R), 2004)

2) Solubility

a) Practically insoluble in water (Prod Info Zyprexa(R), 2004)

1.2 Storage and Stability

A) Preparation

1) Intramuscular route

a) For intramuscular use only. Do not administer intravenously or subcutaneously (Prod Info ZYPREXA(R) ir 2004).

b) For the preparation of solution for intramuscular injection containing approximately 5 milligrams/milliliter (r supplied vial using 2.1 mL of Sterile Water for Injection. The resulting solution should appear clear and yellow (within 1 hour) after reconstitution and any unused portion should be discarded (Prod Info ZYPREXA(R) injec

2) Oral route

a) Orally Disintegrating Tablets

1) For administration of orally disintegrating tablets, peel back foil on blister pack to expose tablet; do N hands to remove the tablet from the blister unit and immediately place the entire tablet in the mouth. Tab swallowed with or without liquid (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular C

B) Oral route

1) Store at controlled room temperature, 20 to 25 degrees C (68 to 77 degrees F) (Prod Info Zyprexa(R), Zyprexa Olanzapine, 2004a). Protect from light and moisture

C) Extemporaneous Formulation - Oral route

1) Olanzapine is practically insoluble in water. A 1-milligram per milliliter (mg/mL) suspension prepared from crus syrup, carboxymethylcellulose and parabens) was found to be stable for 14 days when stored in a refrigerator and preparation and administration is advised as olanzapine may be irritating to the eye and can cause contact derma it is recommended to wear gloves and wash hands before and after exposure (Personal Communication, 2001).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

Dosage in Other Disease States

1.3.1 Normal Dosage

Intramuscular route

Oral route

Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

Parkinson's disease - Psychotic disorder

1.3.1.A Intramuscular route

Agitation - Bipolar I disorder

Agitation - Schizophrenia

1.3.1.A.1 Agitation - Bipolar I disorder

a) The recommended intramuscular dose for the treatment of agitation associated with bipolar mania is may be used when clinically indicated. Efficacy of intramuscular olanzapine has been demonstrated in a ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006).

b) The efficacy of repeated doses of intramuscular olanzapine in agitated patients has not been evaluat persists after the initial dose and additional intramuscular doses are warranted, subsequent doses up to total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the init not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (ie, three 10 mg doses a with an increased risk of orthostatic hypotension. It is recommended that patients requiring subsequent i hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injectior patient with a clinically significant postural change in systolic blood pressure. If ongoing olanzapine thera a range of 5 to 20 mg/day as soon as clinically appropriate (Prod Info ZYPREXA(R) oral tablets, IM injec tablets, 2006).

c) Intramuscular olanzapine for injection is intended for intramuscular use only; do NOT administer intra into the muscle mass (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally di

1.3.1.A.2 Agitation - Schizophrenia

a) The recommended intramuscular dose for the treatment of agitation associated with schizophrenia is mg may be used when clinically indicated. Efficacy of intramuscular olanzapine has been demonstrated ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006).

b) The efficacy of repeated doses of intramuscular olanzapine in agitated patients has not been evaluat persists after the initial dose and additional intramuscular doses are warranted, subsequent doses up to total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the init not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (ie, three 10 mg doses a with an increased risk of orthostatic hypotension. It is recommended that patients requiring subsequent i hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injectior patient with a clinically significant postural change in systolic blood pressure. If ongoing olanzapine thera a range of 5 to 20 mg/day as soon as clinically appropriate (Prod Info ZYPREXA(R) oral tablets, IM injec tablets, 2006).

c) Intramuscular olanzapine for injection is intended for intramuscular use only; do NOT administer intra into the muscle mass (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally di

1.3.1.B Oral route

Agitation - Bipolar I disorder

Agitation - Schizophrenia

Bipolar I disorder, Acute mixed or manic episodes

Bipolar I disorder, Maintenance therapy

Schizophrenia

1.3.1.B.1 Agitation - Bipolar I disorder

a) In one study, rapid initial dose escalation of oral olanzapine was effective in the treatment of acute ag disorder. Investigators used a dosing regimen of 20 to 40 milligrams (mg)/day for 2 days, then 20 to 30 n days. Also effective was the more conventional dosing regimen of olanzapine 10 mg daily with adjunctive olanzapine 5 to 20 milligrams for 3 days (Baker et al, 2003).

1.3.1.B.2 Agitation - Schizophrenia

a) In one study, rapid initial dose escalation of oral olanzapine was effective in the treatment of acute ag disorder. Investigators used a dosing regimen of 20 to 40 milligrams (mg)/day for 2 days, then 20 to 30 n days. Also effective was the more conventional dosing regimen of olanzapine 10 mg daily with adjunctive olanzapine 5 to 20 milligrams for 3 days (Baker et al, 2003).

1.3.1.B.3 Bipolar I disorder, Acute mixed or manic episodes

a) Monotherapy

1) In clinical trials evaluating the short-term (3 to 4 weeks) effects of olanzapine in acute mania, effi to 20 mg daily. The recommended initial dosage of olanzapine is 10 or 15 milligrams (mg) once daily less than 24 hours, by 5 mg daily. Doses above 20 mg/day have not been evaluated for safety in cli

injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006).

b) Combination Therapy

1) In clinical trials evaluating the short-term (6 weeks) effects of olanzapine in acute mania, efficacy (mg) daily. The recommended initial dosage of olanzapine in combination with lithium or valproate is not been evaluated for safety in clinical trials (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R

1.3.1.B.4 Bipolar I disorder, Maintenance therapy

a) Monotherapy

1) Bipolar patients responding to initial olanzapine therapy for an average period of two weeks have monotherapy at a dose of 5 to 20 milligrams/day. The long-term usefulness of olanzapine for the ind olanzapine is used for extended periods of time (Prod Info ZYPREXA(R) oral tablets, IM injection, Z 2006).

1.3.1.B.5 Schizophrenia

a) Initial dosages are 5 to 10 milligrams administered on a once-a-day schedule without regard to meals several days of initiation of therapy is recommended. If dosage adjustments are needed, decrease or inc adjustments should typically occur at intervals of not less than 1 week (Prod Info ZYPREXA(R) oral table disintegrating tablets, 2006).

b) In clinical trials, antipsychotic efficacy occurred at a dosage range of 10 to 15 milligrams/day. Doses a be more efficacious than the 10 milligrams/day dose. The safety of doses above 20 milligrams/day has n ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006).

c) Effective doses of olanzapine in the treatment of schizophrenia have ranged from 7.5 to 40 milligrams al, 1996)(Beasley et al, 1996aa; Anon, 1994b; Anon, 1994aa). Clinical trials have shown that 10 milligrar dose may have greater efficacy in relieving negative symptoms; further studies are needed (Nemeroff, 1

1.3.1.C Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

See Drug Consult reference: CHEMOTHERAPY AND RADIOTHERAPY TREATMENT GUIDELINES FOR N

1.3.1.D Parkinson's disease - Psychotic disorder

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

1.3.1.E Switching to Olanzapine

1) Schizophrenic and schizophreniform patients may be successfully transitioned from clozapine to olanzapi a stable dose of clozapine (Henderson et al, 1998). Olanzapine is increased by 2.5 to 5 mg weekly to a maxi doses should be gradually decreased by increments of 25 to 50 mg per week.

2) Switching patients to olanzapine from conventional antipsychotic therapy or risperidone was most succes implemented at the full therapeutic dose and other antipsychotics were gradually discontinued. In a study of 2 schizophrenia or schizoaffective disorder, 4 treatment strategies were used. Patients were randomized to unc antipsychotic drug and immediate or stepwise initiation of olanzapine. Olanzapine was administered in doses stepwise fashion (1 week of placebo, followed by 1 week of olanzapine 5 mg daily and then 1 week of olanza assessed using the Clinical Global Impressions (CGI) Improvement scale, Patient's Global Impressions (PGI) Syndrome Scale (PNSS). These scoring systems showed that immediate initiation of olanzapine with gradua the safest and most effective approach. However, all strategies were effective; by week 3, the majority of pati clinically unchanged without increased risk of relapse or of drug withdrawal symptoms. Patients who abruptly gradually implemented olanzapine had a significantly greater incidence of sleep disorders than those using o more often in when antipsychotic medication was abruptly discontinued with immediate implementation of ola et al, 2000).

1.3.2 Dosage in Renal Failure

A) Patients with renal impairment DO NOT require a dosage adjustment. The pharmacokinetic parameters were impairment and normal patients. Only 7% of olanzapine is excreted in the urine as unchanged drug (Prod Info Zyp IntraMuscular Olanzapine, 2004b). However, a lower initial dose of 5 milligrams daily should be considered (Prod

1.3.3 Dosage in Hepatic Insufficiency

A) Olanzapine is extensively metabolized, however, no change in dosage is needed. In patients with significant li A and B), little effect was seen on the pharmacokinetics of olanzapine (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R

1.3.4 Dosage in Geriatric Patients

A) Caution should be used when oral olanzapine is administered to the elderly, especially if there are other factor pharmacodynamic parameters (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine

B) The recommended intramuscular dose for elderly patients is 5 milligrams per injection (Prod Info Zyprexa(R) I

1.3.5 Dosage Adjustment During Dialysis

A) Hemodialysis

1) Olanzapine is not removed by dialysis (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMusc

B) Peritoneal Dialysis

1) Olanzapine is not removed by dialysis (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMusc

1.3.6 Dosage in Other Disease States

A) Special Populations
1) The recommended starting oral dose is 5 milligrams in the following populations: patients who are debilita
reactions, who exhibit a combination of factors that may cause a slower metabolism of olanzapine (eg, nonsn
pharmacodynamically sensitive to olanzapine (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraM
2) The recommended intramuscular dose is 2.5 milligrams per injection for patients who are debilitated, have
be pharmacodynamically sensitive to olanzapine (Prod Info Zyprexa(R) IntraMuscular, 2004).
3) No dosage modification is needed but the manufacturer reports that the clearance of olanzapine is 30% lo
Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).
4) No dosage modification is needed but the manufacturer reports that the clearance of olanzapine is 40% h
Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).
5) The combined effects of age, smoking, and gender could cause substantial pharmacokinetic differences in
male smokers may be 3 times higher than that in elderly nonsmoking females (Prod Info Zyprexa(R), Zyprexa
Olanzapine, 2004b). Age over 65, gender, or smoking status alone does NOT require dosage modification.

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.A Anorexia nervosa
See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration
A) Onset
1) Initial Response
a) Schizophrenia: 1 week (Beasley et al, 1996).

2.2 Drug Concentration Levels
A) Therapeutic Drug Concentration
1) Schizophrenia, greater than 9 ng/ml (Perry et al, 1997).
a) In acutely schizophrenic patients receiving olanzapine (n=79), 45% of patients with a trough level above 9
versus only 15% of patients with concentrations less than 9.3 ng/ml responding (Perry et al, 1997).
B) Time to Peak Concentration
1) Oral: 6 hours (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004). Oral:
(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).
a) In an open-label, inpatient trial involving 8 patients (ages 10 to 18 years) receiving olanzapine 2.5 to 20 m
plasma concentration was 115.6 +/- 26.7 nanograms/milliliter. The mean time to maximum concentration was
these adolescent patients are similar to the concentrations observed in nonsmoking adult patients being treat
twice the average concentrations in smokers (Grothe et al, 2000).
2) Intramuscular: 15 to 45 minutes (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanza

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability
1) Oral: Well-absorbed (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2
a) Extensively eliminated by first-pass metabolism; 40% of dose metabolized before reaching systemic
(R), Zyprexa(R) IntraMuscular Olanzapine, 2004; Bever & Perry, 1998a).
B) Effects of Food
1) None (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).

2.3.2 Distribution
A) Distribution Sites
1) Protein Binding
a) 93% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).
1) The primary binding sites are albumin and alpha-1- acid glycoprotein (Prod Info Zyprexa(R), Zyp
Olanzapine, 2004).
B) Distribution Kinetics
1) Volume of Distribution
a) 1000 L (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004).

2.3.3 Metabolism
A) Metabolism Sites and Kinetics
1) Liver, extensively metabolized (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Ola
a) The primary metabolic pathways for olanzapine are direct glucuronidation and oxidation mediated by
monooxigenase system. CYP2D6 appears to be a minor pathway (Prod Info Zyprexa(R), Zyprexa(R) Zy
2004).
b) Forty percent is metabolized via first pass metabolism (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Z
B) Metabolites
1) 10-N-glucuronide, (inactive) (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanz
2) 4'-N-desmethyl olanzapine, (inactive) (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscu

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
a) 57% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004; Anon
B) Total Body Clearance
1) 26.1 L/hr (Kando, 1997).
a) Clearance ranges from 12 to 47 L/hour (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) Intra
b) In 8 pediatric and adolescent patients (ages 10 to 18 years) receiving 2.5 to 20 milligrams olanzapine
9.6 +/- 2.4 liters/hour (Grothe et al, 2000).
C) Other
1) OTHER EXCRETION
a) Feces, 30% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
a) 21 to 54 hours (mean = 30 hours) (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMusc
1) In 8 pediatric and adolescent patients (ages 10 to 18 years) receiving 2.5 to 20 milligrams olanza
life was 37.2 +/- 5.1 hours (Grothe et al, 2000).
2) Although the mean elimination half-life of olanzapine is prolonged in the elderly (young patients:
renal clearance is reduced from 18.2 Liters/hour (L/h) in the young to 17.5 L/h in those 65 years and
than in young patients. Thus, a dose reduction is not necessary in otherwise healthy elderly patients

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING
1) Intramuscular (Powder for Solution)

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of d
trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of d
times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the ra
4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, mos
cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studie
drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findin
may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. C
patients with dementia-related psychosis (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM

2) Oral (Tablet; Tablet, Disintegrating)

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drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findin
may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. C
patients with dementia-related psychosis (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM

3.1 Contraindications

A) specific contraindications have not been determined (Prod Info ZYPREXA(R) oral tablets, orally disintegrating table

3.2 Precautions

A) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attri
sudden death) or infections (eg, pneumonia) (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injec
B) elderly patients with dementia-related psychosis (unapproved use); cerebrovascular events (eg, stroke, transient is
(Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 2009)
C) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration,
increased risk of orthostatic hypotension (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection
D) concomitant use of parenteral benzodiazepine and intramuscular olanzapine is not recommended (Prod Info ZYPF
IM injection, 2009)
E) conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehy
disrupt body temperature regulation (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 200
F) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia (Prod Info ZYPREXA(
injection, 2009)
G) diseases or conditions affecting hemodynamic response, preexisting (Prod Info ZYPREXA(R) oral tablets, orally di
H) elderly patients, especially elderly women, are at increased risk of tardive dyskinesia (Prod Info ZYPREXA(R) oral
2009)
I) glaucoma, narrow angle; condition may be exacerbated due to anticholinergic properties (Prod Info ZYPREXA(R) o
2009)
J) hepatic impairment, significant, preexisting conditions associated with limited hepatic functional reserve, or concom
hepatic impairment (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 2009)
K) hyperglycemia (some extreme cases associated with ketoacidosis or hyperosmolar coma or death) has been repo
disintegrating tablets, IM injection, 2009)
L) hyperlipidemia, hypercholesterolemia, and significantly elevated triglycerides have been reported (Prod Info ZYPRI
injection, 2009)
M) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info ZYPI
IM injection, 2009)
N) neuroleptic malignant syndrome, potentially fatal; has been reported in association with olanzapine therapy; immed
oral tablets, orally disintegrating tablets, IM injection, 2009)
O) paralytic ileus, history; condition may be exacerbated due to anticholinergic properties (Prod Info ZYPREXA(R) ora
2009)
P) prostatic hypertrophy; condition may be exacerbated due to anticholinergic properties (Prod Info ZYPREXA(R) ora
2009)
Q) seizure disorder, history, or conditions that may lower seizure threshold; may increase seizure risk (Prod Info ZYPI
IM injection, 2009)
R) tardive dyskinesia, potentially irreversible, may occur (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tab

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Hepatic Effects

Immunologic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Renal Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Bradyarrhythmia

Chest pain

Hypertension

Hypotension

Orthostatic hypotension

Peripheral edema

Sudden cardiac death

Tachyarrhythmia

3.3.1.A Bradyarrhythmia

1) A 24-year-old, healthy, non-smoking, woman volunteer experienced hypotension (70/30 mmHg) and brad
taking a single oral dose of olanzapine 5 mg. Lying down with feet elevated brought both pulse and blood pre
The maximum plasma concentration of olanzapine in this subject (13 nanograms/mL) was unusually high and
reported range for Tmax (5 to 6 hours). Her Cmax was in the range expected for a single dose of 10 to 15 mg

3.3.1.B Chest pain

1) Incidence: 3% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a)
2) Chest pain has been reported in 3% of patients treated with olanzapine (Prod Info Zyprexa(R), Zyprexa(R
2004a).

3.3.1.C Hypertension

1) Incidence: 2% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a)
2) Hypertension has been reported in 2% of patients treated with olanzapine (Prod Info Zyprexa(R), Zyprexa
Olanzapine, 2004a).

3.3.1.D Hypotension

1) A 24-year-old, healthy, non-smoking, woman volunteer experienced hypotension (70/30 mmHg) and brad
taking a single oral dose of olanzapine 5 mg. Lying down with feet elevated brought both pulse and blood pre
The maximum plasma concentration of olanzapine in this subject (13 nanograms/mL) was unusually high and
reported range for Tmax (5 to 6 hours). Her Cmax was in the range expected for a single dose of 10 to 15 mg

3.3.1.E Orthostatic hypotension

1) Incidence: 3% to 5% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine,
2) Postural hypotension has been reported in 3% to 5% of patients treated with olanzapine (Prod Info Zyprex
IntraMuscular Olanzapine, 2004a).
3) Orthostatic hypotension has been observed in greater than 5% of patients participating in olanzapine clini
beats per minute has been reported in clinical trials with tachycardia occurring in greater than 5% of the patie
orthostatic hypotensive changes (Bronson & Lindenmayer, 2000).
4) Small reductions in orthostatic blood pressure have been reported in olanzapine-treated patients during cl

3.3.1.F Peripheral edema

1) Incidence: 3% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a)
2) Peripheral edema has been reported in 3% of patients treated with olanzapine (Prod Info Zyprexa(R), Zyp
Olanzapine, 2004a).

3.3.1.G Sudden cardiac death

1) In a large, retrospective, cohort study that included a primary cohort of 93,300 users of antipsychotic drug
there was an increased risk of sudden cardiac death in adult participants 30 to 74 years of age (mean age of
to those who were not using antipsychotic drugs (incidence-rate ratio, 2.04; 95% confidence interval (CI), 1.5
treated with atypical antidepressants (clozapine, olanzapine, quetiapine, risperidone), the incidence-rate ratio
(95% CI, 1.03 to 2.46) for those using low doses to 2.86 (95% CI, 2.25 to 3.65) for those using high doses (p=

3.3.1.H Tachyarrhythmia

1) Incidence: 3% (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a)
2) Tachycardia has been reported in 3% of patients treated with olanzapine (Prod Info Zyprexa(R), Zyprexa(
2004a).

3.3.2 Dermatologic Effects

Dermatological finding

Sweating symptom

3.3.2.A Dermatological finding

1) Summary
a) A 36-year-old African-American man developed a PUSTULAR SKIN ERUPTION 2 weeks after begin
began on his face and spread to his hips and buttocks. One day later he developed ERYTHEMATOUS P
no lymphadenopathy or fever. Olanzapine was discontinued and warm compresses were applied. The e
1999).
2) Pustular eruptions, sweating and erythematous plaques are reported with olanzapine administration.

3.3.2.B Sweating symptom

1) Summary
a) The manufacturer reports that sweating has been associated with olanzapine therapy (Prod Info Zypr
IntraMuscular Olanzapine, 2004a).

3.3.3 Endocrine/Metabolic Effects

Diabetes mellitus

Diabetic ketoacidosis

Galactorrhea

Hypercholesterolemia

Hyperglycemia

Hypoglycemia

Hypothermia

Increased appetite

Increased body temperature

Metabolic syndrome

Prolactin level raised

Serum triglycerides raised

Summary

Weight gain

Weight loss

3.3.3.A Diabetes mellitus

1) Summary

a) Diabetic mellitus was reported infrequently (0.1% to 1%) in clinical trials (n=8661) representing 4165 multiple doses of oral olanzapine at doses 1 mg/day or more (Prod Info ZYPREXA(R) oral tablets, IM inj tablets, 2008).

b) As with other atypical antipsychotics, hyperglycemia has been reported in patients on olanzapine. Th nonfasting levels, from baseline to the average of the 2 highest serum concentrations was 15 mg/dL, dur Effectiveness in patients treated for a median olanzapine-exposure duration of 9.2 months. Olanzapine i difficult to assess the relationship because of an increased risk of diabetes mellitus in patients with schiz mellitus in the general population. In general, epidemiological studies show that atypical antipsychotics ir hyperglycemia. Olanzapine appears to have a greater risk of glucose abnormalities compared with other oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

c) The risks and benefits of olanzapine should be considered prior to prescribing in patients with an esta with borderline increased blood glucose levels (fasting 100 to 126 mg/dL or nonfasting 140 to 200 mg/dL recommended. For patients with risk factors for diabetes mellitus (obesity, family history of diabetes), fas initiation and periodically during olanzapine therapy. All patients should be monitored for signs and symp polyphagia, and weakness). Fasting blood glucose should be tested if symptoms of hyperglycemia devel discontinuation of olanzapine; however, some patients may continue to need antidiabetic therapy despite ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

2) Incidence: 0.1% to 1% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally di

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

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

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

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

7) Olanzapine-induced glucose dysregulation has been reported as an adverse effect, possibly due to drug-i with a severe exacerbation of type 2 diabetes in a 51-year-old woman with a major depressive disorder and s

with sertraline and haloperidol decanoate. After 4 weeks, sertraline was replaced by fluoxetine due to continu haloperidol was replaced by olanzapine due to persistent auditory and visual hallucinations. Prior to initiation well-controlled by diet (glycosylated hemoglobin 6.5%, baseline fasting blood glucose 89 to 132 mg/dL). Twe control diminished and continued to worsen despite treatment with glipizide, metformin, and diet. At week 26, due to inadequate antidepressant response. At week 35 (fasting blood glucose 120 to 461 mg/dL, glycosylate was initiated and titrated to 70 units per day. Olanzapine was tapered during weeks 39 and 40 and discontinu stopped, the patient's fasting blood glucose levels had decreased to within 85 and 163 mg/dL. By the time of units/day NPH 70/30 (Bettinger et al, 2000).

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

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

3.3.3.B Diabetic ketoacidosis

1) Summary

a) Diabetic acidosis was reported rarely (less than 0.1%) in clinical trials (n=8661) representing 4165 pa multiple doses of oral olanzapine at doses 1 mg/day or more (Prod Info ZYPREXA(R) oral tablets, IM inje tablets, 2008).

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

c) The risks and benefits of olanzapine should be considered prior to prescribing in patients with an esta with borderline increased blood glucose levels (fasting 100 to 126 mg/dL or nonfasting 140 to 200 mg/dL recommended. For patients with risk factors for diabetes mellitus (obesity, family history of diabetes), fas initiation and periodically during olanzapine therapy. All patients should be monitored for signs and symp polyphagia, and weakness). Fasting blood glucose should be tested if symptoms of hyperglycemia devel discontinuation of olanzapine; however, some patients may continue to need antidiabetic therapy despite ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

2) Incidence: less than 0.1% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orall

3) A case report described a near fatal case of olanzapine-induced ketoacidosis in a 44-year-old African Am for approximately one month (Straker et al, 2002).

4) Diabetic ketoacidosis following 3 months of olanzapine therapy was reported in a 31-year-old man with no was started on insulin and olanzapine was discontinued. Fifteen days later, his insulin requirements decrease has remained metabolically stable, free of diabetic symptoms (Gatta et al, 1999).

5) At least 25 fatalities have been reported in association with olanzapine-induced diabetic ketoacidosis (Tor Lindenmayer & Patel, 1999).

6) A 50-year-old African American man developed diabetic ketoacidosis after receiving 8 months of olanzapi olanzapine 30 mg daily with divalproex 750 mg twice daily. He began insulin therapy and after olanzapine wa (Lindenmayer & Patel, 1999).

7) A 39-year-old man developed diabetic ketoacidosis after receiving olanzapine 10 mg for a treatment-refra laboratory evidence of diabetes. His BMI was 40 kg/m(2). He was admitted with asthenia, polyuria, dehydrati His HbA1C was 14.7%. He was maintained on insulin 3 times daily. When olanzapine was discontinued, insu blood glucose and HbA1C became normal (Gatta et al, 1999).

3.3.3.C Galactorrhea

1) A case of galactorrhea with elevated serum prolactin levels was reported in a 33-year-old woman after rec treatment of schizophreniform disorder. During the fifth week of olanzapine therapy, the patient developed sp reported missing her menstrual period. Her serum prolactin level was 146.55 nanograms (ng)/mL (normal ran and replaced with quetiapine (25 to 100 mg/day). Symptoms of galactorrhea resolved within 3 weeks of stopp to decrease. Quetiapine therapy was continued without recurrence of galactorrhea (Mendhekar et al, 2004).

3.3.3.D Hypercholesterolemia

1) Summary

a) Increases in total cholesterol have been observed during treatment with olanzapine. The mean increa lipoprotein (LDL) from baseline were 5.3 mg/dL and 3 mg/dL, respectively, in olanzapine-treated patients mg/dL and 4.3 mg/dL, respectively, in placebo-treated patients (statistically significant), in an analysis of 12-weeks duration. There were no statistically significant differences between olanzapine-treated and pla lipoprotein cholesterol. Patients with lipid dysregulation at baseline experienced greater increases in fast compared to patients without these factors. Lipid dysregulation was defined as patients diagnosed with c treated with lipid-lowering agents, or patients with high baseline lipid levels. Baseline and follow-up lipid r olanzapine (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergatin

2) Incidence: up to 24% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

3) In an analysis of 5 placebo-controlled monotherapy studies of up to 12-weeks duration, the fasting total ch olanzapine-treated patients compared with up to 12% of placebo-treated patients. The fasting low density lipo approximately 24% of olanzapine-treated patients compared with up to 14% of placebo-treated patients. The

increase of fasting cholesterol and LDL cholesterol (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPRE 2008):

Fasting Total Cholesterol In Adults

Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 40 mg/dL or more	olanzapine	745	21.6% *
	placebo	402	9.5%
Increase from Normal (less than 200 mg/dL) to High (240 mg/dL or more)	olanzapine	392	2.8%
	placebo	207	2.4%
Increase from Borderline (200 mg/dL to less than 240 mg/dL) to High (240 mg/dL or more)	olanzapine	222	23% *
	placebo	112	12.5%
KEY: mg/dL = milligrams/deciliter; * = statistically significant compared to placebo			

Fasting Low-Density-Lipoprotein Cholesterol In Adults

Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 30 mg/dL or more	olanzapine	536	23.7% *
	placebo	304	14.1%
Increase from Normal (less than 100 mg/dL) to High (160 mg/dL or more)	olanzapine	154	0%
	placebo	82	1.2%
Increase from Borderline (100 mg/dL to less than 160 mg/dL) to High (160 mg/dL or more)	olanzapine	302	10.6%
	placebo	173	8.1%
KEY: mg/dL = milligrams/deciliter; * = statistically significant compared to placebo			

4) In an analysis of 3 placebo-controlled monotherapy studies of up to 6 weeks duration in adolescents, the f approximately 39% of olanzapine-treated patients compared with up to 8% of placebo-treated patients. The f in up to approximately 49% of olanzapine-treated patients compared with up to 11% of placebo-treated patie degree of increase of fasting total cholesterol and LDL cholesterol (Prod Info ZYPREXA(R) oral tablets, IM in disintergating tablets, 2008):

Fasting Total Cholesterol In Adolescents

Category Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 40 mg/dL or more	olanzapine	138	14.5% *
	placebo	66	4.5%
Increase from Normal (less than 170 mg/dL) to High (200 mg/dL or more)	olanzapine	87	6.9%
	placebo	43	2.3%
Increase from Borderline (170 mg/dL to less than 200 mg/dL) to High (200 mg/dL or more)	olanzapine	36	38.9% *
	placebo	13	7.7%
KEY: mg/dL = milligrams/deciliter; * = statistically significant compared to placebo			

Fasting Low-Density-Lipoprotein Cholesterol In Adolescents

Category Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 30 mg/dL or more	olanzapine	137	17.5%
	placebo	63	11.1%
Increase from Normal (less than 110 mg/dL) to High (130 mg/dL or more)	olanzapine	98	5.1%
	placebo	44	4.5%
Increase from Borderline (110 mg/dL to less than 130 mg/dL) to High (130 mg/dL or more)	olanzapine	29	48.3% *
	placebo	9	0%
KEY: mg/dL = milligrams/deciliter; * = statistically significant compared to placebo			

5) Random cholesterol levels of 240 mg/dL or more has been reported during postmarketing reports (Prod Ir ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

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

7) After an average of 16 months of olanzapine therapy, 9 patients had marked increases in triglyceride leve 170 mg/dL to a mean of 240 mg/dL. Five patients had at least a 50% increase in levels. Cholesterol levels re mean weight gain of 10 kg (Sheitman et al, 1999).

3.3.3.E Hyperglycemia

1) Summary

a) As with other atypical antipsychotics, hyperglycemia has been reported in patients on olanzapine. Th nonfasting levels) from baseline to the average of the 2 highest serum concentrations was 15 mg/dL, du Effectiveness in patients treated for a median olanzapine-exposure duration of 9.2 months. Olanzapine i difficult to assess the relationship because of an increased risk of diabetes mellitus in patients with schiz

mellitus in the general population. In general, epidemiological studies show that atypical antipsychotics ir hyperglycemia. Olanzapine appears to have a greater risk of glucose abnormalities compared with other oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

b) The risks and benefits of olanzapine should be considered prior to prescribing in patients with an esta with borderline increased blood glucose levels (fasting 100 to 126 mg/dL or nonfasting 140 to 200 mg/dL recommended. For patients with risk factors for diabetes mellitus (obesity, family history of diabetes), fas initiation and periodically during olanzapine therapy. All patients should be monitored for signs and symp polyphagia, and weakness). Fasting blood glucose should be tested if symptoms of hyperglycemia devel discontinuation of olanzapine; however, some patients may continue to need antidiabetic therapy despite ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

2) Incidence: 0.1% to 17.4% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orall

3) The mean increases in fasting glucose levels were 2.76 mg/dL in olanzapine-treated adults compared witl analysis of 5 placebo-controlled trials of adults treated with monotherapy olanzapine up to 12 weeks. Patients were patients with glucose dysregulation at baseline defined as: diagnosis with diabetes mellitus or related a baseline random glucose concentrations of 200 mg/dL or greater, and/or a baseline fasting glucose level of 1 glucose levels (less than 100 mg/dL) and baseline borderline fasting glucose levels (100 mg/dL or greater an 2.2% (n=543) and 17.4% (n=178), respectively, had high glucose levels of 126 mg/dL or greater. In comparis of the placebo-treated patients had high glucose levels (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYI 2008).

4) The mean changes in fasting glucose levels were an increase of 2.68 mg/dL in olanzapine-treated adoles placebo-treated children (statistically significant), in an analysis of 3 placebo-controlled trials of adolescents t of 6 weeks in schizophrenia trials or 3 weeks in bipolar disorder trials. In adolescents with normal fasting gluc borderline fasting glucose levels (100 mg/dL to less than 126 mg/dL) treated with olanzapine, 0% (0 out of 12 glucose levels of 126 mg/dL or greater. In comparison, 1.9% (1 out of 53) and 0% (0 out of 13), respectively, levels (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets,

5) Hyperglycemia was reported infrequently (0.1% to 1%) in clinical trials (n=8661) representing 4165 patien doses of oral olanzapine at doses 1 mg/day or more (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPR 2008).

6) An 89-year-old man with a two-year history of mixed dementia with psychosis and behavioral disturbance olanzapine for psychotic symptoms and agitation. The patient received olanzapine 2.5 mg twice daily for 2 da increase, fasting glucose levels had increased from a baseline of 114 mg/dL to 138 mg/dL, with a fasting fing patient also experienced worsening renal function, including increased BUN (37 to 45 mg/dL) and creatinine to 125 mg/dL 2 days after discontinuing olanzapine and starting aripiprazole 5 mg/day. Due to worsening agit 2.5 mg twice daily and the hyperglycemia returned, with fasting blood glucose levels increasing from 97 mg/d discontinuation, fasting blood glucose levels returned to normal (104 mg/dL) (Kohen et al, 2008).

7) A 15-year-old African American boy developed hyperglycemia, along with weight gain and hypertriglyceric behavior disorders. At baseline, when the boy had been taking olanzapine for 3 months and valproic acid for normal ranges. His BMI was 28.7 kg/m(2). Four months later, buspirone was added to his treatment. Within 2 Three months later, he had experienced weight loss (BMI=27.5 kg/m(2)) and developed polyuria and polydips Olanzapine was discontinued. Without hypoglycemic drugs, insulin treatment, or dietary changes, his serum did his serum triglyceride and cholesterol levels. Twenty weeks after the discontinuation of olanzapine, his BM

3.3.3.F Hypoglycemia

1) Incidence: 0.1% to 1% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally di

2) Hypoglycemia was reported infrequently (0.1% to 1%) in clinical trials (n=8661) representing 4165 patient doses of oral olanzapine at doses 1 mg/day or more (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPR 2008).

3) Hypoglycemic coma was reported in a frail, 95-year-old woman following olanzapine administration for the associated with Alzheimer's dementia. Three days after the initiation of olanzapine at a dose of 2.5 mg daily, sleepy, and she could not be woken by verbal or tactile stimulation. She was treated with 33% glucose and re however, hypoglycemia was noted again the following day. Olanzapine was withdrawn and the blood glucose administration of 33% glucose. A direct cause and effect correlation could not be established because the pa been documented to possibly induce hypoglycemia. While a drug interaction between enalapril and olanzapir that there was a correlation between enalapril and hypoglycemia because the patient had been receiving ena et al, 2003).

3.3.3.G Hypothermia

1) Hypothermia developed in a 54-year-old hemodialysis patient with end-stage renal disease following the u day course of oral olanzapine 2.5 mg daily for the treatment of sudden-onset night delirium with visual halluci delirium resolved, but then reappeared 7 days later. He was given olanzapine again at the same dose for 10 medication, his body temperature suddenly decreased to less than 34 degrees Celsius. Hypothermia persiste administration, and did not resolve until 6 days after olanzapine was discontinued (Fukunishi et al, 2003).

3.3.3.H Increased appetite

1) Incidence: 24% (Tollefson et al, 1997a)

2) Excessive appetite was seen more commonly with olanzapine therapy than with haloperidol (24% vs 12.4 associated with a clinically significant greater increase in weight over haloperidol therapy (p less than 0.001). mass index was the predominant predictor of weight gain. Patients with a low pre-study body mass index wer

treatment. Treatment effect on weight change was consistent between male and female patients (Tollefson e

3.3.3.I Increased body temperature

1) Disruption of the body's ability to reduce core body temperature may occur with antipsychotic agents. Elev following therapeutic doses in clinical trials. Patients experiencing conditions that may contribute to an elevat strenuously, exposure to extreme heat, or dehydration) should use appropriate care (Prod Info ZYPREXA(R) orally disintergating tablets, 2008).

3.3.3.J Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.K Prolactin level raised

1) Summary

a) Prolactin levels are modestly-elevated and persist during treatment with olanzapine. The clinical signi however, galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients on pr elevating potential of olanzapine should be considered in patients with prolactin-dependent breast cance ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

b) A dose-related increase in prolactin elevation occurred in 31.2% to 61.1% of olanzapine-treated patie in an 8-week randomized, double-blind, fixed-dose study (n=599). Elevated prolactin levels (greater than 18.77 ng/mL in males) occurred in 31.2% in patients on 10 mg/day; 42.7% in patients on 20 mg/day; and significant differences between 10 mg/day and 40 mg/day and between 20 mg/day and 40 mg/day (Seab

2) Incidence: 31.2% to 61.1% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) ora

3) A case of galactorrhea with elevated serum prolactin levels was reported in a 33-year-old woman after rec treatment of schizophreniform disorder. During week 5 of olanzapine therapy, the patient developed spontane reported missing her menstrual period. Her serum prolactin level was 146.55 nanograms (ng)/mL (normal rar and replaced with quetiapine (25 to 100 mg/day). Symptoms of galactorrhea resolved within 3 weeks of stopp to decrease. Quetiapine therapy was continued without recurrence of galactorrhea (Mendhekar et al, 2004).

4) High dose olanzapine was associated with mild extrapyramidal symptoms (EPS), elevated serum prolactin an average weight gain of 8 kg in 8 men with schizophrenia and schizoaffective disorder. These patients, who risperidone or clozapine at adequate doses, were dosed with olanzapine 20 to 40 mg for a mean of 40 weeks

5) Olanzapine has produced small elevations in serum prolactin (about 0.1 to 0.2 nanomoles (nmol)/L), that a greater increases have occurred with haloperidol (Anon, 1994a; Beasley et al, 1996). Cases of unwanted pre conventional neuroleptic medications to olanzapine, possibly due to a normalization of prolactin levels and a 1998).

3.3.3.L Serum triglycerides raised

1) Summary

a) Elevations in serum triglycerides have been observed, at times a greater than 500 mg/dL increase, du increase in fasting triglyceride from baseline was 20.8 mg/dL in olanzapine-treated patients compared wi placebo-treated patients (statistically significant), in an analysis of 5 placebo-controlled monotherapy stu lipid dysregulation at baseline experienced greater increases in fasting triglyceride levels compared to pa was defined as patients diagnosed with dyslipidemia or related adverse events, patients treated with lipid lipid levels. Baseline and follow-up lipid monitoring of lipids is recommended in patients on olanzapine (P ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

2) Incidence: up to 40% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

3) In an analysis of 5 placebo-controlled monotherapy studies of up to 12-weeks duration, the fasting triglyce olanzapine-treated patients compared with up to 26% of placebo-treated patients. The table below provides t triglycerides (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating ta

Fasting Triglycerides In Adults

Category Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 50 mg/dL or more	olanzapine	745	39.6% *
	placebo	402	26.1%
Increase from Normal (less than 150 mg/dL) to High (200 mg/dL or more)	olanzapine	457	9.2%*
	placebo	251	4.4%
Increase from Borderline (150 mg/dL to less than 200 mg/dL) to High (200 mg/dL or more)	olanzapine	135	39.3% *
	placebo	65	20%
KEY: mg/dL = milligrams/deciliter; * = statistically significant compared to placebo			

4) In an analysis of 3 placebo-controlled monotherapy studies of up to 6 weeks duration in adolescents, the f approximately 60% of olanzapine-treated patients compared with up to 35% of placebo-treated patients. The increase of fasting triglycerides (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) ora

Fasting Triglycerides In Adolescents

Category Change from Baseline	Treatment Arm	N	Portion of Patients
Increase by 50 mg/dL or more	olanzapine	138	37% *
	placebo	66	15.2%
Increase from Normal (less than 150 mg/dL)	olanzapine	67	26.9%

to High (200 mg/dL or more)	placebo	28	10.7%
Increase from Borderline (150 mg/dL to less than 200 mg/dL) to High (200 mg/dL or more)	olanzapine	37	59.5%
	placebo	17	35.3%
KEY: mg/dL = milligrams/deciliter; * = statistically significant compared to placebo			

5) Random triglyceride levels of 1000 mg/dL or more has been reported during postmarketing reports (Prod ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

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

7) After an average of 16 months of olanzapine therapy, 9 patients had marked increases in triglyceride leve 170 mg/dL to a mean of 240 mg/dL. Five patients had at least a 50% increase in levels. Cholesterol levels re mean weight gain of 10 kg (Sheitman et al, 1999).

3.3.3.M Summary

1) In clinical trials of olanzapine, diabetes mellitus (0.1% to 1%), diabetic ketoacidosis (0.1%), elevated serur to 24%), hyperglycemia (0.1% to 17.4%), hypoglycemia (0.1% to 1%), increased body temperature, and weig ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008). There hav and diabetic ketoacidosis following olanzapine use. Elevated prolactin levels have been observed in case rep clinical trials (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating ta trial of 22 patients where olanzapine orally disintegrating tablets were substituted for standard oral tablets, sig Luxton-Andrew, 2008). In a trial comparing haloperidol and olanzapine, increased appetite was reported at a (Tollefson et al, 1997a). A case report described galactorrhea (not associated with childbirth) in a female pati 2004). A case of hypothermia was reported in a 54-year-old man with end-stage renal disease. The hypother (Fukunishi et al, 2003).

3.3.3.N Weight gain

1) Summary

a) Weight gain (greater than 7% of their baseline weight) occurred in 56% of patients treated with olanza with an average weight gain of 5.4 kg. Regular monitoring of weight should be performed. Before initiatin potential consequences of weight gain (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) Z

2) Incidence: up to 57% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

3) An average weight gain of 2.6 kg in olanzapine-treated patients compared with a loss of 0.3 kg in placebo observed in an analysis of 13 monotherapy trials with a median exposure of 6 weeks. After a median duration compared with 3% of placebo-treated patients (statistically significant) gained at least 7% of their baseline we olanzapine-treated compared with 0.3% of placebo-treated patients (statistically significant) gained at least 15 index did not make a difference in the amount gained. The discontinuation rate due to weight gain was 0.2% patients, respectively. The table below provides the weight gain observed in olanzapine-treated patients from tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008) :

Amount Gained	6 weeks	6 months	12 months	24 months
	n=2976	n=1536	n=778	n=442
0 kg gain or weight loss	27%	21%	20%	22%
0 to 5 kg (0 to 11 lb)	57%	34%	25%	22%
5 to 10 kg (11 to 22 lb)	15%	26%	25%	22%
10 to 15 kg (22 to 23 lb)	2%	12%	16%	18%
greater than 15 kg (greater than 33 lb)	0%	6%	14%	16%
Key: kg = kilograms; lb = pounds				

4) An average weight gain of 4.6 kg in olanzapine-treated adolescents and 0.3 kg in placebo-treated adolesc analysis of 4 placebo-controlled trials of adolescents (ages 13 to 17 years) treated with monotherapy olanzap or 3 weeks in bipolar disorder trials. After a median duration of 4 weeks, 40.6% of olanzapine-treated compar (statistically significant) gained at least 7% of their baseline weight. After a median duration of 19 weeks, 7.1% placebo-treated patients gained at least 15% of their baseline weight. Baseline body mass index (BMI) did no however, mean changes in weight were greater in adolescents with BMI above normal at baseline. The disco in the olanzapine and placebo treated patients, respectively. .(Prod Info ZYPREXA(R) oral tablets, IM injectio tablets, 2008).

5) Weight gain was more frequent compared to placebo during short-term trials (6 weeks) of monotherapy ol in combination with lithium or valproate. The frequency of weight gain was 6% and 1% in olanzapine-treated (n=118), respectively, in 6-week, placebo-controlled schizophrenia trials. The frequency of weight gain was 5 and placebo-treated patients (n=294), respectively, in short-term, placebo-controlled clinical trials. When use frequency was 26% and 7% in olanzapine-treated patients (n=229) and placebo-treated patients (n=115), res bipolar mania trials of 6 weeks duration. (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYD

6) A dose-related increase in weight gain of 1.9 kg to 3 kg occurred in olanzapine-treated patients with schiz randomized, double-blind, fixed-dose study (n=599). The mean baseline-to-endpoint increase in weight was 1 on 20 mg/day, and 3 kg in patients on 40 mg/day. There were statistically significant differences among the 3

IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).
7) Adolescent patients taking olanzapine experienced greater weight gain and increased in body mass index retrospective study involving 103 patients younger than 18 years of age. Patients received olanzapine (n=50, mean daily dose 510.9 mg) for at least 2 weeks. Weight and height were measured at baseline and 14 or mo baseline in the olanzapine group was 3.8 kg (p less than 0.001) compared to 0.03 kg in the quetiapine group. showed slight, but significant, increases in height from baseline (0.006 meters, p=0.042 and 0.006 meters, p baseline differences, the mean weight change between groups was significant (3.4 kg, p less than 0.001). BM olanzapine group (p less than 0.001) compared to a decrease of 0.2 kg/m(2) in the quetiapine group. After co difference in change in BMI was significant (0.9 kg/m(2), p=0.008) (Patel et al, 2004).
8) Excessive appetite was seen more commonly with olanzapine therapy than with haloperidol (24% versus also associated with a clinically significant greater increase in weight over haloperidol therapy (p less than 0.0 body mass index was the predominant predictor of weight gain. Patients with a low pre-study body mass inde olanzapine treatment. Treatment effect on weight change was consistent between male and female patients
9) In a continuing day-treatment program, 15 out of 16 patients receiving olanzapine gained weight. The mea olanzapine dose of 14 mg and mean treatment duration of 7 months (Gupta et al, 1999).
10) A prospective, multicenter, observational study showed that olanzapine treatment of outpatients (n=2128 group of patients (n=821) receiving a variety of other antipsychotic drug therapies. Drugs used in the control zuclopenthixol, fluphenazine, thioridazine, perphenazine, pimozide, clozapine, pipotiazine, sulpiride, chlorpro lorazepam. Overall, olanzapine had a significantly lower incidence of adverse events than the control group (weight gain occurred significantly more frequently in olanzapine-treated patients. Over a 6-month period, few concomitant anticholinergic medication in comparison to patients in the control group (36% vs 58%, p less tha

3.3.3.O Weight loss

1) Weight loss was reported when the formulation of olanzapine was changed from standard oral tablets (SO open-label, prospective study of 22 adult patients with schizophrenia and a BMI of 25 kg/m(2) or greater who relapses requiring hospitalization within 3 months of study recruitment and no changes in medication required minimum of 1 year. Olanzapine ODT (mean dose of 13.9 mg) was substituted for SOT. Participants' weights months. At 3, 6, and 12 months, the mean changes in weight compared with baseline were -2.5 +/- 0.8 kg (p= kg (p=0.01), respectively. At 12 months, the average decrease in BMI was 1 +/- 0.3 kg/m(2) (p=0.001) and th Patients who received a 20-mg or greater dose of olanzapine ODT lost a greater percentage of their body we less than 20 mg (5.6 +/- 1.2% vs 1.9 +/- 0.9%; p=0.04). (Chawla & Luxton-Andrew, 2008).

3.3.4 Gastrointestinal Effects

Constipation

Excessive salivation

Gastrointestinal tract finding

Nausea and vomiting

Pancreatitis

Xerostomia

3.3.4.A Constipation

1) Summary
a) The manufacturer reports that constipation (9-11%) has occurred with olanzapine therapy (Prod Info IntraMuscular Olanzapine, 2004a). A relatively common adverse gastrointestinal effect of olanzapine is c which appears to be dose-related (Anon, 1995); (Beasley et al, 1996). In patients receiving a mean of 12 incidences of constipation were 8% and 15% (Beasley et al, 1996). The incidence of constipation with ol greater than observed with haloperidol 10 to 20 mg daily (Beasley et al, 1996). Anticholinergic effects, wh effects of olanzapine therapy (Isbister et al, 2001); (Beasley et al, 1996)(Prod Info Zyprexa(R), Zyprexa(R 2004a).
2) Incidence: 5-6%

3.3.4.B Excessive salivation

1) Summary
a) Hypersalivation has occurred with olanzapine therapy. A 20-year-old woman experienced morning gr sleep while receiving olanzapine 10 milligrams/day (mg/d). Her symptoms worsened with an increased d salivation has been reported in premarketing clinical trials and in an accidental pediatric ingestion (Prod IntraMuscular Olanzapine, 2004a; Yip & Graham, 1997).

3.3.4.C Gastrointestinal tract finding

1) Summary

a) The manufacturer reports that INCREASED SALIVATION, THIRST and DYSPEPSIA (7-11%) have o DYSMOBILITY has been associated with antipsychotic therapy. (Prod Info Zyprexa(R), Zyprexa(R) Zydis 2004a). Dyspepsia is not dose-related. (Beasley et al, 1996). ANTICHOLINERGIC EFFECTS, including adverse effects of olanzapine therapy. These effects are dose-related (Isbister et al, 2001); (Beasley et a also been one case report of acute hemorrhagic pancreatitis (Doucette et al, 2000).

2) The manufacturer reports that constipation, increased salivation, vomiting, thirst, dry mouth, dyspepsia, ar Dry mouth and nausea appear to be dose-related. Esophageal dysmobility has been associated with antipsy

3.3.4.D Nausea and vomiting

1) Summary

a) Vomiting (4%) and nausea (greater than or equal to 2%) have occurred with olanzapine therapy. Nau nausea tends to increase with dose (2% with 12 milligrams (mg) daily, 9% with 16 mg daily) and in highe observed with haloperidol 10 to 20 mg daily (Beasley et al, 1996)(Prod Info Zyprexa(R), Zyprexa(R) Zydi 2004a).

3.3.4.E Pancreatitis

1) Summary

a) ACUTE HEMORRHAGIC PANCREATITIS has been reported as a probable adverse event of olanza onset of symptoms. Other concomitant drugs were ruled out as contributing to pancreatitis. Death due to case (Doucette et al, 2000). This is a rare adverse effect of olanzapine.

b) In one study of reported cases (n=192) of antipsychotic-induced pancreatitis, 33% of the cases were daily dose of 15 milligrams. In most patients, time to onset of pancreatitis was within 6 months after initia

c) Olanzapine was the probable cause of acute hemorrhagic pancreatitis in a 72-year-old female admitt verapamil overdose. Past medical history included multiple sclerosis, left temporal cerebral infarct (2 wee and drug abuse. Prior to admission she was taking ketorolac, morphine, and temazepam. Olanzapine (5 prior to admission for recent cognitive decline. The patient's chief complaint of abdominal pain began 24 ingested 10 of her husband's verapamil 240 mg sustained release tablets. Laparotomy revealed hemorrh patient died due to peritonitis related to pancreatitis. Using the Naranjo Probability Scale, olanzapine was pancreatitis in this patient (Doucette, 2000). Other authors have pointed out possible discrepancies in th medications and chronic alcoholism which they believe could have contributed to the acute pancreatitis (

3.3.4.F Xerostomia

1) Summary

a) The manufacturer reports that dry mouth (9-22%) has occurred with olanzapine therapy. Dry mouth a Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). A relatively common adverse gastr (secondary to anticholinergic activity), which appears to be dose-related (Anon, 1995); (Beasley et al, 19 (mg) daily and 16 mg daily, respective incidences of dry mouth were 5% and 13% (Beasley et al, 1996). higher doses (12.5 to 17.5 mg daily) is greater than observed with haloperidol 10 to 20 mg daily (Beasley dry mouth, are common adverse effects of olanzapine therapy (Isbister et al, 2001); (Beasley et al, 1996 Zyprexa(R) IntraMuscular Olanzapine, 2004a).

2) Incidence: 5-15%

3.3.5 Hematologic Effects

Agranulocytosis

Leukopenia

Neutropenia

Pancytopenia

3.3.5.A Agranulocytosis

1) Summary

a) Agranulocytosis has not been reported with administration of olanzapine either during clinical studies was given to the hematologic parameters during premarketing studies of olanzapine and no evidence of ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 2007).

b) Unlike clozapine, a structurally related drug, olanzapine has not been shown in preclinical trials to ca 1997a); (Beasley et al, 1996)(Anon, 1994a; Anon, 1995). However, due to the structural similarities of th hematologic reactions. Subsequently, however, there have been reports of agranulocytosis with olanzap (Fachinfo, Zyprexa(R), 1998)(Naumann et al, 1999). There have also been several cases of olanzapine clozapine-induced granulocytopenia reported (Konakanchi et al, 2000).

2) LITERATURE REPORTS

a) Fifteen days after starting olanzapine (5 milligrams daily), a 46-year-old male presented to the hospita concurrently taking cyanamide. A white blood cell count of 0.5 x 10(9)/liter (L) with a neutrophil count of (cyanamide were stopped and antibiotic therapy was initiated. By the sixth hospital day, his white blood c between olanzapine therapy and new onset agranulocytosis was noted (Tolosa-Vilella et al, 2002).

b) Neutropenia was reported in a 39-year-old African American woman receiving olanzapine for paranoi received clozapine for 7 years, but this was discontinued due to the development of granulocytopenia. C 1000 milligrams (mg) three times daily, nifedipine 60 mg daily, metformin 1000 mg three times daily, insu evening) and lorazepam 2 mg once daily. Her absolute neutrophil count (ANC) was 3110/millimeter (mm millimeter (/mm) at the time clozapine was switched to olanzapine (10 mg once daily). After 7 days of ola day 14, it had decreased to 1050 cells/mm. Olanzapine was reintroduced 6 months later without incident therapy in patients with clozapine-induced granulocytopenia until the patient's hematologic status has no

c) During clozapine-induced agranulocytosis in 2 patients with schizophrenia, olanzapine [doses greater safe and effective treatment. Additionally, olanzapine did not worsen the severe neutropenia or agranulo Semaan, 2000).

d) A 27-year-old man who had been previously treated with clozapine therapy and had a normal leukocy olanzapine. Five months after discontinuing clozapine therapy, olanzapine therapy was begun and rapidl days his white blood cell (WBC) count decreased to 3.4 x 10(9)/Liter (L). Olanzapine therapy was discon decreased to 2.3 x 10(9)/L. His neutrophil count also decreased to 0.39 x 10(9)L. He was successfully tr micrograms/kilogram (mcg/kg)(Naumann et al, 1999).

3.3.5.B Leukopenia

1) Summary

a) Leukopenia was reported infrequently in clinical trials (n=8661) representing 4165 patient-years of ex olanzapine at doses 1 mg/day or more. Careful attention was given to the hematologic parameters during evidence of neutropenia was demonstrated (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tab

b) Unlike clozapine, a structurally related drug, olanzapine has not been shown in preclinical trials to ca (Anon, 1994a; Anon, 1995). However, due to the similarities of the two drugs, there may be a potential fo of olanzapine adversely prolonging the recovery time of clozapine-induced granulocytopenia have been

2) Incidence: 0.1% to 1% (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 200

3) LITERATURE REPORTS

a) Two patients treated with olanzapine for levodopa-induced psychosis developed leukopenia. A 56-ye (2400 microliters) after 4 months of therapy. She was tapered off olanzapine and recovered over 4 week similar reaction. In the other case, a 58-year-old man who had previously had a decline in his white blood decline in his WBC (2100 microliters) 13 months after starting olanzapine therapy. After discontinuation o after 2 weeks (Meissner et al, 1999).

3.3.5.C Neutropenia

1) Summary

a) Neutropenia was reported during postmarketing surveillance. Careful attention was given to the hema olanzapine and no evidence of neutropenia was demonstrated (Prod Info ZYPREXA(R) oral tablets, oral

b) Significant hematologic abnormalities have not been reported during olanzapine therapy in available 1996)(Anon, 1994a; Anon, 1995). However, neutropenia has been reported with olanzapine therapy (Oy 1998; Benedetti et al, 1999). Unlike clozapine, a structurally related drug, olanzapine has not been show leukopenia or agranulocytosis. However, due to the similarities of the two drugs, there may be a potentia cases of olanzapine adversely prolonging the recovery time of clozapine-induced granulocytopenia have

2) LITERATURE REPORTS

a) A patient previously treated with clozapine developed neutropenia associated with olanzapine therap schizoaffective disorder (bipolar type), chronic paranoid schizophrenia, and schizoid personality disorder (mg) daily for over 1 year. His white blood cell (WBC) count ranged from 4000 to 6000 cells per cubic mi discontinued, however, when the absolute neutrophil count (ANC) fell below 1000 cells/mm(3). After 11 7300 cells/mm(3) (ANC not reported). Olanzapine therapy was initiated at 10 mg once daily and titrated week (olanzapine dose 15 mg at bedtime), WBC fell to 5500 cells/(mm(3) At 30 mg/day, the WBC count (3)). Olanzapine was discontinued and the patient's WBC count slowly began to return to normal, and th patients who have previously taken clozapine may have an increased risk for neutropenia with olanzapin

b) A 60-year-old African American male with chronic undifferentiated schizophrenia had been treated wi gallbladder surgery. While receiving clozapine, his WBC counts ranged between 4000 and 6000 cells/m course of olanzapine (30 mg once daily), which was discontinued due to hyperglycemia and weight gain. over a 17-month period, the patient's WBC count declined to 3100 cells/mm(3) with an ANC of 1023 cell after 5 days, the patient's WBC count had risen to 4500 cells/mm(3) with an ANC of 1986 cells/ mm(3). hematologic monitoring performed every other day. Within 1 week, the patient's WBC count again declin mm(3). Olanzapine was continued with intensive monitoring. The patient's WBC ranged between 4000 a patients who have previously taken clozapine may have an increased risk for neutropenia with olanzapin

c) During clozapine-induced agranulocytosis in 2 patients with schizophrenia, olanzapine [doses greater safe and effective treatment. Additionally, olanzapine did not worsen the severe neutropenia or agranulo Semaan, 2000).

d) A 31-year-old woman who had previously experienced neutropenia with clozapine, experienced neut 1999). Olanzapine was introduced 5 days after clozapine withdrawal; the neutrophil count had normalize

(mg) was given on the first day and 10 mg daily starting on the second day. After 1 week, her neutrophil discontinued and the neutrophil count normalized after 4 weeks.
e) Thirty-two patients with a history of clozapine-induced neutropenia or agranulocytosis did not experie treatment (Prod Info Zyprexa(R), 1998). However, clinical experience with olanzapine, especially with lor

3.3.5.D Pancytopenia

1) LITERATURE REPORTS

a) A case report describes a 36-year-old male who experienced olanzapine-induced pancytopenia. Rele delusions, starvation and abuse of suppositories to purge himself. Upon admission, his RBC 4.67 x 10(1 4.52 x 10(9)/L were within normal range. On day 2, he started olanzapine 10 mg daily. By day 8 of olanz indicative of pancytopenia (values provided in the following table). On day 9, olanzapine was discontinue began to recover. He started risperidone on day 20. On day 29, his RBC, WBC and neutrophils continue He did not experience recurrence of pancytopenia while taking risperidone (Pattichis et al, 2008).

Day	Olanzapine dose	Red Blood Cells	White Blood Cells	Ne
Normal Ranges		4.5 to 6 x 10(12)/L	4 to 11 x 10(9)/L	1.8
Baseline		4.67	6.48	4.5
8	10 mg	4.65	6.67	3.9
9	discontinued			
10	0	4.11	3.57	1.7
11				1.7
15		3.95	2.79	1.6
17		3.78	2.8	1.8
19		3.81	3.16	2.4
23		3.6	3.61	2.6
25		3.82	4.83	3.2
29		3.75	6.12	4.8
KEY: mg = milligrams				

b) Olanzapine was associated with pancytopenia and exacerbated motor disability in a 67-year-old man (mg) daily was added to a regimen of levodopa 1.1 grams (g) and benserazide 275 mg once daily to trea paranoid delusions. After 1 week, the dose was increased to 10 mg/day. Complete blood count (CBC) va therapy, visual hallucinations and delusions decreased in frequency, but motor symptoms, neck rigidity, worsened. Levodopa was increased to 1.3 g/day and benserazide was increased to 325 mg/day. After 4 modest reduction in white blood cells (WBC), red blood cells (RBC), and platelets. One week later the he olanzapine was discontinued. Subsequently, WBC, RBC, and platelet counts increased. Within 4 weeks normal limits and remained normal for the following year. This report suggests that olanzapine should be disease and that hematologic monitoring may be necessary (Onofrj and Thomas, 2001).

3.3.6 Hepatic Effects

Cholestatic hepatitis

Hepatitis

Increased liver function test

3.3.6.A Cholestatic hepatitis

1) Incidence: rare (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegra
2) In the postmarketing period, there have been rare reports of hepatitis and very rare cases of cholestatic o tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006a).

3.3.6.B Hepatitis

1) Incidence: rare (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegra
2) In the postmarketing period, there have been rare reports of hepatitis and very rare cases of cholestatic o tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006a).

3.3.6.C Increased liver function test

1) Summary

a) Increases in serum alanine aminotransferase (ALT) above 200 International Units/Liter (IU/L) occurre tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006a). Elevations of aspartate glutamyl transferase (GGT) have been observed in approximately 10% of patients. These changes appe withdrawal of therapy. Close monitoring of liver function is advised, especially with use of higher doses a (Bronson & Lindenmayer, 2000; Beasley et al, 1996; Beasley et al, 1996a; Prod Info ZYPREXA(R) oral t disintegrating tablets, 2006a).

2) Incidence: 2% to 10% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

3) LITERATURE REPORTS

a) In placebo-controlled premarketing trials, ALT (SGPT) elevations (greater than or equal to 3 times the 2% (6/243) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. This dif six olanzapine-treated patients experienced jaundice. In two olanzapine-treated patients, liver enzymes r patients in the treatment group discontinued olanzapine therapy. Liver enzymes normalized in 2 of these determine the outcome and the other patient, seropositive for hepatitis C, had persistent enzyme elevatic (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2

b) Within the larger olanzapine premarketing database of about 2400 patients with baseline SGPT less elevation to greater than 200 IU/L was 2% (50/2381). None of these patients experienced jaundice or oth most had transient changes that tended to normalize while olanzapine treatment was continued. Among approximately 1% (23/2500) discontinued treatment due to transaminase increases (Prod Info ZYPREXA (R) orally disintegrating tablets, 2006a).

c) High dose olanzapine was associated with mild extrapyramidal symptoms (EPS), elevated serum pro and an average weight gain of 8 kilograms (kg) in 8 men with schizophrenia and schizoaffective disorder neuroleptics and risperidone or clozapine at adequate doses, were dosed with olanzapine 20 to 40 millig experienced increases in serum ALT concentrations; in one patient also taking pravastatin, ALT rose fro 2000a).

d) In another trial, the incidence of TRANSAMINASEMIA was comparable to that seen with haloperidol

e) Elevations of aspartate and alanine aminotransferases and gamma-glutamyl transferase (GGT) have (Beasley et al, 1996a) . These changes appear to be dose-dependent and are reversible upon withdrawa have not been reported in available trials. However, close monitoring of liver function is advised, especia prolonged therapy.

f) The incidence of aminotransferase elevations was greater with olanzapine than with haloperidol in on

3.3.7 Immunologic Effects

3.3.7.A Immunology finding

1) Summary

a) FLU SYNDROME (greater than 1%) has occurred with olanzapine therapy (Prod Info Zyprexa(R), Zy Olanzapine, 2004a). Olanzapine-induced HYPERSENSITIVITY syndrome, consisting of fever, rash, eos 34-year-old man 60 days after initiation of olanzapine therapy. Symptoms resolved following the disconti confirmed drug-induced hypersensitivity syndrome (Raz et al, 2001).

2) Hypersensitivity syndrome and flu syndrome have occurred with olanzapine therapy.

3.3.8 Musculoskeletal Effects

3.3.8.A Musculoskeletal finding

1) Summary

a) The manufacturer reports that BACK PAIN, JOINT PAIN (5%), EXTREMITY PAIN (5%), and TWITCH olanzapine therapy (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2 PHOSPHOKINASE (CPK) have been reported during clinical trials (Prod Info Zyprexa(R), Zyprexa(R) Zy 2004a). Marked elevation of serum creatine kinase (CK) associated with olanzapine therapy, with no oth syndrome, has been reported. No psychomotor agitation was present. Drug discontinuation resulted in re

2) Back pain, joint pain, extremity pain, elevated creatine phosphokinase and twitching are reported with ola

3.3.9 Neurologic Effects

Akathisia

Asthenia

Cerebrovascular disease

Disturbance in speech

Dizziness

Extrapyramidal disease

Insomnia

Neurological finding

Parkinsonism

Restless legs syndrome

Seizure

Somnolence

Status epilepticus

Tardive dyskinesia

Tremor

3.3.9.A Akathisia

1) Incidence: 1% to 27% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

2) Akathisia has been reported in 1% (IM injection) to 27% (oral) of patients treated with olanzapine compare ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3.3.9.B Asthenia

1) Incidence: 2% to 20% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

2) Asthenia has been reported in 2% to 20% of patients treated with olanzapine compared with patients treat tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3.3.9.C Cerebrovascular disease

1) The manufacturer has reported cerebrovascular adverse events (ie, stroke transient ischemic attack) in ol Placebo-controlled trials revealed a significantly higher incidence of cerebrovascular adverse events in elderl were treated with olanzapine as compared with placebo (Prod Info ZYPREXA(R) oral tablets, IM injection, ZY 2008; Pers Comm, 2004).

3.3.9.D Disturbance in speech

1) Four older patients (70 to 86 years old) presented with speech dysfunction or general decreases in functio (mg/d). Within 3 days to 4 weeks patients developed the inability to articulate clearly or unintelligible slurred s functioning in the presence of increased or new incontinence, inability to feed oneself, and unsteady gait. Pat once the olanzapine was discontinued (Gail & Noviasky, 1998).

3.3.9.E Dizziness

1) Incidence: 4% to 18% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis

2) Dizziness was reported in 4% (IM injection) to 18% (oral) of patients treated with olanzapine compared wi ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3.3.9.F Extrapyramidal disease

1) The manufacturer reports that extrapyramidal events occurred in 15% to 32% of patients, specific occurre to 11%, dystonic events 2% to 3%, dyskinesia, tardive dyskinesia, and other residual events (movement diso ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008). Extrapyra olanzapine therapy of schizophrenia (Glazer, 2000a; Tollefson et al, 1997a); (Beasley et al, 1996)(Anon, 199 have been reported in less than 9% of patients treated, with parkinsonian tremor occurring in approximately 5 (Tollefson et al, 1997a; Anon, 1995); (Beasley et al, 1996)(Anon, 1994a).

2) A prospective, multicenter, observational study showed that olanzapine treatment of outpatients (n=2128) group of patients (n=821) receiving a variety of other antipsychotic drug therapies. Drugs used in the control g zuclopenthixol, fluphenazine, thioridazine, perphenazine, pimozide, clozapine, pipotiazine, sulpiride, chlorpro lorazepam. Overall, olanzapine had a significantly lower incidence of adverse events than the control group (and weight gain occurred significantly more frequently in olanzapine-treated patients. Akathisia, dystonia, ext were significantly higher in the control group. Abnormal ejaculation and impotence occurred significantly mor month period, fewer olanzapine-treated patients received a concomitant anticholinergic medication in compar 58%, p less than 0.001) (Gomez et al, 2000).

3) High dose olanzapine was associated with mild extrapyramidal symptoms (EPS), elevated serum prolacti
an average weight gain of 8 kilograms (kg) in 8 men with schizophrenia and schizoaffective disorder. These p
and risperidone or clozapine at adequate doses, were dosed with olanzapine 20 to 40 milligrams (mg) for a n
rigidity alone or combined with cogwheeling of the elbow, wrist, or shoulder joints (Bronson & Lindenmayer, 2
4) The incidence of extrapyramidal symptoms (EPS) as a result of antipsychotic treatment was less in olanza
patients. This finding was confirmed in an international, multicenter, double-blind, prospective study involving
doses of olanzapine 17 milligrams/day (mg/d) or risperidone 7 milligrams/day (mg/d) for 28 weeks. The use o
of anticholinergic medications. Data suggests that the therapeutic dose threshold for EPS may be wider for o
needed for verification (Glazer, 2000a).
5) Extrapyramidal effects have occurred in clinical trials and appear to be dose-related (greater than 20 mg/d
appear to be more sensitive to extrapyramidal side effects of olanzapine (Granger & Hanger, 1999).
6) An 81-year-old woman treated with olanzapine 5 mg daily developed rigidity and hypertonicity. She had n
were normal. She had been independent but over several weeks declined, eventually requiring the assistanc
and within 1 week, she was totally independent again (Granger & Hanger, 1999).
7) A rate of 1.4% has been reported for acute dystonic reactions in patients taking olanzapine. Two case rep
woman who had severe torticollis and lingual dystonia with dysarthria, respectively. Both were controlled with
1998).
8) In one comparative trial, akathisia, tremor, and dystonia were reported in 16%, 15%, and 13% of schizoph
[mean, 16 milligrams (mg) daily]. Corresponding incidences in those treated with olanzapine in higher doses
studies, olanzapine has produced numeric improvements relative to baseline in the Simpson-Angus scale (fo
akathisia) during treatment, whereas numerical worsening of these scales occurred in haloperidol-treated pat
See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.G Insomnia

1) Incidence: 1% to 12% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally dis
2) Insomnia has been reported in 1% (IM injection) to 12% (oral) of patients treated with olanzapine compare
ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3.3.9.H Neurological finding

1) Olanzapine has been shown to have acute central nervous system depressant effects in humans during c
frequent adverse effect, occurring at an incidence of 26%, and appears to be dose-related. asthenia and dizz
patients, respectively, in clinical trials (Beasley et al, 1996).

3.3.9.I Parkinsonism

1) Contrary to common belief, the results of a retrospective cohort study suggest that atypical antipsychotics
dose and potency are considered (Rochon et al, 2005).
2) In a retrospective review of 12 Parkinson's disease patients receiving olanzapine, only 1 patient was able
disease (Molho & Factor, 1999). Several other studies also reported a worsening of Parkinson's disease sym
1999; Rudolf et al, 1999; Jimenez-Jimenez et al, 1998).
3) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar risk fo
antipsychotic therapy. In a population-based, retrospective cohort study, adults (aged 66 years and older) wit
year for the development of parkinsonism symptoms associated with typical or atypical antipsychotic use. As
antipsychotic therapy (ie, olanzapine, risperidone, quetiapine), incident parkinsonism was 30% more likely to
chlorpromazine, haloperidol, perphenazine) (adjusted HR, 1.3; 95% CI, 1.04 to 1.58), and 60% less likely to d
(HR, 0.4; 95% CI, 0.29 to 0.43). Older adults using higher potency typical antipsychotics had almost a 50% g
compared with patients prescribed atypical antipsychotics (all were considered lower potency) (HR, 1.44; 95%
lower potency typical antipsychotics, the risk of developing parkinsonism was no different from that in adults t
0.48 to 1.15). In addition, a positive dose-related relationship was observed between the occurrence of incide
antipsychotics. The risk for developing parkinsonism was more than twice as great in patients using a high-do
those prescribed a low-dose atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patie
have a similar risk for the development of parkinsonism as patients receiving high-dose atypical antipsychotic
antipsychotics may not be safer than typical antipsychotics when dose and potency are considered (Rochon
4) In a retrospective review of 12 Parkinson's disease patients receiving olanzapine, only 1 patient was able
disease. Nine out of 12 patients had their psychosis improve with olanzapine therapy. Nine out of 12 also had
available Unified Parkinson's Disease Rating Scale scores, average declines in scores were 9 points. Only 1
Factor, 1999).
5) A 72-year-old man had his Parkinson's disease worsen with olanzapine treatment for hallucinations. The d
became very rigid. He was unable to stand or walk. After discontinuing olanzapine, his functioning returned o
6) A 68-year-old man with Parkinson's disease developed a severe akinetic-rigid syndrome after receiving ol
was later successfully treated with clozapine (Rudolf et al, 1999).
7) Parkinson's disease was reported to worsen in 2 patients after olanzapine was substituted for clozapine. C
hematological assessments. However, after 4 to 7 days, olanzapine 5 milligrams/day (mg/d) resulted in worse
(Jimenez-Jimenez et al, 1998).

3.3.9.J Restless legs syndrome

1) A 41-year-old man developed restless legs syndrome while receiving olanzapine therapy for schizophreni
and increased to 20 mg daily after 6 weeks. At that time, he began to experience paresthesias of both legs oc
He experienced some relief by applying cold packs and walking around. A sleep lab evaluation also showed

dose was decreased to 10 mg daily with only a slight decrease in symptoms. Nine days later the patient disc immediately (Kraus et al, 1999).

3.3.9.K Seizure

1) Seizures have been reported in only 0.9% of patients in pre- marketing clinical trials of olanzapine. Patien the seizure threshold may be more prone to seizures following olanzapine therapy (Lee et al, 1999; Prod Info (R) ZYDIS(R) orally disintergating tablets, 2008).

2) Drug interactions with other drugs that lower the seizure threshold, such as clomipramine, have been repo olanzapine (Deshauer et al, 2000a).

3) A 31-year-old woman with schizoaffective disorder, organic mental disorder due to anoxic brain injury, and generalized tonic-clonic seizures 13 days after starting olanzapine. Previously, she had been seizure-free for haloperidol 40 milligrams (mg) twice daily to olanzapine 5 mg twice daily. Her other medications included lithi nitrofurantoin, and docusate. Multiple confounding factors may have contributed to her seizures (Lee et al, 19

3.3.9.L Somnolence

1) Incidence: 2% to 52% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally di

2) Somnolence was reported in 6% to 52% of patients treated with olanzapine compared with patients treate tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3) During five placebo-controlled trials, somnolence was reported in at least 2% of elderly patients (n=1184) olanzapine, at a rate significantly greater than placebo-treated patients (Prod Info ZYPREXA(R) oral tablets, disintergating tablets, 2008).

3.3.9.M Status epilepticus

1) A 48-year-old female with psychotic disorder experienced status epilepticus within 2 days following antips olanzapine and dose increase of mirtazapine. A brain MRI 10 days prior revealed no pathological findings, ar head trauma. Laboratory tests at hospital admission for psychogenic vomiting and anorexia showed no bioch was prescribed quetiapine 600 mg which was abruptly discontinued due to the lack of efficacy and suspicion tablets found). Therefore, the patient was switched to orodispersible olanzapine 10 mg, and the dose was qu initiated 4 days prior to the seizure and then increased to 60 mg 2 days prior to the incident. On day 16 of hos tonic-clonic seizure which progressed to status epilepticus. CT tomography revealed no abnormalities, and n neurological signs. Olanzapine and mirtazapine were discontinued and IV phenytoin was initiated. Phenytoin complications and the patient remained seizure-free (Spyridi et al, 2009).

2) Fatal status epilepticus associated with olanzapine therapy in a woman with no underlying cause or predis had been on olanzapine therapy for 5 months prior to the seizures. Subsequent to the seizures she died from intravascular coagulation. The authors classified this as a probable adverse event due to olanzapine (Wyders

3.3.9.N Tardive dyskinesia

1) Incidence: rare

2) Tardive dyskinesia may occur occasionally with olanzapine (Glazer, 2000a; Ananth & Kenan, 1999; Herra Tardive dyskinesia has been reported during clinical trials (Prod Info ZYPREXA(R) oral tablets, IM injection, 2008).

3) A 40-year-old woman developed tardive dystonia with olanzapine therapy for her psychosis. She had prev therapy. After beginning olanzapine 10 mg at bedtime, she developed severe, frequent torticollis. She also di She was switched to clozapine and her dystonia decreased by 50% after 4 months (Dunayevich & Strakowsk

4) Two cases of tardive dyskinesia associated with olanzapine therapy were described. A 30-year-old woma months after beginning olanzapine 10 milligrams/day (mg/d). She had previously experienced parkinsonism v developed athetoid movements of the tongue and chewing movements of the jaw after 7 months of olanzapir the tardive dyskinesia continued (Herran & Vazquez-Barquero, 1999).

5) Tardive dyskinesia may occur occasionally with olanzapine. A patient diagnosed with paranoid schizophre daily. Five years later, the patient developed abnormal movements of his upper extremities and neck. A diagn dystonia was made after ruling out all other causes. The patient continued to receive olanzapine with improve in his tardive dyskinesia (Ananth & Kenan, 1999).

6) A long-term follow-up study, which utilized results from 3 other studies, reported that haloperidol-treated p incidence rate/year 12 times higher than that of olanzapine-treated patients (n=513). Both medications were i 2000a). (Tollefson, 1997a)

7) Data combined from 3 studies evaluating patients treated with olanzapine (n=707) or haloperidol (n=197) lower incidence of tardive dyskinesia. At any visit after baseline, 7.1% of patients in the olanzapine group and manifested treatment-emergent tardive dyskinesia (p less than 0.001). At the last study visit, 2.3% of olanzap manifested tardive dyskinesia (p equal to 0.001) (Tollefson, 1997a).

3.3.9.O Tremor

1) Incidence: 1% to 23% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally di

2) Tremors have been reported in 1% (IM injection) to 23% (oral) of patients treated with olanzapine compar ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3.3.10 Ophthalmic Effects

Esotropia

Eye / vision finding

3.3.10.A Esotropia

1) Esotropia developed in a 14-year-old African American female with psychotic depression, who received ol fluoxetine 40 mg/d) for 6 months. The patient, who had no history of strabismus, complained of a severe hea A neurologic examination revealed no focal neurologic findings. Computed tomography and magnetic resona week of discontinuation of olanzapine, diplopia and headache had cleared, with reported resolution of esotro

3.3.10.B Eye / vision finding

1) Summary

a) The manufacturer reports that AMBLYOPIA (3%) and CONJUNCTIVITIS (greater than 1%) have bee Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Esotropia with diplopia olanzapine and fluoxetine therapy. When olanzapine was discontinued, symptoms cleared within one we

2) Amblyopia, diplopia, esotropia and conjunctivitis are reported with olanzapine therapy.

3.3.12 Psychiatric Effects

Aggressive behavior

Mania

Obsessive-compulsive disorder

Panic attack

Psychiatric sign or symptom

3.3.12.A Aggressive behavior

1) Summary

a) Two cases of patients developing AGITATION, CONFUSION, PARANOID BEHAVIOR and aggressic cases of aggression in patients beginning olanzapine were reported. The aggressive behavior worsened Agitation has been reported in up to 23% of olanzapine-treated patients in clinical trials, as compared to nervousness may be a part of the disease process as opposed to a pharmacologic effect of the drug (Pr

3.3.12.B Mania

1) Summary

a) Mania and hypomania have been described following olanzapine Administration (Aubrey et al, 2000)(1998).

2) LITERATURE REPORTS

a) A review of the literature identified 10 cases of mania or hypomania related to olanzapine therapy. Pa schizophrenia (n=6), schizoaffective disorder (n=2), pervasive developmental disorder (n=1), or an unsp development of manic symptoms ranged between 2 days and 35 days. Six of 10 patients were receiving patients, the use of concomitant medications makes causality difficult to assess. Remission of symptoms olanzapine (n=6). In the other 4 patients, hypomania or mania resolved with a decrease in olanzapine do

b) A 31-year-old woman with psychotic disorder experienced hypomania after receiving olanzapine 20 m second day of olanzapine therapy, she developed pressured speech, social disinhibition, and euphoric m her symptomatology remitted.

c) Two schizophrenic patients experienced manic-like activation after the start of olanzapine treatment. but had never experienced mania. In one case the mania resolved with a decrease in olanzapine dose fr second case olanzapine was discontinued (Lindenmayer & Klebanov, 1998).

3.3.12.C Obsessive-compulsive disorder

1) Summary

a) Two cases of patients experiencing olanzapine-induced OBSESSIVE-COMPULSIVE DISORDER (O 1999). A 35-year-old woman developed obsessive-compulsive disorder (OCD) after having olanzapine a 35-year-old man with schizophrenia and obsessive- compulsive disorder (OCD), had his OCD symptoms al, 1998).

2) LITERATURE REPORTS

a) Two cases of patients experiencing olanzapine-induced obsessive-compulsive disorder (OCD) were switched to olanzapine 15 to 25 milligrams (mg). The first man developed OCD 14 days after beginning

head and the compulsion to check doors. This disappeared with fluoxetine therapy. The second develop isolation, repeated hand-washing, checking doors and the alarm system. He also had impulsion phobias (Mottard & De La Sablonniere, 1999).

b) A 35-year-old woman developed obsessive-compulsive disorder (OCD) after having olanzapine 10 m major depression with psychotic features, borderline personality, and bulimia. After 1 week she develope changed to venlafaxine which successfully treated her OCD (Al-Mulhim et al, 1998).

c) A 35-year-old man with schizophrenia and obsessive-compulsive disorder (OCD), had his OCD symp (Morrison et al, 1998). His fluvoxamine was increased from 200 to 300 milligrams/day (mg/d) which help

3.3.12.D Panic attack

1) Summary

a) CASE REPORT - A 36-year-old woman with schizophrenia began experiencing panic attacks after be Olanzapine was started at 5 milligrams (mg) twice daily and increased to 3 times daily after 18 days. Par were successfully treated with alprazolam 0.5 mg as needed (Mandalos & Szarek, 1999).

3.3.12.E Psychiatric sign or symptom

1) Summary

a) The manufacturer reports that the following adverse reactions have occurred with olanzapine therapy (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Relapse of p olanzapine administration (Kostakoglu et al, 1999). The manufacturer reports that INTENTIONAL INJUR olanzapine therapy. (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, administration (Ramos & Budman, 1998).

2) Hostility, anxiety, aggression, koro and personality disorder are reported with olanzapine administration.

3) LITERATURE REPORTS

a) Two cases are reported where patients initially responded to olanzapine therapy and then relapsed a to 20 milligrams (mg) over 2 to 3 weeks for chronic paranoid schizophrenia. A 38-year-old man showed a fourth week through the sixth week. After 7 weeks, he had reemergence of the paranoid hallucinations, h old woman also had an increase in paranoid delusions and reemergence of auditory hallucinations, lack weeks. The authors conclude that a rapid displacement of these drugs due to loose binding could play a

b) A 19-year-old schizophrenic man developed KORO after having his olanzapine abruptly stopped to b sudden overwhelming fear that his penis and left testicle were shrinking and receding into his abdomen d days, the olanzapine was restarted with his symptoms resolving (Ramos & Budman, 1998). Hostility and have been reported in approximately 15% and 10% of patients treated, respectively, although the freque patients (Beasley et al, 1996).

3.3.13 Renal Effects

Urinary incontinence

Urogenital finding

3.3.13.A Urinary incontinence

1) Summary

a) There has been one reported case of urinary incontinence successfully treated with ephedrine followi

2) LITERATURE REPORTS

a) Ephedrine successfully counteracted urinary incontinence associated with olanzapine in a 61-year-old patient developed urinary incontinence when olanzapine (dose not reported) was added to lithium (dose mania, psychosis, agitation, and verbalized homicidal thoughts. Incontinence remitted 24 hours after eph regimen. (Vernon, 2000).

3.3.13.B Urogenital finding

1) Summary

a) The manufacturer reports that AMENORRHEA (1%), HEMATURIA (1%), METRORRHAGIA (1%), UR INFECTION (2%), and VAGINITIS (greater than 1%) have been associated with olanzapine therapy (Pro (R) IntraMuscular Olanzapine, 2004a).

b) A prospective, multicenter, observational study showed that olanzapine treatment of outpatients (n=2 group of patients (n=821) receiving a variety of other antipsychotic drug therapies. Drugs used in the cor sertindole, zuclopenthixol, fluphenazine, thioridazine, perphenazine, pimozide, clozapine, pipotiazine, su clothiapine, and lorazepam. Overall, olanzapine had a significantly lower incidence of adverse events tha 0.001). Somnolence and weight gain occurred significantly more frequently in olanzapine-treated patient hypertonia, and tremor were significantly higher in the control group. Abnormal ejaculation and impotenc the control group. Over a 6-month period, fewer olanzapine-treated patients received a concomitant anti the control group (36% versus 58%, p less than 0.001) (Gomez et al, 2000).

2) Amenorrhea, hematuria, metrorrhagia, urinary incontinence, urinary tract infection, vaginitis and priapism

3.3.14 Reproductive Effects

3.3.14.A Priapism

1) Summary

a) Priapism and instances of PAINFUL ERECTIONS have been reported with Olanzapine (Kuperman et et al, 1998; Heckers et al, 1998).

2) LITERATURE REPORTS

a) Priapism developed in a 26-year-old man treated with olanzapine 10 milligrams per day for disorganiz sexually overactive, he had previously taken varied psychotropic medications (including risperidone) with hours of discontinuation of olanzapine, priapism disappeared (Kuperman, 2000).

b) There are reports of men with painful erections occurring 1 to 3 days after beginning olanzapine. One symptoms of sexual dysfunction receiving olanzapine 15 mg nightly (Gordon & De Groot, 1999). The oth involving the spinal cord and a history of prostate surgery receiving olanzapine 5 mg daily. Both required return (Heckers et al, 1998).

c) One report of an African-American man with a history of hypersexual behavior receiving olanzapine 1 increased frequency and duration of erections (up to 2 hours). Within 1 week of olanzapine discontinuati (Deirmenjian et al, 1998).

3.3.15 Respiratory Effects

Cough

Dyspnea

Pharyngitis

Pulmonary aspiration

Pulmonary embolism

Rhinitis

Summary

3.3.15.A Cough

1) Incidence: 6% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disinterga

2) Increased cough was reported in 6% of patients treated with oral olanzapine at doses of 2.5 mg/day or gre with placebo (n=294) in the acute phase of short-term, placebo controlled trials (Prod Info ZYPREXA(R) oral disintergating tablets, 2008).

3.3.15.B Dyspnea

1) Incidence: 3% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disinterga

2) Dyspnea was reported in 3% of patients treated with oral olanzapine at doses of 5 mg/day or greater plus those treated with lithium or valproate alone (n=115) in the acute phase of short-term, placebo-controlled, co oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3.3.15.C Pharyngitis

1) Incidence: 4% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disinterga

2) Pharyngitis was reported in 4% of patients treated with oral olanzapine at doses of 2.5 mg/day or greater placebo (n=294) in the acute phase of short-term, placebo controlled trials. Pharyngitis was also reported in 4 of 5 mg/day or greater plus lithium or valproate (n=229) compared with 1% of those treated with lithium or val term, placebo-controlled, combination, clinical trials (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPRE 2008).

3.3.15.D Pulmonary aspiration

1) Aspiration has been associated with antipsychotic therapy. Aspiration pneumonia has resulted in morbidit Alzheimer's disease. Olanzapine should be used cautiously in patients at increased risk for aspiration pneum injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008).

3.3.15.E Pulmonary embolism

1) A case report described 3 episodes of pulmonary embolism in a 25-year-old man after treatment with olan schizoaffective disorder. His physical health was generally good and there was no personal or family history or physical activity level changed under neuroleptic medication. Smoking a pack of cigarettes per day was his

antipsychotic therapy included olanzapine 20 mg/day, paroxetine 20 mg/day and oral valproate 2000 mg/day treatment, the patient presented with a complaint of sudden back pain radiating to the left front part of his tho breath and experienced an episode of hemoptysis. CT scan revealed bilateral pulmonary embolism. Ultrasou DVT. His coagulopathy workup did not demonstrate any abnormalities. Olanzapine was discontinued and ora of 2 to 3) was initiated and maintained for 6 months. Twelve weeks after olanzapine was discontinued, he wa of psychotic symptoms. After 3 weeks of risperidone treatment, the patient presented with chest pain, cough, pulmonary emboli were observed on a chest spiral CT scan. Concomitant DVT in lower extremities was ruled (evidenced by low INR) appeared to be the cause of this second episode of pulmonary embolism. Therefore, confirm adherence. Sixteen weeks later, the patient presented with thoracic pain and dyspnea. Spiral chest C indicated bilateral pulmonary embolism with no DVT in the lower limbs. Because antipsychotic agents appear the patient was administered anticoagulant therapy and amisulpride 400 mg/day which resulted in improveme valproate 2 g/day therapy was continued after being maintained throughout the 3 episodes of pulmonary emb
2) A case report described a pulmonary embolism in a 28-year-old male patient after beginning olanzapine th Olanzapine therapy was initiated at 10 mg/day and gradually increased to 30 mg/day. Following 10 weeks of spiral CT, which was performed after the patient complained of respiratory pain and experienced two episode discontinued and the patient's symptoms resolved with anticoagulant therapy. Because tests for possible coa risks factors for this patient, olanzapine was believed to be the causal effect for the development of the pulmo

3.3.15.F Rhinitis

1) Incidence: 7% (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disinterga
2) Rhinitis was reported in 7% of patients treated with oral olanzapine at doses of 2.5 mg/day or greater (n=5 placebo (n=294) in the acute phase of short-term, placebo controlled trials (Prod Info ZYPREXA(R) oral table disintergating tablets, 2008).

3.3.15.G Summary

1) Cough, dyspnea, pharyngitis, and rhinitis were reported at a higher incidence with olanzapine treatment c controlled trials. Additionally, antipsychotic therapy has been associated with aspiration. Aspiration pneumoni with advanced Alzheimer's disease. Therefore, caution should be used when olanzapine is administered in th tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008). Two case reports described man and a 29-year-old man following oral olanzapine therapy. Both patients experienced improvement after therapy was initiated (Borras et al, 2008; Waage & Gedde-Dahl, 2003).

3.3.16 Other

Summary

Death

Drug withdrawal

Extrapyramidal disease

Neuroleptic malignant syndrome

3.3.16.A Summary

1) OTHER EFFECTS
a) In a large trial comparing haloperidol and olanzapine in schizophrenic patients, discontinuation of ther with olanzapine. Withdrawal syndrome has been reported with olanzapine therapy.
2) OTHER FINDINGS
a) In a large trial comparing haloperidol and olanzapine in schizophrenic patients (n=1996), discontinuat less often with olanzapine (3.6% versus 7.4% of patients) (Anon, 1995).

3.3.16.B Death

1) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antip for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with de conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched stratified based on place of residence (community versus long-term care facilities). In order to adjust for differ matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evalua antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted ha 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (9 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 1 conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk

risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown results and cause of death could not be examined (Gill et al, 2007).
2) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater ris antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medi and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medicatio and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in th was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were associated with haloperidol was 2.14 (95% CI, 1.86 to 2.45) and loxapine was 1.29 (95% CI, 1.19 to 1.40), wh olanzapine. The increased mortality risk for conventional versus atypical drug therapy was greatest when dos (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results
3) The findings of one meta-analysis suggest that there may be a small increased risk of death associated w treatment of dementia in elderly patients. The study analysis (n=5110), including 15 randomized, double-blind antipsychotic use (ie, aripiprazole (n=3), olanzapine (n=5), quetiapine (n=3), risperidone (n=5)) in elderly pati dementia, found that death occurred more often in patients receiving atypical antipsychotic therapy as compa respectively). The overall odds ratio, as assessed by meta-analysis, for death in elderly patients receiving aty 1.54 (95% confidence interval (CI), 1.06 to 2.23; p=0.02), and the risk difference was 0.01 (95% CI, 0.004 to with atypical antipsychotic use was 1.65 (95% CI, 1.19 to 2.29; p=0.003); however this increased risk was on analysis; meta-analyses of individual drugs did not show a statistically significant increased risk. A similar dro and placebo-treated patients (32.2% vs 31.4%, respectively), with no significant difference in dropouts found
4) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as l the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conv 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was ass as compared with atypical antipsychotics at all timepoints studied after beginning therapy (within 180 days: re 1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.5 In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI, 1.15 to 1.45), v a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI, 1.29 to 1.56) v antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Additional studies whi elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeuti

3.3.16.C Drug withdrawal

1) Summary

a) CASE REPORT - Within 3 days of stopping olanzapine therapy, a 33- year-old female developed myo depression, restlessness, and blurred vision. Because myoclonus is consistent with serotonergic hyperac represented a SEROTONERGIC REBOUND phenomena (Nayudu & Scheftner, 2000).

3.3.16.D Extrapyramidal disease

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.16.E Neuroleptic malignant syndrome

1) Summary

a) Neuroleptic malignant syndrome (NMS), due to dopaminergic blockade, associated with olanzapine th taking concomitant or recently discontinued neuroleptics appear to be more susceptible to drug-induced myoglobin levels may be elevated; and high fever and rigidity are present. Generally after stopping the d NMS resolves (Stanfield & Privette, 2000; Nyfort-Hansen & Alderman, 2000; Sierra-Biddle et al, 2000; M 1999); (Burkhard et al, 1999)(Apple & Van Hauer, 1999; Cohen et al, 1999); (Johnson & Brusner, 1998)(
b) Symptoms have begun as early as 2 to 4 days and as late as 1 year. Patients have presented with ty muscle rigidity, mental status changes, and autonomic instability. Increases in serum creatine kinase hav 41,900 international units/L. Some patients previously had NMS with other neuroleptics including risperic discontinuation of olanzapine and with treatments including dantrolene, bromocriptine, or benzodiazepine however, the patient was also receiving clozapine and no rigidity was noted (Moltz & Coeytaux, 1998).

2) LITERATURE REPORTS

a) A case report describes a 56-year-old male who experienced neuroleptic malignant syndrome (NMS) history included sleep disturbances, preoccupied and hallucinatory behaviors and persecutory thoughts. treatments with thioridazine, then trifluperazine with chlordiazepoxide, which caused extrapyramidal sym year, he was noncompliant with treatments of fluoxetine, clonazepam, escitalopram and olanzapine befo schizophrenia based on ICD-10 criteria. Upon admission, he started olanzapine 5 mg twice daily and alp olanzapine was increased to 15 mg/day. On day 5, his perspiration and blood pressure (BP, 150/86 mmH EPS or dehydration. On day 6, he experienced fever (102 degrees Farenheit), confusion, diaphoresis, ta tremors, upper and lower limb rigidity, leucocytosis, uremia and elevated creatinine phosphokinase. He v olanzapine and alprazolam were discontinued and he received amoxicillin 500 mg three times daily and his sensorium improved and the rigidity and tremors resolved. After 7 days, he was discharged on loraze he started amisulpride 50 mg nightly. He has continued success with amisulpride 100 mg and clonazepa
b) Atypical neuroleptic malignant syndrome, also described as fever- delirium-autonomic instability synd

30-year-old man developed fever, difficulty swallowing, sinus tachycardia, delirium, elevated white blood
olanzapine (10 milligrams/day) was initiated for the treatment of violent behavior. No rigidity, hyperreflexi
observed. Olanzapine was discontinued and symptoms completely resolved within 2 days (Robinson et a
c) A 23-year-old woman developed clinical features consistent with neuroleptic malignant syndrome (NM
daily for schizoaffective disorder. Other medications included lithium and fluoxetine. After 40 days of olar
admission to the hospital, her trunk and limbs were hypertonic and hyperextended, with generalized trem
blood pressure fluctuations, and an elevated body temperature of 38.6 degrees Celsius. Laboratory data
metabolic acidosis, hypernatremia, hypokalemia, a lithium levels of 0.7 milliequivalents per liter (mEq/L),
Cultures of cerebrospinal fluid and blood were negative. A urine toxicology screen was consistent with ar
intensive care unit, the patient recovered fully (Sierra-Biddle et al, 2000).
d) A 42-year-old man with a history of schizophrenia developed symptoms consistent with neuroleptic m
olanzapine therapy. At the onset of symptoms, the patient was also taking ranitidine, benztropine mesyla
respiratory distress, intermittent apnea, decreased mental status, fever (rectal temperature of 41 degrees
stimulus, rigid muscle tone, and dry mucous membranes. On admission, vital signs included a pulse of 1
111/79. Respiratory effort was absent. Laboratory tests revealed a serum creatinine phosphokinase (CP
hemoglobin 12.4 grams%, hematocrit 35%, serum sodium 141 millimoles/liter (mmol/L), blood urea nitro
creatinine 0.8 mg/dL. Olanzapine was discontinued. The patient was intubated and mechanically ventilat
bromocriptine and empiric antibiotic therapy. The patient's hospital course was complicated by pneumon
discharge, he demonstrated obvious cognitive deficits and left hemiplegia (Stanfield & Privette, 2000).
e) Other cases have reported only elevations in serum creatine kinase without other symptoms of NMS

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 ZYPREXA(R) oral tablets, IM
disintergating tablets, 2008) (All Trimesters)

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

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
malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in a
occurrence of fetal damage, the significance of which is considered uncertain in humans.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) There is insufficient evidence to clearly establish the safety of olanzapine during pregnancy and it is recon
the potential benefit justifies the potential risk to the fetus (Prod Info ZYPREXA(R) oral tablets, IM injection, Z
2008). Limited data to date do not suggest an increased risk of major malformation (Aichhorn et al, 2008; Ern
notably, schizophrenic women may have higher prevalence rates of social and lifestyle behaviors (e.g. smoki
status) associated with risky neonatal outcomes (Patton et al, 2002). Patients with histories of chronic psycho
maintained on medication therapy throughout gestation, as these patients and their fetuses represent a high

5) Literature Reports

a) A prospective, observational study of 54 women (mean age, 30.7 years), recruited from the Emory Wome
antipsychotic medication during pregnancy, showed permeability of the placental barrier. Outcomes were det
samples taken at delivery and through data collected from maternal reports and medical records. Placental p
to maternal plasma concentrations) showed a significant difference between antipsychotic medications, with
the highest, followed by haloperidol 65.5% (95% CI, 40.3%-90.7%), risperidone 49.2% (95% CI, 13.6%-84.8%
showing the lowest placental passage ratio. There was a greater frequency of pre-term deliveries (21.4%, p=
than 0.07), and neonatal intensive care admission (30.8%, p=less than 0.09) in infants exposed to olanzapine
b) There are no adequate and well-controlled studies with olanzapine use during pregnancy. Seven pregnan
which resulted in 2 normal births, 1 neonatal death due to cardiovascular defect, 3 therapeutic abortions and
oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008). However, in 23 prospec
in risk of spontaneous abortion, stillbirth, prematurity, or major malformation in those infants exposed to olanz
expanded data from this latter report produced similar conclusions; data included 96 pregnancies, among wh
spontaneous abortions, 2.1% in premature deliveries, 3.1% in stillbirths, and 1% in major malformation (Ernst
assess the fetal safety of atypical antipsychotics, interim results from 32 exposures to risperidone, olanzapine
births with no malformations, 3 spontaneous abortions, 2 stillbirths, and 7 therapeutic abortions (McKenna et
c) Occasional spontaneous case reports of in utero exposure to olanzapine have produced viable newborns,
established (Mendhekar et al, 2002; Nagy et al, 2001; Littrell et al, 2000; Kirchheiner et al, 2000). A case repo
blood) level of 11 nanograms (ng)/mL compared with 34 ng/mL in the maternal plasma drawn before birth in a
mg during pregnancy. During gestation, the maternal olanzapine plasma levels were between 25 and 34 ng/m
only complication being gestational diabetes which was resolved with diet. Delivery was uncomplicated and h
normally during the first 6 months (Aichhorn et al, 2008).
d) In another case report, a 37-year-old woman with a 7-year history of paranoid schizophrenia gave birth to
25 mg/day starting at week 8 until week 32 when she discontinued it against medical advice. She had not be
preceding her pregnancy (Lim, 2001). An isolated case of maternal use of up to 20 mg of olanzapine and 2 m
gestation until 10 days prior to delivery has been reported. In this case, a healthy baby was delivered with Ap
minutes; at 3 months of age, the infant showed age-appropriate milestones (Mendhekar et al, 2002). A single
the 18th week of pregnancy through delivery and during breastfeeding also exists. Delivery was uncomplicate

months of age, the infant showed no abnormal findings at 11 months of age (Kirchheiner et al, 2000).

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 benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) Limited data from studies of nursing mothers treated with olanzapine have demonstrated that olanzapine i ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergating tablets, 2008; Gardiner e described jaundice, cardiomegaly, somnolence, and a heart murmur in the infant of a mother receiving olanza after bottle-feeding was initiated on day 7 of life. Another case from the same report demonstrated no advers olanzapine doses at 2 months of age (Goldstein et al, 2000a). Undetectable infant olanzapine plasma levels (32.8 to 39.5 nanograms/mL were reported in another case (Kirchheiner et al, 2000a). Because olanzapine ha it is recommended that women treated with olanzapine should not breast-feed (Prod Info ZYPREXA(R) oral t disintergating tablets, 2008).

3) Literature Reports

a) In a study of healthy, nursing women, olanzapine was excreted in breast milk. The estimated mean infant olanzapine dose (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintergati to 20 mg/day of olanzapine, the median infant dose ingested through breast milk was approximately 1% (Gar plasma samples from five nursing mothers treated with olanzapine 2.5 mg to 10 mg daily, milk-to-plasma rati theoretical value of 0.38 that was determined using the known pharmacokinetic parameters of the drug. Base and assuming 100% bioavailability, relative infant dose was estimated to be 0% to 2.5% of the weight-adjuste report, breast milk was collected by an electric pump and olanzapine concentrations were measured by gas c olanzapine was excreted in the breast milk in relatively small amounts. Breast milk/plasma concentration ratio

b) Limited data from cases of olanzapine exposure via breast milk fail to affirm or eliminate the potential for a described an infant exposed in utero to olanzapine (maternal dose 5 mg/day) who was born with cardiomega However, jaundice and sedation continued despite the initiation of bottle-feeding on day seven of life. In the s months of age (maternal dose 10 mg/day) had no adverse effects (Goldstein et al, 2000a). Another case repo plasma levels (less than 2 ng/mL) despite maternal steady-state trough levels of 32.8 to 39.5 nanograms/mL throughout pregnancy and during breastfeeding (Kirchheiner et al, 2000a).

4) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.2 to 0.84 (mean 0.46) (Buist & A, 2001; Croke et al, 2002)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

3.5.1 Drug-Drug Combinations

Activated Charcoal

Belladonna

Belladonna Alkaloids

Betel Nut

Carbamazepine

Ciprofloxacin

Clomipramine

Dehydroepiandrosterone

Eszopiclone

Fluvoxamine

Haloperidol

Levodopa

Levomethadyl

Lithium

Mirtazapine

Phenylalanine

Ritonavir

St John's Wort

Tetrabenazine

Tramadol

3.5.1.A Activated Charcoal

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

3.5.1.B Belladonna

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

3.5.1.C Belladonna Alkaloids

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

3.5.1.D Betel Nut

1) Interaction Effect: increased extrapyramidal side effects of olanzapine (difficulty with movement or abnorm

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

3.5.1.E Carbamazepine

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

3.5.1.F Ciprofloxacin

1) Interaction Effect: an increased risk of olanzapine toxicity (increased sedation, orthostatic hypotension)
2) Summary: Ciprofloxacin was suspected of inhibiting the metabolism of olanzapine in a 54-year-old female 1A2 (CYP1A2) has been shown in vitro to be responsible for the formation of some of the metabolites of olan

inhibitor of CYP1A2. Although olanzapine has a wide therapeutic range and a correlation between plasma co established, this interaction may be clinically significant (Markowitz & DeVane, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving olanzapine and ciprofloxacin concurrently should be monitored fo increased sedation and orthostatic hypotension.
7) Probable Mechanism: inhibition by ciprofloxacin of cytochrome P450 1A2-mediated olanzapine metabolis
8) Literature Reports
a) A 54-year-old female was admitted to the hospital with suicidal ideation and lacerations to her wrists. 10 mg at bedtime, nefazodone 100 mg twice daily, atenolol 25 mg daily, levothyroxine 0.25 mg daily, and tapered off prior to electroconvulsive therapy, and ciprofloxacin 250 mg twice daily for seven days was in Immediately before her last dose of ciprofloxacin, the plasma olanzapine concentration was 32.6 ng/mL. her olanzapine concentration had decreased by more than 50% to 14.6 ng/mL. Although this patient did increased olanzapine level, higher doses of ciprofloxacin could potentially cause more inhibition of olanz

3.5.1.G Clomipramine

1) Interaction Effect: an increased risk of seizures
2) Summary: Psychotropic drugs have been shown to reduce the seizure threshold. A case report describes who received treatment with olanzapine and clomipramine concomitantly. This combination resulted in seizur olanzapine and clomipramine. It is advised to use caution when administering olanzapine concomitantly with seizure threshold (Deshauer et al, 2000a).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: It is advised to use caution when administering olanzapine concomitantly with clom seizure threshold.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 34-year-old male with schizophrenia and obsessive-compulsive disorder (OCD) without any underly following long-term noncompliance. Inpatient olanzapine treatment (20 mg/day) was initiated and positive Patient was discharged and readmitted because of inability to control symptoms. Clomipramine 250 mg myoclonic jerks were reported which quickly progressed to general motor seizures and postictal somnole paroxysmal slowing on the EEG was consistent with seizure activity. Clomipramine and olanzapine were controlled with diazepam 30 mg per day for three days. This pattern repeated upon re-challenge with the Presumably from the temporal relationship between clomipramine and olanzapine administration and sei adverse event is due to an interaction between these two drugs. Clomipramine and olanzapine are both 1A2 and 2D6. One theory is that coadministration may result in elevated levels of both compounds. Altho occurs is not yet known, it is advised to use caution when administering olanzapine concomitantly with cl seizure threshold (Deshauer et al, 2000).

3.5.1.H Dehydroepiandrosterone

1) Interaction Effect: reduced effectiveness of olanzapine
2) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/decil patients with psychosis (Howard, 1992a). In case reports, patients have been resistant to antipsychotics whe Patients being treated with olanzapine should avoid DHEA supplementation.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and olanzapine. If DHE orally per day may be used to normalize DHEA levels.
7) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness
8) Literature Reports
a) A 24-year-old female diagnosed with schizophrenia was resistant to daily doses of haloperidol 20 mill carbonate 1200 mg, and lithium carbonate 900 mg plus thioridazine 300 mg. The patient appeared Cush hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). Dexamethasone 1 mg orally at bedtime resu The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. A normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with seve therapy (Howard, 1992).
b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accom and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual ha hygiene, agitation, and combativeness. He was diagnosed with chronic paranoid schizophrenia; schizopl schizoaffective disorder, excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpron also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazine 1(1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg daily. Baseline DHEA level exceeded 900 mc dexamethasone 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, psych conversational, and was making good eye contact. Once dexamethasone was discontinued, rapid decor

"substantial amounts of psychotropic medications". DHEA increased to 536 mcg/dL. The author conclud florid psychosis resistant to conventional antipsychotic therapy (Howard, 1992).

3.5.1.I Eszopiclone

1) Interaction Effect: decreased psychomotor function

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

3) Severity: minor

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: unknown

3.5.1.J Fluvoxamine

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

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

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

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

7) Probable Mechanism: inhibition of olanzapine elimination

8) Literature Reports

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

b) Addition of fluvoxamine to olanzapine therapy may result in olanzapine-induced side effects or intoxic being treated for not less than 3 months with 10-20 mg/day of olanzapine. The dose of olanzapine was u study and remained stable throughout the study period. Fluvoxamine 100 mg/day was added to olanzapi continued for 8 weeks. Olanzapine concentrations increased during fluvoxamine treatment 1.58-fold from 4, and 1.81-fold from week 0 to week 8. Percentage change from week 0 to week 8 ranged from 12% to metabolite were not significantly changed. Even though all eight patients had higher olanzapine blood se ratio of increase of olanzapine blood serum concentrations from week 0 to week 8 did not correlate signi than 0.05). This study confirmed that the addition of fluvoxamine to a stable dose of olanzapine increase Combined olanzapine and fluvoxamine should be used cautiously and controlled clinically and by therap side effects or intoxication (Hiemke et al, 2002).

3.5.1.K Haloperidol

1) Interaction Effect: an increased risk of parkinsonism (cogwheeling rigidity, unstable gait)

2) Summary: A patient receiving haloperidol experienced extreme parkinsonism following the addition of olar pharmacokinetic interaction between olanzapine, a weak cytochrome P450 2D6 (CYP2D6) inhibitor, and halo Pharmacodynamically, the small amount of dopamine (D2) blockade from olanzapine may have been enough 1999a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Patients should be closely monitored for signs and symptoms of increased parkinso haloperidol therapy. Doses of haloperidol may need to be decreased.

7) Probable Mechanism: competitive inhibition of cytochrome P450 2D6-mediated haloperidol metabolism; ir

8) Literature Reports

a) A 67-year-old hospitalized male with bipolar disorder who had stopped taking his medications was re mg nightly, and valproate 750 mg twice daily. He had been experiencing some mild parkinsonian sympto worsen when haloperidol was reinstituted. Following stabilization on this regimen, it was decided to chan minimize any parkinsonism that was a result of his medications. While tapering the haloperidol and initiat parkinsonism that resulted in an inability to walk. His mental status remained unchanged. Haloperidol wa and two days later the patient's parkinsonism side effects had resolved back to baseline. Benztropine wa symptoms did not reoccur while on olanzapine (Gomberg, 1999).

3.5.1.L Levodopa

1) Interaction Effect: decreased levodopa effectiveness

2) Summary: Concurrent use of olanzapine may antagonize the pharmacological effects of levodopa (Prod I this interaction is unknown.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: Monitor patients for levodopa efficacy.
7) Probable Mechanism: pharmacological antagonism

3.5.1.M Levomethadyl

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

3.5.1.N Lithium

1) Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brai
2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few pat antagonist, particularly haloperidol. A causal relationship between these events and the concomitant adminis not been established (Prod Info LITHOBID(R) slow-release oral tablets, 2005). Coadministration of lithium an wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and dyskinesias in isol have occurred with therapeutic lithium levels (Amdisen, 1982; Prakash, 1982; Addonizio et al, 1988a). Howev such combinations with no severe adverse consequences (Goldney & Spence, 1986). The mechanism is not decreases neostriatal dopaminergic activity, probably through a direct action on the G protein and the capaci adenyl cyclase (Carli et al, 1994). Hyperglycemic reactions have also occurred during combined phenothiazir
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, espec particularly haloperidol, and lithium are used. Serum lithium levels should be monitored periodically. Some cli therapeutic range.
7) Probable Mechanism: unknown
8) Literature Reports

a) Concomitant haloperidol and lithium therapy has resulted in symptoms of encephalopathy, confusion, patients with mania (Cohen & Cohen, 1974; Loudon & Waring, 1976; Thomas, 1979). Irreversible neurol Hurwitz, 1983; Keitner & Rahman, 1984).

b) Seizures, encephalopathy, delirium, and abnormal EEG occurred in four patients during combined lit Serum lithium levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had pr another phenothiazine. Three of these patients developed symptoms within eight days of initiating combi

c) The addition of lithium to neuroleptic therapy exacerbated extrapyramidal symptoms (EPS) in a small received at least five days of treatment with either oral thiothixene, haloperidol, or fluphenazine in mean initiation of the lithium and were experiencing drug-induced extrapyramidal symptoms. Oral lithium was a achieve a therapeutic serum concentration. The maximum levels attained were 0.65 to 1.27 mEq/L. The the addition of lithium. However, only three patients developed marked symptoms and no patient develo symptoms included gait, shoulder shaking, elbow rigidity, and tremor.

d) Ten patients treated with clozapine and lithium were studied (Blake et al, 1992). Of the ten patients, f including jerking of limbs, facial spasms and tics, tremor of hands and arms, tongue twitching, and stumb These effects reversed when lithium was discontinued or given at a lower dose. On rechallenge, one of t keeping serum lithium no greater than 0.5 mEq/L, clozapine could be safely coadministered.

e) Chlorpromazine serum levels can be significantly reduced in the presence of lithium treatment. If use result in rebound elevation of chlorpromazine levels, resulting in chlorpromazine toxicity. In patients on a withdrawal of the lithium may precipitate chlorpromazine cardiotoxicity. In this report, such toxicity was m associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation

f) However, other data do not support that such adverse events are frequent or indeed causally related antagonist antipsychotic drugs and lithium have been used successfully in many patients with manic-dep interaction may only become significant with very high doses of one or both drugs or with failure to disco (Miller & Menninger, 1987).

g) A 69-year-old patient with oxygen-dependent chronic obstructive pulmonary disorder and a 25-year h 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been maintained or 10 years. In addition, she was given amantadine (100 mg twice daily) for tremor. Three weeks after the s decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, polyuria, depr was then admitted to the hospital for delirium. Her lithium serum level was 1.36 mEq/L at the time of the Although her lithium level decreased to 0.41 mEq/L, she continued to experience profound delirium, trem week. After she started to respond to commands, she was restarted on lithium (300 mg at bedtime) beca later, she was discharged with a regimen of lithium and low-dose lorazepam for treatment of insomnia. It by the concurrent use of lithium and risperidone. Other factors could also have caused delirium, such as pulmonary pathology. In addition, amantadine, which facilitates the release of presynaptic dopamine and contributed (Chen & Cardasis, 1996).

3.5.1.O Mirtazapine

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Concurrent use of olanzapine with mirtazapine and tramadol in a 53-year-old male resulted in s
Fetchko, 2002). If olanzapine is used concomitantly with mirtazapine and/or tramadol, monitor closely for sym
can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide suppor
Shannon, 2005).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with coadministration of olanzapine, mi
If 2 or more of these drugs are are used concomitantly, monitor closely for symptoms of serotonin syndrome
hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivit
the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). S
serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therap

7) Probable Mechanism: additive serotonergic pharmacologic effects

8) Literature Reports

a) A 53-year-old male on mirtazapine and tramadol experienced serotonin syndrome 8 days after olanza
mirtazapine 45 mg/day for depression and tramadol 150 mg/day for chronic back pain. Olanzapine 10 m
admitted 8 days later after being found by the police wandering the streets in inappropriate dress and in
tachycardic (120 bpm), and had flushing, twitching of his face, tremors, myoclonus, hyperreflexia, and ar
spoke with a stutter. He had marked derailment, appeared perplexed, had prominent perceptual abnorm
The creatine phosphokinase was normal. All medications were discontinued and within 12 hours he sign

3.5.1.P Phenylalanine

1) Interaction Effect: increased incidence of tardive dyskinesia

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

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

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

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

8) Literature Reports

a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics ir
studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients with no tardive
than or equal to 100 milligrams (mg) of a chlorpromazine equivalent for at least 3 months (n=10), and (3)
exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in gr
powdered phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood sample
administration and 2 hours after administration. Three patients in group 1 (with tardive dyskinesia) had th
this group as a whole had higher (though nonsignificant) mean phenylalanine levels than the other group
Abnormal Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phen
significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient
phenylalanine level and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.0
than 0.05). In all patients, phenylalanine loading increased plasma phenylalanine levels approximately ei
as a result of conversion of phenylalanine to tyrosine. Plasma levels of competing large neutral amino ac
et al, 1992).

3.5.1.Q Ritonavir

1) Interaction Effect: reduced olanzapine effectiveness

2) Summary: An open-label study involving 14 healthy volunteers revealed a significant alteration in pharma
exposure of olanzapine when administered in the presence of ritonavir. Baseline blood samples were drawn
mg tablet. Venous blood samples were then obtained at specified times. After a 14-day washout period, subj
400 mg BID for 4 days, then 500 mg BID for 4 days. Blood samples were again drawn at specified times. On
follows: Statistically significant reductions in the mean olanzapine area under the plasma concentration-time
hr/mL) (p less than 0.001); the half-life by 50% (from 32 hr to 16 hr) (p less than 0.00001) and the peak plasm
ng/mL) (p less than 0.002). The oral clearance of olanzapine increased by 115% (from 20 L/hr to 43 L/hr) (p l
well-tolerated and a clear relationship between plasma concentrations and toxicity has not been defined, the
study (Penzak et al, 2002).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor patients for olanzapine efficacy. Doses of olanzapine may need to be adjus
Patients stabilized on olanzapine and ritonavir, who have their ritonavir discontinued, should have be monitor
systemic exposure to olanzapine.

7) Probable Mechanism: induction or CYP1A2- and glucuronosyl transferase-mediated metabolism of olanza

3.5.1.R St John's Wort

1) Interaction Effect: reduced olanzapine efficacy

2) Summary: This interaction is based on in vitro information that St. John's Wort induced CYP1A2 enzymes reduced blood theophylline concentrations and loss of efficacy (Nebel et al, 1999). Since olanzapine is metab olanzapine may be similarly affected. If St. John's Wort and olanzapine are taken together, their dosages sho increased dosages of olanzapine may be required. Discontinuation of St. John's Wort should be done careful dose reduction may be required.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of olanzapine with St. John's Wort. If patients elect to remai consistent dosing. Olanzapine dosage may need to be increased. Patients should not discontinue St. John's downward adjustments in olanzapine dose may be necessary as well as monitoring for increased side effects constipation, dry mouth, asthenia).

7) Probable Mechanism: induction of cytochrome P450 1A2 enzymes by St. John's Wort

3.5.1.S Tetrabenazine

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

2) Summary: Tetrabenazine causes a small increase in the correct QT interval. As the degree of prolongatio torsade de pointes-type VT. The concomitant use of tetrabenazine with other drugs known for QT prolongatic randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an approximate XENAZINE(R) oral tablets, 2008). In addition to QT prolongation, tetrabenazine may also cause adverse reac extrapyramidal disorders, which may be exaggerated when coadministered with neuroleptic drugs (eg, olanz

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of tetrabenazine with olanzapine or other neuroleptic drugs may ir QT interval prolongation and increased risk of torsade de pointes. Other adverse reactions, such as neurolep disorders may be enhanced when given with a dopamine agonist such as olanzapine (Prod Info XENAZINE(I

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

3.5.1.T Tramadol

1) Interaction Effect: an increased risk of serotonin syndrome

2) Summary: Concurrent use of olanzapine with mirtazapine and tramadol in a 53-year-old male resulted in s Fetchko, 2002). If olanzapine is used concomitantly with mirtazapine and/or tramadol, monitor closely for sym can be life-threatening. If serotonin syndrome develops, discontinue the offending agents and provide suppor Shannon, 2005).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: A case of serotonin syndrome was reported with coadministration of olanzapine, mi If 2 or more of these drugs are are used concomitantly, monitor closely for symptoms of serotonin syndrome hyper-reflexia, tremor, muscle rigidity, clonus, peripheral hypertonicity, and shivering), autonomic hyperactivit the presence of bowel sounds, and diarrhea), and mental status changes (including agitation and delirium). S serotonin syndrome develops, discontinue the offending agents and provide supportive care and other therap

7) Probable Mechanism: additive serotonergic pharmacologic effects

8) Literature Reports

a) A 53-year-old male on mirtazapine and tramadol experienced serotonin syndrome 8 days after olanz mirtazapine 45 mg/day for depression and tramadol 150 mg/day for chronic back pain. Olanzapine 10 m admitted 8 days later after being found by the police wandering the streets in inappropriate dress and in tachycardic (120 bpm), and had flushing, twitching of his face, tremors, myoclonus, hyperreflexia, and ar spoke with a stutter. He had marked derailment, appeared perplexed, had prominent perceptual abnorm The creatine phosphokinase was normal. All medications were discontinued and within 12 hours he sign

3.5.2 Drug-Food Combinations

3.5.2.A Ethanol

1) Interaction Effect: excessive central nervous system depression

2) Summary: Coadministration of olanzapine and ethanol will potentiate the orthostatic hypotension observe ethanol (45 mg/70 kg) had no effect on olanzapine pharmacokinetics, these drugs should not be taken conco depressive effects of both drugs (Prod Info Zyprexa(R), 1999d).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of olanzapine and ethanol should be avoided if at all possible. If the should be used.

7) Probable Mechanism: additive central nervous system depression

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic

1) Physical Findings

a) Improvement of schizophrenic symptoms on standard examination/testing

1) Positive symptoms (distortion of normal function) include hallucinations, irritability, delusions, incoher

2) Negative symptoms (loss or diminution of function) include blunted affect, emotional or social withdra

B) Toxic

1) Laboratory Parameters

a) Fasting blood glucose at beginning of treatment and periodically thereafter for patients with diabetes melli obesity, family history of diabetes) (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM inject

b) Fasting blood glucose for any patient who develops symptoms of hyperglycemia (Prod Info SYMBYAX(R)

c) Baseline and follow-up lipid panels are suggested (Prod Info ZYPREXA(R) oral tablets, orally disintegratin

d) Liver function tests periodically during therapy for patients with significant hepatic disease (Prod Info ZYP IM injection, 2007).

e) ECG at baseline and periodically during treatment (Pacher & Kecskemeti, 2004)

2) Physical Findings

a) Examination/questioning to detect extrapyramidal effects (ie, continuous pacing, restlessness, fine tremor Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 2007).

b) Temperature

c) Vital signs, especially during initial dose titration (Prod Info ZYPREXA(R) oral tablets, orally disintegrating

d) Assess for orthostatic hypotension, bradycardia, and hypoventilation, especially prior to subsequent intrar tablets, orally disintegrating tablets, IM injection, 2007).

e) Monitor body weight regularly during treatment (Prod Info ZYPREXA(R) oral tablets, orally disintegrating t

f) Monitor all patients for signs and symptoms of hyperglycemia (ie, polydipsia, polyuria, polyphagia, and wea hyperglycemia during atypical antipsychotic treatment should undergo fasting blood glucose testing. In some atypical antipsychotic was stopped; however, some patient required ongoing anti- diabetic treatment despite Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 2007).

g) Monitor patients for signs and symptoms of neuroleptic malignant syndrome (ie, hyperpyrexia, muscle rigi autonomic instability) (Prod Info ZYPREXA(R) oral tablets, orally disintegrating tablets, IM injection, 2007).

4.2 Patient Instructions

A) Olanzapine (By mouth)

Olanzapine

Treats psychotic mental disorders, such as schizophrenia or 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 olanzapine.

How to Use This Medicine:
Tablet, Dissolving Tablet

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed for you. Do not use more medicine or use it more often than your doctor tells you to.
You may take this medicine with or without food.
If you are using the disintegrating tablet, make sure your hands are dry before you handle the tablet. Do not o you are ready to take it. Remove the tablet from the blister pack by peeling back the foil, then taking the table the tablet in your mouth. It should melt quickly. After the tablet has melted, swallow or take a drink of 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 d
the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Kee
until you are ready to take it.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after
need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a

You must be careful if you are also using other medicine that might cause similar side effects as olanzapine.
pressure, overheating, or liver problems. Make sure your doctor knows about all other medicines you are usi
Make sure your doctor knows if you are also using carbamazepine (Tegretol®), fluoxetine (Prozac®), fluvoxa
omeprazole (Prilosec®), or rifampin (Rifadin®).
Make sure your doctor knows if you are also using medicine to treat high blood pressure (such as atenolol, h
quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, Zestril®).
Make sure your doctor knows if you are using medicine to treat anxiety (such as alprazolam, diazepam, Valiu
medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relieve
Do not drink alcohol while you are using this medicine.
Tell your doctor if you smoke. You might need a different amount of this medicine if you smoke.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have diabetes, liver disease, pro
have a history of seizures, breast cancer, or severe constipation.
Make sure your doctor knows about any heart or blood problems you have now or have had in the past. This
Tell your doctor if you have ever had neuroleptic malignant syndrome (NMS) caused by any medicine for psy
This medicine may increase your cholesterol and fats in the blood. If this condition occurs, your doctor may g
of cholesterol and fats in the blood.
This medicine may increase your weight. Your doctor may need to check your weight regularly during treatm
This medicine may raise or lower your blood sugar, or it may cover up symptoms of very low blood sugar (hy
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
until you no longer feel dizzy. Get up slowly.
This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If
tired, or confused. You might vomit or have an upset stomach. Do not get too hot while you are exercising. A
are too hot and cannot cool down.
Some side effects are more likely to happen in elderly people who have memory problems or other reduced r
person who will be using this medicine has Alzheimer's disease or similar problems (often called "dementia").
Zyprexa® Zydis® contains phenylalanine (aspartame). This is only a concern if you have a disorder called ph
have this condition, talk to your doctor before using this medicine.

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
Blurred or other changes in vision.
Change in how much or how often you urinate.
Fast or uneven heartbeat.
Fever, sweating, confusion, muscle stiffness.
Increased restlessness or excessive movements.
Jerky muscle movement you cannot control (often in your face, tongue, or jaw).
Lightheadedness or fainting.
Numbness or weakness in your arm or leg, or on one side of your body.
Severe sleepiness, slurred speech, trouble breathing.
Shakiness, problems with balance or walking.
Swelling in your hands, ankles, or feet.
Swollen breasts, or liquid discharge from your nipples (men or women).
Trouble swallowing.

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

Back pain.
Constipation, upset stomach.
Dry mouth, increased thirst, watering of mouth.
Increased appetite.
Missed menstrual period.
Redness or swelling in your eye.
Sleepiness or unusual drowsiness.

Stuffy or runny nose.
Trouble sleeping.
Weakness.
Weight gain.

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

B) Olanzapine (Injection)

Olanzapine

Treats an episode of agitation (being overexcited, tense, hostile, or anxious) in a person who has schizophrenia o

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

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.
If your doctor wants you to keep using this medicine, you will need to change to the oral (tablet) form.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, a
You must be careful if you are also using other medicine that might cause similar side effects as olanzapine.
pressure, overheating, or liver problems. Make sure your doctor knows about all other medicines you are usir
Make sure your doctor knows if you are also using carbamazepine (Tegretol®), fluoxetine (Prozac®), fluvoxa
omeprazole (Prilosec®), or rifampin (Rifadin®).
Make sure your doctor knows if you are also using medicine to treat high blood pressure (such as atenolol, hy
quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, Zestril®).
Make sure your doctor knows if you are using medicine to treat anxiety (such as alprazolam, diazepam, Valiu
medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relieve
Do not drink alcohol while you are using this medicine.
Tell your doctor if you smoke. You might need a different amount of this medicine if you smoke.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have diabetes, liver disease, pros
have a history of seizures, breast cancer, or severe constipation.
Make sure your doctor knows about any heart or blood problems you have now or have had in the past. This
Tell your doctor if you have ever had neuroleptic malignant syndrome (NMS) caused by any medicine for psy
This medicine may increase your cholesterol and fats in the blood. If this condition occurs, your doctor may g
of cholesterol and fats in the blood.
This medicine may increase your weight. Your doctor may need to check your weight regularly during treatme
This medicine may raise or lower your blood sugar, or it may cover up symptoms of very low blood sugar (hyp
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
until you no longer feel dizzy. Get up slowly.
This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If
tired, or confused. You might vomit or have an upset stomach. Do not get too hot while you are exercising. Av
are too hot and cannot cool down.
Some side effects are more likely to happen in elderly people who have memory problems or other reduced r
person who will be using this medicine has Alzheimer's disease or similar problems (often called "dementia")

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
Blurred or other changes in vision.
Change in how much or how often you urinate.
Fast or uneven heartbeat.
Fever, sweating, confusion, muscle stiffness.
Increased restlessness or excessive movements.
Jerky muscle movement you cannot control (often in your face, tongue, or jaw).
Lightheadedness or fainting.
Numbness or weakness in your arm or leg, or on one side of your body.
Severe sleepiness, slurred speech, trouble breathing.
Shakiness, problems with balance or walking.
Swelling in your hands, ankles, or feet.
Swollen breasts, or liquid discharge from your nipples (men or women).
Trouble swallowing.

If you notice these less serious side effects, talk with your doctor:
Back pain.
Constipation, upset stomach.
Dry mouth, increased thirst, watering of mouth.
Increased appetite.
Missed menstrual period.
Pain where the shot is given.
Redness or swelling in your eye.
Sleepiness or unusual drowsiness.
Stuffy or runny nose.
Trouble sleeping.
Weakness.
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 olanzapine) and typical antipsychotic drugs had a similar d according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The st 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had 1 outpa cardiac death was defined as occurring in the community and excluded deaths of patients admitted to the hospital, no causes not related to ventricular tachyarrhythmia. Current use was defined as the interval between the time the prescr Low and high doses was defined as comparable to less than 100 milligrams (mg) of chlorpromazine, and doses compa respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 p p less than 0.001). The risk of sudden cardiac death in current olanzapine users in 27,257 person-years was 2.04 (95 sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug gr 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 high-dose use. results, there was a secondary analysis performed in a cohort of patients matched by propensity score, which resulted cohort analysis (Ray et al, 2009). In an editorial in The New England Journal of Medicine, it has been suggested that a with clear evidence of benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients), there shoul administration. It has also been suggested (although not formally tested) that ECGs be performed before and shortly a existing or emergent QT interval prolongation (Schneeweiss & Avorn, 2009).

B) Clinical effects of olanzapine appear similar to those of clozapine in schizophrenic patients. Olanzapine when com symptoms and is associated with a lower incidence of extrapyramidal effects. Olanzapine has been shown to be supe suggest the possibilities that maintenance of long-term response may be better than haloperidol (Beasley et al, 1997; more expensive than haloperidol, however, savings have been demonstrated that make the 2 agents approximately e These include olanzapine's reduced need for medical services due to lower relapse rates and its greater efficacy in all

C) Olanzapine offers a potential advantage over clozapine as it does not appear to cause severe neutropenia or agra clozapine are a lower propensity to induce orthostatic hypotension, tachycardia, seizures, and hyperthermia, although clinical trials. Clozapine is primarily indicated in severely disturbed patients who are refractory to typical antipsychotics symptoms (including tardive dyskinesia) related to other agents. Olanzapine may have a similar role, although further imposed by a risk of agranulocytosis, indications for olanzapine may be extended (eg, first-line therapy in some types psychosis are needed (eg, schizoaffective disorders, psychotic mood disorders, major depression with psychotic featu Olanzapine is effective for treating schizophrenia and has a favorable adverse effect profile (Bever & Perry, 1998).

See Drug Consult reference: CHEMOTHERAPY AND RADIOTHERAPY TREATMENT GUIDELINES FOR NAUSEA A
See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHREN

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Olanzapine is an antipsychotic agent (thienobenzodiazepine derivative) structurally similar to clozapine. Pharm those of clozapine, and both agents are classified as "atypical" antipsychotic agents mainly by virtue of their effica schizophrenia and lower propensity for extrapyramidal effects compared to conventional or typical antipsychotics A disadvantage of clozapine is its ability to induce agranulocytosis in up to 2% of patients; olanzapine was primari alternative (Anon, 1994; AMA Department of Drugs, 1994).

2) Similar to clozapine, olanzapine is both a dopamine (D) and serotonin (5-HT) antagonist; both compounds hav mediated than D-mediated responses (Moore et al, 1992; Fuller & Snoddy, 1992). Receptor binding studies have D4, 5-HT2A, and 5-HT2C receptors, as well as histamine-1, alpha-1 adrenergic, and muscarinic (particularly M1) 1994a; Higgins, 1993). The drug binds more potently to the 5-HT2A receptor than the D2 receptor (3-fold); greate been reported (Tollefson et al, 1994; Fuller & Snoddy, 1992; Beasley et al, 1996). Results of neuroendocrine stud potent than clozapine with respect to blockade of 5-HT2 and D2 receptors (Fuller & Snoddy, 1992).

3) Olanzapine induces near saturation of the 5-HT(2) receptor at all doses (Kapur et al, 1998). Even a dose of 5 m (2) occupancy, however, is dose-related:

DOSE	D(2) RECEPTOR OCCUPANCY
5 mg/day	55%
10 mg/day	73%

15 mg/day	75%
20 mg/day	76%
20 mg/day	83%

4) D(2) receptor occupancy was measured at 88% in a single patient taking olanzapine 40 mg/day.

B) REVIEW ARTICLES

1) A review of the side effects of antipsychotic medications, including olanzapine, in the elderly is available. Of pa incidence of sedation and abnormal gait which can lead to falls and other accidents (Masand, 2000).

2) Reviews of the adverse effects related to olanzapine are available. The management of these side effects, inc appetite, and weight gain is discussed (Zarate, 2000). Safety data from comparative clinical trials is also available

3) Comprehensive reviews on olanzapine have been published (Tollefson & Kuntz, 1999; Falsetti, 1999; Bever &

4) The pharmacologic properties and therapeutic efficacy of olanzapine in the management of psychoses are rev

5) An indepth overview of the efficacy of olanzapine in clinical trials has been published (Beasley et al, 1997).

6) A review of clinical trails evaluating olanzapine dosing is available (Nemeroff, 1997).

7) A study reviewing the safety profile of olanzapine has been published (Beasley et al, 1997a).

8) The use of atypical antipsychotic medications in adults (Markowitz et al, 1999; Brown et al, 1999), older adults 1999; Lewis, 1998; Toren et al, 1998) has been reviewed.

9) The mechanisms of neuroleptic-induced extrapyramidal symptoms and tardive dyskinesia and their relationshi (Glazer, 2000).

10) A review of atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease was co

4.5 Therapeutic Uses

Adverse reaction to cannabis - Induced psychotic disorder

Agitation, acute - Psychotic disorder

Agitation - Bipolar I disorder

Agitation - Schizophrenia

Alzheimer's disease - Psychotic disorder

Anorexia nervosa

Anxiety - Dementia

Bipolar I disorder, Acute mixed or manic episodes

Bipolar I disorder, Maintenance therapy

Borderline personality disorder

Cancer - Nausea - Pain

Catatonia

Chemotherapy-induced nausea and vomiting; Prophylaxis

Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

Cocaine dependence

Delirium

Dementia

Depressed bipolar I disorder

Depression, Treatment-resistant

Essential tremor

Fibromyalgia

Gilles de la Tourette's syndrome

Headache, Chronic, refractory

Huntington's disease

Obsessive-compulsive disorder, Refractory

Parkinson's disease - Psychotic disorder

Pervasive developmental disorder

Posttraumatic stress disorder

Repetitive self-excoriation

Schizophrenia

Schizophrenia, Refractory

Schizophrenic prodrome

Senile dementia of the Lewy body type

Severe major depression with psychotic features

Tardive dyskinesia

Trichotillomania

4.5.A Adverse reaction to cannabis - Induced 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:

As effective as haloperidol for the treatment of cannabis-induced psychotic disorder (Berk et al, 1999b)

3) Adult:

a) Olanzapine was as effective as haloperidol in the treatment of cannabis-induced psychotic disorder. In a c episode associated with cannabis use were randomized to receive either olanzapine 10 milligrams (n=15) or a significant improvement in both groups as compared to baseline measured on the Brief Psychiatric Rating S haloperidol). There was no significant difference between the 2 groups. Olanzapine was associated with fewe

4.5.B 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 (ODT) and risperidone oral solution (OS) yielded similar improve
Negative Syndrome Scale (PANSS-EC) and the Clinical Global Impression (CGI) scale in 87 patients tre
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
Negative Syndrome Scale (PANSS-EC) and the Clinical Global Impression (CGI) scale in 87 patients treated
emergency setting, according to an open-label, flexible-dose study. Patients with a baseline PANSS-EC scor
were assigned to receive initial doses of either olanzapine ODT 10 milligram (mg) (n=34) or risperidone OS 3
based on previous effective treatments, or monthly assignments to olanzapine or risperidone according to the
continued agitation could be re-dosed at any time, and after 1 hour could receive adjunctive drug therapy. PA
time. The mean CGI change from baseline was similar between the olanzapine and risperidone group (2.8 vs
PANSS-EC score over time ANOVA (at baseline and every 15 minutes for 1 hour) revealed no significant ma
treatment over time (p=0.09 and p=0.41, respectively). There was a significant mean change in heart rate in t
risperidone OS group (-9.2 vs 1.1 beats/minute, p=0.03). There were no significant differences between the t
extrapyramidal symptoms (Hatta et al, 2008).

4.5.C Agitation - Bipolar I disorder

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (intramuscular formulation only); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Intramuscular olanzapine is indicated for the treatment of acute AGITATION ASSOCIATED WITH BIPOL
IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006)

3) Adult:

a) Intramuscular olanzapine effectively reduced symptoms of agitation in patients with schizophrenia or bipol
trials. The primary efficacy measure in these trials was the change in the Positive and Negative Syndrome Sc
2 hours post-injection. The mean baseline PANSS Excited Component score was 18.4 (range, 13 to 32) out
moderate levels of agitation. The first trial included agitated inpatients meeting DSM-IV criteria for schizophre
doses (2.5 mg, 5 mg, 7.5 mg and 10 mg) were evaluated and all doses were significantly better as compared
2 hours post-injection. However, the effect was larger and more consistent for the 5 mg, 7.5 mg, and 10 mg d
inpatients with schizophrenia (n=311), received a fixed 10 mg dose of intramuscular olanzapine or placebo. A
placebo on the PANSS Excited Component at 2 hours post-injection. In the third trial, agitated inpatients with
episode with or without psychotic features) (n=201), received one fixed intramuscular olanzapine dose of 10 r
as compared with placebo on the primary outcome measure. Examination of population subsets such as age
responsiveness on the basis of these sub-groupings (Prod Info Zyprexa(R) IntraMuscular, 2004).

b) Rapid initial dose escalation (RIDE) of orally administered olanzapine was effective in the treatment of acu
bipolar disorder. In a randomized, double-blind, multicenter study, acutely agitated patients (n=148) received
milligrams (mg)/day for 2 days, then 20 to 30 mg/day for 2 days) or "usual clinical practice" (UCP) therapy (ol
4 days of blinded treatment before entering an open-label phase in which all patients received olanzapine 5 t
therapies produced significant mean reductions in the Positive and Negative Syndrome Scale-Excited Compo
(mean reduction, -7.01 and -5.51, respectively, p less than 0.001, both values). However, patients in the RIDI
those in the UCP group on days 2, 3, and 4 as measured by mean changes in PANSS-EC scores (p=0.03, p=
similar in both groups with headache, somnolence, dizziness, nervousness, and insomnia being reported mo

4.5.D Agitation - Schizophrenia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (intramuscular formulation only); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Intramuscular olanzapine is indicated for the treatment of agitation associated with schizophrenia (Prod I
ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006)

In a multicenter, double-blind, placebo-controlled study (n=270), intramuscular (IM) olanzapine was more
agitation among patients with schizophrenia, but there was no significant differences in efficacy between
2002).

Treatment with olanzapine intramuscular (IM) injection was no different from IM haloperidol in reducing a
schizophrenia in a multicenter, double-blind, placebo-controlled study (n=311) (Wright et al, 2001).

3) Adult:

a) Intramuscular

1) Intramuscular olanzapine effectively reduced symptoms of agitation in patients with schizophrenia or
trials. The primary efficacy measure in these trials was the change in the Positive and Negative Syndrom

baseline to 2 hours post-injection. The mean baseline PANSS Excited Component score was 18.4 (rang
suggesting mostly moderate levels of agitation. The first trial included agitated inpatients meeting DSM-I
intramuscular olanzapine doses (2.5 mg, 5 mg, 7.5 mg and 10 mg) were evaluated and all doses were si
PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consister
second placebo-controlled trial, agitated inpatients with schizophrenia (n=311), received a fixed 10 mg d
olanzapine was statistically superior to placebo on the PANSS Excited Component at 2 hours post-inject
I Disorder (and acute manic or mixed episode with or without psychotic features) (n=201), received one f
placebo. Olanzapine was significantly better as compared with placebo on the primary outcome measure
race, and gender did not show any differential responsiveness on the basis of these sub-groupings (Proc
2) In a multicenter, double-blind, placebo-controlled study (n=270), intramuscular (IM) olanzapine was m
of agitation among patients with schizophrenia, but there was no significant differences in efficacy betwe
agitated patients (mean age, 36.3 +/- 10.7 years (yr), range 18 to 73 yr) diagnosed with schizophrenia, s
disorder underwent 5:1 randomization of active treatment to placebo to olanzapine 2.5 milligram (mg) (m
Excited Component (PANSS-EC) score, 18.3 +/-2.4; n=48), olanzapine 5 mg (mean PANSS-EC score, 1
PANSS-EC score, 18.9 +/- 2.6; n=46), olanzapine 10 mg (mean PANSS-EC score, 19.3 +/- 2.6; n=46) in
injection (mean PANSS-EC score, 19.3 +/- 3.1; n=40) or placebo IM injection (mean PANSS-EC score, 1
allowed to receive a maximum of 3 injections within the 24-hour treatment period. Concomitant benzodia
after the administration of the first injection. The primary endpoint was the mean change in Positive and
(PANSS-EC) score from baseline to 2 hours after the first IM injection. Response was defined as a 40%
the first injection, there was a dose-response correlation across all IM olanzapine doses in reducing agita
change in PANSS-EC was -5.5 +/- 4.6 in the olanzapine 2.5-mg arm, -8.1 +/-5.3 in the olanzapine 5-mg
+/- 4.9 in the olanzapine 10-mg arm, -7.5 +/- 5.9 in the haloperidol 7.5-mg compared with -2.9 +/- 4.7 in t
rates were 50%, 62.6%, 73.9% and 80.4% in patients who received IM olanzapine 2.5 mg, 5 mg, 7.5 mg
patients who received IM haloperidol was 60% compared to 20% in the placebo arm (all p=0.003 or less
the differences in mean change on the PANSS-EC (last observation carried forward) was significant in th
the remaining 5-mg, 7.5-mg or 10-mg arms (p=0.12 or higher). The most common adverse effect reporte
hypotension (range, 2.2% to 4.4%) while no patients reported hypotension in the haloperidol or placebo
reported acute dystonia compared to zero patients in the olanzapine and placebo arms. IM olanzapine w
parkinsonism (0.7% vs 16.7%; p=0.03 or less) and akathisia (1.2% vs 7.9%) than IM haloperidol (Breier
3) In a multicenter, double-blind, placebo-controlled study (n=311), treatment with olanzapine intramusc
haloperidol in reducing agitation in patients with schizophrenia. Patients (mean age, 38.2 +/- 11.6 years
with a diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder were randomize
IM injection (mean Positive and Negative Syndrome Scale Excited Component (PANSS-EC) score, 18.4
(mean PANSS-EC score, 18.2 +/-3.2; n=126) or placebo IM injection (mean PANSS-EC score, 18.4 +/-3
carried-forward response rate was defined as a 40% reduction in the PANSS-EC scores at 2 hours follow
hours following the first injection, the mean change in the PANSS-EC scores (primary endpoint) was -7.7
+/- 5 for patients who received haloperidol, and -3.6 +/- 5.2 for patients who received placebo (p not repo
better response rates than a 33.3% response rate with placebo (p less than 0.001), there was no signific
olanzapine and haloperidol arms (73.3% vs 69%; p=0.52). Acute dystonia was reported in 7.1% of patier
olanzapine arm. Extrapyramidal side effects were reported more frequently in the haloperidol compared
Significantly more patients (20.6%) who received haloperidol required anticholinergics compared with 4.6
who received placebo (all p=0.003 or less) (Wright et al, 2001).

b) Oral

1) Rapid initial dose escalation (RIDE) of oral olanzapine was effective in the treatment of acute agitatio
In a randomized, double-blind, multicenter study, acutely agitated patients (n=148) received either RIDE
for 2 days, then 20 to 30 mg/day for 2 days) or "usual clinical practice" (UCP) therapy (olanzapine 10 mg
blinded treatment before entering an open-label phase in which all patients received olanzapine 5 to 20 r
therapies produced significant mean reductions in the Positive and Negative Syndrome Scale-Excited Co
hours (mean reduction, -7.01 and -5.51, respectively, p less than 0.001, both values). However, patients
in agitation those in the UCP group on days 2, 3, and 4 as measured by mean changes in PANSS-EC sc
Adverse events were similar in both groups with headache, somnolence, dizziness, nervousness, and in
(Baker et al, 2003).

4.5.E Alzheimer's disease - Psychotic disorder

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk
Drug Administration, 2009).
Olanzapine doses of 5 or 10 mg daily were shown to be safe and effective in decreasing behavioral and
disease in elderly patients in a 6-week, multicenter, double-blind, placebo-controlled trial (n=206) (Street
Somnolence and gait disturbances increased in olanzapine-treated patients (Street et al, 2000)

3) Adult:

a) Low doses of olanzapine (5 milligrams (mg) or 10 mg daily) were safe and significantly superior to placebo

symptoms associated with Alzheimer's disease in elderly patients. In a 6-week, multicenter, double-blind, pla were randomized to receive a fixed daily dose of olanzapine 5, 10, or 15 mg or placebo. Efficacy was measu aggression, hallucinations, and delusion items ("Core Total") of the Neuropsychiatric Inventory-Nursing Home Disruptiveness score, to assess patient-related caregiver distress. Core Totals were significantly improved in Occupational Disruptiveness scores were significantly reduced in those receiving 5 mg doses. Somnolence o receiving olanzapine than placebo. Gait disturbances were more common in those receiving olanzapine 5 or impairment, increased extrapyramidal symptoms, and central anticholinergic effects in olanzapine-treated pa patients (Street et al, 2000). In an 18-month, open extension of this trial with 105 patients, behavioral and psy final average Core Total score having decreased to 6 from 7.9 at the start of the open trial (p=0.002). Nearly additional reduction in Core Total score. Measures of cognitive status showed no change. Levels of akathisia symptoms and parkinsonian symptoms did not increase. Although weight did not change significantly for the weight gain (average, 4.3 kilograms) or weight loss (average, 4.4 kilograms). Somnolence and accidental inju events. Five milligrams was the modal dose (the dose prescribed for a patient for the most number of days) f (Street et al, 2001).

4.5.F Anorexia nervosa

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:

Significantly improved body mass index and obsessive symptoms compared to placebo in patients with a trial (n=34) (Bissada et al, 2008)

Associated with a mean weight gain of 8.75 pounds in a small, 10-week, open-label trial in patients with

See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

3) Adult:

a) Treatment with olanzapine resulted in greater weight gain and decreased obsessive symptoms compared 10-week, double-blind clinical trial. Women (n=34) with DSM-IV criteria for anorexia nervosa (restricting or bi 17.5 kilograms/square meter (kg/m(2)) or less attended a day hospital program at the Ottawa Hospital for eat group therapy 4 days a week for 12 to 14 weeks. In addition, patients were randomized to receive olanzapine milligrams (mg) daily, increased by 2.5 mg/week up to a maximum dose of 10 mg/day, or placebo (n=18; mea started after a 2-week baseline period, continued for 10 weeks, and was followed by a 1-week posttreatment 6.61 +/- 2.32 mg/day for study completers (n=14). A significant (p less than 0.001) increase in BMI occurred f significantly (p=0.03) greater rate of increase occurred in the olanzapine group (16.39 +/- 1.13 at baseline (n= to the placebo group (15.93 +/- 1.39 at baseline (n=18) to 19.66 +/- 1.32 at week 13 (n=12)). Weight restorati kg/m(2), occurred in 87.5% of olanzapine patients and 55.6% of placebo patients (p=0.02) with mean time to interval (CI) 6.74-9.39) for the olanzapine group and 10.06 weeks (95% CI 8.75-11.36) for the placebo group significant reductions in depression (p less than 0.001) and anxiety (p=0.02), as measured by the Personality in obsessions (p=0.003) and compulsions (p=0.001), as measured by the Yale-Brown Obsessive Compulsive in these scores in the olanzapine group compared to the placebo group was in obsessive symptoms (p=0.02) tolerance or development of diabetes mellitus, were observed (Bissada et al, 2008).

b) Weight gain occurred in patients with anorexia nervosa when treated with olanzapine. In a small, open-lab or binge/purge subtype) without schizophrenia, schizoaffective disorder or bipolar disorder received olanzapi (n=18). Patients attended weekly group psychoeducational sessions. Of the 14 patients that completed the st pounds and 4 patients lost an average of 2.25 pounds. Of these patients, those that gained weight had signifi compared to both week 5 and week 10 (p=0.0195 and p=0.0092, respectively). Three patients attained their i event was sedation. Controlled studies are needed to substantiate these findings (Powers et al, 2002).

c) A 49-year-old woman with anorexia nervosa and obsessive-compulsive symptoms improved with olanzap obsessive-compulsive problems were mainly fear of food contamination, preoccupation with nutritional issues She had no insight into her problems and was depressed. She weighed 31.2 kilograms when she was started following months, her confusion cleared and her insight changed markedly. Approximately 6 months later her

4.5.G Anxiety - Dementia

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:

Reduced anxiety in elderly dementia patients (Mintzer et al, 2001)

3) Adult:

a) Olanzapine treatment reduced anxiety in elderly patients with Alzheimer's-type dementia independently of somnolence, or benzodiazepine use. A post hoc analysis was performed on a subset of patients (n=120) from evaluated the efficacy of olanzapine (3 dosages) versus placebo for 6 weeks for the treatment of psychosis a disease. The subgroup (mean age 83 years) was selected for exhibiting clinically significant anxiety, defined

Neuropsychiatric Inventory/Nursing Home instrument (NPI/NH). Anxiety scores of patients receiving olanzapi more than scores of patients receiving placebo (p=0.034). Improvement in anxiety with olanzapine 5 mg/day for improvement in hallucinations. With higher doses of olanzapine (10 and 15 mg/day), improvement in anxie with placebo. Somnolence was the only adverse effect that occurred significantly more frequently with olanza peripheral or central potential anticholinergic adverse events occurred more frequently with olanzapine than v effects collectively occurred more frequently with olanzapine 15 mg/day than with placebo (26% vs 6%, p=0.(and placebo treatments in the occurrence of extrapyramidal symptoms (Mintzer et al, 2001).

4.5.H Bipolar I disorder, Acute mixed or manic episodes

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (oral formulations only); Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated for the treatment of acute manic or mixed episodes associated with bipolar I disorder (Prod Info (R) ZYDIS(R) orally disintegrating tablets, 2006)
The combination of olanzapine with lithium or valproate is indicated for the short-term treatment of acute (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2

3) Adult:

a) Monotherapy

1) In a small open-label study, olanzapine was found to be somewhat effective as an adjunctive treatme three, severely ill, BPD patients (10 men) with a history of poor response or intolerance to therapeutic co were enrolled in this long-term study (mean 303 days). The Clinical Global Impressions Scale for use in olanzapine effectiveness. The depression subscale decreased by 0.9 (p less than 0.006), the mania sub score decreased by 1.3 (p less than 0.0003). Ten of the 23 patients had a decrease of at least 2 points o rated as in remission. There were 6 dropouts in the study, 2 due to adverse effects, 2 due to lack of resp follow-up. The mean final dose of olanzapine was 8.2 milligrams (mg) per day with 16 patients taking lith and one each taking gabapentin and lamotrigine concurrently. The most common adverse events were s cases of tardive dyskinesia were reported during the study (Vieta et al, 2001).

2) Olanzapine was more effective than placebo in the treatment of patients with acute bipolar mania. In patients were assigned to receive olanzapine 5 to 20 milligrams (mg) daily (n=55) or placebo (n=60) for 4 significantly greater mean improvement in symptoms over placebo, as determined by the total Young-Ma clinically evident within the first week of treatment and was maintained throughout the study. Significantly 50% or more decrease in total YMRS score from baseline (65% versus 43%, p=0.02) and euthymia as m endpoint) (61% versus 36%, p=0.01). The incidence of extrapyramidal symptoms was similar between ol weight gain, treatment-emergent somnolence, and elevations in aspartate aminotransferase (AST) and a significantly more often in olanzapine-treated patients (Tohen et al, 2000).

3) Olanzapine exhibited superior efficacy over placebo in the treatment of acute mania (Tohen et al, 199 study, patients with manic or mixed episodes associated with bipolar disorder were randomized to receiv placebo (n=69). The olanzapine dose could be adjusted between a range of 5 to 20 mg daily. At the end was 14.9 mg daily. The olanzapine group had a significantly greater improvement in total scores on the Y 0.02). Olanzapine was well-tolerated with no dropouts due to adverse effects.

4) In 2 case reports, olanzapine effectively augmented mood stabilizers in 2 patients with nonpsychotic first was a 34-year-old male with bipolar I disorder that entered a nonpsychotic mixed mood state after in previously been euthymic on lithium and divalproex. Olanzapine 10 milligrams (mg) was added at bedtim the first time in over 2 weeks. He reported complete remission of his symptoms by the next morning. A 4 to a mixed mood state after previously taking divalproex, lorazepam, and levothyroxine. Olanzapine 10 m first time in 10 days. Her mood was also improved by the next morning. Both of these patients had rapid been an indirect benefit of improved sleep with olanzapine or may have actually been due to a direct mo

b) Combination Therapy

1) In patients with bipolar manic or mixed episodes who do not respond adequately to lithium or valproa treatment. In a randomized, double-blind, placebo-controlled trial, patients with bipolar disorder who had therapy (ie, maintaining a score of 16 or more on the Young Mania Rating Scale (YMRS)) received eithe milligrams/day) (n=229) or placebo (n=115). Both groups improved during the course of treatment, but th YMRS score from baseline, while the monotherapy group improved by 40% (p=0.003). Particular items c were irritability, speech, language/thought disorder, and disruptive/aggressive behavior. Sixty-eight perce or greater improvement in YMRS score), compared to 45% of the monotherapy group (p=0.01). Median 28 days with monotherapy. Patients in the co-therapy group showed significantly greater improvement in monotherapy group (p less than 0.001). Among patients experiencing a mixed episode with moderate to Hamilton Depressive scale from baseline to 6 weeks was 10.3 for co-therapy and 1.6 for monotherapy (p adverse events in the co-therapy group were somnolence, dry mouth, weight gain, increased appetite, tr significant changes from baseline were observed in extrapyramidal symptoms (Tohen et al, 2002a).

2) Combination therapy with olanzapine and lithium or valproate was effective in the treatment of acute with manic or mixed episodes. In two 6-week, randomized, placebo-controlled trials, patients (n=175, n= uncontrolled manic or mixed symptoms and with a score of 16 or higher on the Young Mania Rating scal

of 5 to 20 milligrams (mg) once daily, starting at 10 mg/day) or placebo, in combination with their original milliequivalents/liter (mEq/L) to 1.2 mEq/L) or valproate (in a therapeutic range of 50 micrograms/milliliter olanzapine in combination with lithium or valproate was more effective than either lithium or valproate alo Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

4) Pediatric:

a) Monotherapy

1) Olanzapine monotherapy effectively treated symptoms of psychosis, depression, and mania in a grou disorder (BPD). In this open-label, 8-week study, 23 youths, 5 to 14 years old, discontinued their current 2.5 milligrams (mg) per day. Olanzapine was increased by 2.5 mg/day every 3 days to a maximum dose 4.3 mg per day). Lorazepam (up to 4 mg/day) and benztropine (up to 2 mg/day) were allowed as needed symptoms respectively. Patients taking guanfacine or clonidine for attention deficit hyperactivity disorder medications, but could not adjust the dose during the study. Psychiatric symptoms were assessed at bas Rating Scale (YMRS), the Clinical Global Impressions Severity Scale (CGI-S), the Brief Psychiatric Ratin Rating Scale (CDRS). Extrapyramidal symptoms were assessed on the same schedule using the Simps the Abnormal Involuntary Movement Scale (AIMS). Significant improvement from baseline to endpoint w (38%, p less than 0.001), and BPRS (62%, p less than 0.001). The most frequently reported adverse effe (n=10), abdominal pain (n=7) and weight gain (n=7). There was no significant difference in extrapyramid had treatment-emergent akathisia. There were small statistically significant decreases in hematocrit, hem significant increases in alanine transferase (ALT) and prolactin levels. One patient dropped out of the stu symptoms (Frazier et al, 2001).

4.5.I Bipolar I disorder, Maintenance therapy

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (oral formulations only); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated for maintenance monotherapy in bipolar patients who have responded to initial treatment with o injection, ZYPREXA(R) ZYDIS(R) orally disintegrating tablets, 2006)

3) Adult:

a) Continuation olanzapine therapy was more effective than placebo in delaying the time to relapse in patien blind, placebo-controlled trial, bipolar patients with a mixed or manic episode who responded to initial, open-l (mg)/day for approximately two weeks) received either continuation of olanzapine at their same dose (n=225) Response during the initial phase of the study was defined as a decrease in the Young Mania Rating Scale (the Hamilton Depression Rating Scale (HAM-D) score to 8 or less. Relapse was defined as an increase of the hospitalization for either mania or depression. Patients treated with olanzapine showed a significantly longer placebo (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

4.5.J 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:

Improved symptoms in all 4 cores areas of BPD in a 6-month study (Zanarini & Frankenburg, 2001)

3) Adult:

a) Olanzapine was superior to placebo for reducing symptoms of borderline personality disorder (BPD) in a s for BPD and did not meet criteria for major depression were randomized in a 2:1 ratio to receive olanzapine o The starting dose of olanzapine was 1.25 milligrams/day and was adjusted according to perceived response was 5.3 mg. Olanzapine was significantly more effective than placebo in the affective area of anxiety (p=0.00 area of paranoia (p=0.003), and in the area of trouble relationships (p=0.016). Subjects in the olanzapine gro subjects in the placebo group (p=0.012). However, average weight gain of olanzapine- treated subjects was s movement disorders were observed (Zanarini & Frankenburg, 2001).

4.5.K Cancer - Nausea - Pain

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:

Preliminary data indicated safety and efficacy in patients with moderate nausea related to advanced can

study (n=15) (Passik et al, 2002)

3) Adult:

a) In an open-label, pilot study of 15 patients with advanced cancer and associated pain, the administration c nausea. Patients with nausea due to chemotherapy were excluded. Patients (female, n=11; male, n=4) aged primarily breast, lung, and ovarian cancers were receiving opioid analgesics for stable cancer pain and had m nausea) to 10 (worst nausea imaginable)). Patients received olanzapine 2.5 milligrams (mg), 5 mg, and 10 m washout and placebo run-in period. Nausea was measured using the nausea item (scale of 0 (no nausea) to Assessment of Cancer Treatment-General (FACT-G) scale. The proportion of patients who reported scores c decreased from 60% at baseline, to 40% in the 2.5-mg group (p less than 0.04 compared to baseline), and 6. 0.0001 compared to baseline). It could not be determined if efficacy was a dose-response or cumulative effec scores, was highest at the 5-mg dose level (79.5) and differed significantly from baseline (66.6; $p < 0.005$). A Simpson Angus Scale, and the Mini Mental Status Exam, adverse effects related to olanzapine were minimal baseline (Passik et al, 2002).

4.5.L 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:

Olanzapine was effective in the treatment of catatonia in one case report (DelBello et al, 2000)

3) Adult:

a) A 16-year-old African American male was successfully treated for catatonia with a combination of lorazepa admission, the patient had become increasingly noncommunicative and had not slept for 1 week. He was una incontinent of urine and feces. An electroencephalogram (EEG) showed diffuse mild slowing without any evic a dose of 1 milligram (mg) four times daily (QID) and increased to 2 mg three times daily (TID) without improv started, and 3 days later, olanzapine was added and titrated to 10 mg twice daily (BID). Over the next 14 day and attempted to wash and dress himself. On day 21, lorazepam was tapered and discontinued due to exces Valproic acid was discontinued on day 28 By day 42, the patient was interacting with peers and communicati the patient was discharged, experiencing only an occasional auditory hallucination. Olanzapine therapy was c year (DelBello et al, 2000).

4.5.M Chemotherapy-induced nausea and vomiting; Prophylaxis

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effectively prevented acute chemotherapy-induced nausea and vomiting in combination with standard ar vomiting when continued alone, in patients receiving moderately and highly emetogenic chemotherapy ir et al, 2007)

Effective, in combination with granisetron and dexamethasone, for the prevention of acute and delayed c patients receiving moderately and highly emetogenic chemotherapy in a single-arm, phase 2 clinical trial

3) Adult:

a) Use of olanzapine, in combination with palonosetron and dexamethasone, effectively prevented acute che continued monotherapy with olanzapine prevented most cases of delayed nausea and vomiting in patients re chemotherapy in a single-arm, phase 2 clinical trial. Patients (n=40; median age, 61 years; range, 36-84 year cancer (n=12), colon cancer (n=7), small cell lung cancer (n=2), lymphoma (n=2), and bladder cancer (n=2), meter (mg/m(2)) or greater) or moderately (carboplatin area under the curve (AUC) 5 or greater, irinotecan, c doxorubicin 25 mg/m(2) or greater) emetogenic chemotherapy were scheduled to receive antiemetic prophyla and olanzapine on day 1 of their first cycle of chemotherapy. Doses consisted of 8 mg of dexamethasone giv emetogenic chemotherapy or 20 mg orally or IV for highly emetogenic chemotherapy, 0.25 mg of palonosetro and 10 mg of olanzapine orally. On days 2 through 4, only olanzapine 10 mg orally daily was administered. A chemotherapy up to 6 cycles. Rescue antiemetics were administered per physician discretion. For the 8 patie in cycle 1, 100% had complete responses (no emesis and no rescue medication) in the acute (0 to 24 hours) the delayed (24 to 120 hours) and overall (0 to 120 hours) periods. For the 32 patients who received moderat complete responses in the acute period, 75% in the delayed period, and 72% in the overall period. Nausea, v M.D. Anderson Symptom Inventory (MDASI), occurred in 11 patients in the delayed period (highly emetogeni Results in subsequent cycles were not significantly different from those in the first cycle. No grade 3 or 4 adv (Navari et al, 2007).

b) The combination of olanzapine, granisetron, and dexamethasone were effective for the prevention of acut vomiting in patients receiving moderately and highly emetogenic chemotherapy in a single-arm, phase 2 clini range, 25-84 years) with breast cancer (n=16), small cell lung cancer (n=4), non-small cell lung cancer (n=3), (n=4), receiving highly (cisplatin 70 milligrams/square meter (mg/m(2)) or greater) or moderately (carboplatin,

mg/m(2), or doxorubicin 25 mg/m(2) or greater) emetogenic chemotherapy were scheduled to receive antiem orally each morning for 2 days prior to chemotherapy (days -2 and -1), then dexamethasone (20 mg orally or micrograms/kilogram IV or 2 mg orally 30 to 60 minutes prior to chemotherapy) on day 1. In addition, olanzap through day 4, and dexamethasone 8 mg twice daily for days 2 and 3 and 4 mg twice daily on day 4. Antieme chemotherapy up to 6 cycles. Rescue antiemetics were administered per physician discretion. For the 10 pat chemotherapy in cycle 1, 100% had complete responses (no emesis and no rescue medication) in the acute responses each in the delayed (24 to 120 hours) and overall (0 to 120 hours) periods. For the 20 patients wh 100% had complete responses in the acute period and 85% had complete responses each in the delayed an daily by patients using the M.D. Anderson Symptom Inventory (MDASI), occurred only in patients receiving m (15%), delayed (35%), and overall (35%) periods. Results in subsequent cycles were not significantly differer adverse events due to the study drugs were observed (Navari et al, 2005).

4.5.N Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

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

4.5.O Cocaine dependence

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:

Olanzapine was ineffective in the treatment of cocaine dependence (Kampman et al, 2003)

3) Adult:

a) Olanzapine was not an effective therapy for the treatment of cocaine dependence. In a randomized, place dependent patients (n=30) received olanzapine (initial, 2.5 milligrams (mg)/day, titrated to 10 mg/day) or plac phase. Urine benzoylecgonine tests (UBT) were obtained twice a week. A significant time by medication grou results whereby the estimated odds of a positive UBT went up by 4% between visits for olanzapine-treated pa by 6% for patients in the placebo group (95% CI, 0.92 to 0.968) (p=0.01). In addition, treatment retention was olanzapine group. Patients in the placebo group attended a significantly greater median number of treatment vs 18, respectively; p=0.029). Finally, olanzapine was not superior to placebo in any of the secondary outcom anxiety symptoms, and self-reported cocaine use. The most common adverse effects reported during the stu constipation (13%), dizziness (10%), dry mouth (7%), nausea (7%), restlessness (7%), and urticaria (3%) (Ka

4.5.P Delirium

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:

May produce significant improvement in patients with delirium (Kim et al, 2001; Sipahimalani & Masand,
Attenuated delirium in hospitalized cancer patients, with no report of any extrapyramidal effects (Breitbar

3) Adult:

a) A 7-day course of oral olanzapine produced resolution of delirium or reduction of symptom severity in hos (DSM-IV), according to an open-label observational study (n=79). Enrollees (mean age 60.6 years) had a me from mild (17%) to moderate (61%) to severe (23%). Mean olanzapine starting dose was 3 milligrams (mg), v mean 6.3 mg at days 4 to 7. Subjects were given olanzapine as a single dose at bedtime or in 2 divided dose patients (76%) achieved complete resolution of delirium (defined as a Memorial Delirium Assessment Scale (decreased from baseline 19.85 to 12.73 at day 2/3 (p=0.001) and to 10.78 at study endpoint (days 4 to 7) (p= strongly associated with a poor response were age above 70 years, central nervous system spread of cancer factors which tended to correlate with less successful outcomes were a history of dementia, severe delirium a Side effects were few and relatively mild; sedation was the most commonly reported adverse effect (30% inci cohort. Olanzapine was withdrawn in 2 subjects whose delirium seemed to worsen when taking the drug (Bre

b) Fourteen patients given olanzapine demonstrated a 50% or greater reduction in delirium scores in an ope females), patients (mean age 46 years) with varying etiologies of delirium. Mean olanzapine treatment doses occurring in an average of 3.8 days. The pretreatment Delirium Rating Scale (DRS) score showed a significa following a mean duration of 6.6 days. Eleven of the 14 patients that had a 50% or greater decrease in DRS v brain injury had a DRS score that increased from 19 to 21. None of the patients had comorbid psychiatric dia medications during this study. The authors said that adverse effects due to olanzapine were minimal althoug placebo control group for comparison (Kim et al, 2001).

c) In an open-label study of 22 adult patients (mean age approximately 64 years) with varying etiologies of d of 11 patients given haloperidol showed marked improvement in the Delirium Rating Scale (DRS; greater tha were 8.2 milligrams (mg) with olanzapine and 5.1 mg with haloperidol. Pretreatment DRS were similar in both haloperidol group. Mean improvement in the DRS was 7.6 with olanzapine and 10 with haloperidol. Peak resp agents. Some of the patients in each group had comorbid psychiatric diagnoses and were taking other psych

olanzapine experienced side effects, while 3 haloperidol patients experienced extrapyramidal symptoms and Masand, 1998).

d) A 59-year-old cancer patient with delirium was successfully treated with olanzapine (Passik & Cooper, 19 patient's symptoms and she was started on olanzapine 5 milligrams (mg) daily. She improved dramatically wi olanzapine 10 mg with 2.5 mg as needed during the day. Her mental status returned to normal over 72 hours

4.5.Q Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.R Depressed bipolar I 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 monotherapy and olanzapine plus fluoxetine combination therapy reduced depressive sympt al, 2003)

3) Adult:

a) Both olanzapine monotherapy and olanzapine plus fluoxetine combination therapy were more effective tha In a randomized, double-blind, placebo-controlled, multi- center, international study, patients with bipolar I dis Montgomery-Asberg Depression Rating Scale (MADRS) received olanzapine (n=370; 5 to 20 milligrams (mg) plus fluoxetine (n=86; 6 and 25 mg/day, 6 and 50 mg/day, or 12 and 50 mg/day; mean dose, 7.4 and 39.3 mg objective of the study compared olanzapine monotherapy versus placebo with regard to change in the MADR all 8 weeks of the study, treatments with both olanzapine and olanzapine-fluoxetine combination produced sig symptoms (as measured by the MADRS) as compared with placebo (p less than 0.001, all values). Also, a si MADRS score at weeks 4, 6, and 8 were observed with olanzapine-fluoxetine combination therapy as compa p=0.01, respectively). The rate of response (defined as at least a 50% improvement in the MADRS total score significantly higher in olanzapine-treated patients as compared with placebo (39% vs 30.4%, respectively; p= significantly higher in the olanzapine-fluoxetine group as compared with both the placebo (56.1% vs 30.4%, r groups (56.1% vs 39%, respectively; p=0.006). There were no statistically significant differences between gro mania. Adverse events were similar between the combination therapy and monotherapy groups, however, the higher rate of nausea and diarrhea (Tohen et al, 2003).

4.5.S Depression, Treatment-resistant

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:

Ineffective as a single agent in resistant depression
Possibly effective as augmentation therapy with antidepressants (Parker, 2002)

3) Adult:

a) Some patients experiencing a recurrence of depression while under medical treatment responded very qu regimen. In a case series of 10 patients, 4 patients, all of whom had unipolar depression, were judged to be r treatment. Of the 6 responders, 5 had bipolar conditions and were receiving venlafaxine, desipramine, anafra taking lithium. Each received olanzapine augmentation of 2.5 milligrams (mg) or 5 mg each night. Daily rating the first day, 73% by day 4, and 89% by day 6. Anxiety and insomnia scores, in particular, showed notable im showed linear improvement over the week. Two patients emerged with what they described as a "high." Beca majority, it is uncertain whether the improvement with olanzapine was through an effect on a switching mecha

b) Patients with treatment-resistant, nonpsychotic, unipolar depression treated with olanzapine combined wit improvement than either agent alone across a variety of measures. In an 8-week, double-blind study, 28 patie treatment groups: olanzapine plus placebo, fluoxetine plus placebo or olanzapine plus fluoxetine. The mean r and 13.5 mg for the monotherapy and combined therapy groups, respectively. The mean modal dose of fluox and combination group. Patients receiving combination therapy experienced greater improvements over base Scale scores than with either agent alone and in total Hamilton Depression scale scores than olanzapine trea (at least 50% improvement in Montgomery-Asberg Depression Rating Scale score) in the combination therap olanzapine alone (60% versus 0%). Both drugs were well tolerated alone or in combination. Adverse effects i weight gain, headache, dry mouth, and nervousness. Increased appetite and weight gain occurred significant (Shelton,et al, 2001).

4.5.T Essential tremor

1) Overview

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

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

2) Summary:
May be effective in the treatment of essential tremor (Yetimalar et al, 2003)

3) Adult:
a) Results of an open-label study suggest that olanzapine may be effective in the treatment of essential trem with essential tremor received divided, oral doses of olanzapine 5 to 20 milligrams daily. Six months following significantly reduced from 3.3 (baseline) to 1.12 (scale, 1 to 4; p=0.0001). Mild, transient sedation was the mo studies are needed to further substantiate these findings (Yetimalar et al, 2003).

4.5.U Fibromyalgia

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:
Treatment with olanzapine led to reduction in pain symptoms and improvement in daily life functioning in review (n=51); treatment discontinuation was high (53%), mostly due to weight gain (30%), somnolence/ (Freedenfeld et al, 2006)

3) Adult:
a) A retrospective chart review showed that treatment with olanzapine led to reduction in pain symptoms and (n=51) with fibromyalgia. Records of all fibromyalgia patients 18 to 65 years of age (mean age, 44 years; fem during a 3-year period at one center were reviewed. Comorbid psychiatric conditions were present in 88% of treated being major depressive disorder (81%) and anxiety disorder (42%). At the time of treatment with olan Patients with a history olanzapine use prior to receiving treatment for fibromyalgia were excluded. While olan for treatment of fibromyalgia symptoms, it was also used for relief of other symptoms, such as anxiety and sle Inventory (BPI) were evaluated separately, and results from 1 month pretreatment and posttreatment with ola was determined to be when the patient had reached the maximal therapeutic dose, defined as when then pat physician and/or when the olanzapine dose was unchanged for a month. Pretreatment ratings on pain and in pain variables, significant improvements occurred in the mean current pain level, worst pain level, least pain l scales measuring pain interference with daily functioning, significant improvements occurred in interference v enjoyment, and concentration. For patients with dosing information in their records (n=41), the majority (80.5 milligrams or less per day. Based on physician rating data (n=29), the majority experienced at least moderate (62%). Treatment discontinuation occurred in 53% (27/51) of patients, with the most common reasons being and no treatment benefit (11%). Overall, weight gain occurred in 24% and somnolence/sedation occurred in 2

4.5.V Gilles de la Tourette's syndrome

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

2) Summary:
Effective in a small study of 14 patients (Stamenkovic et al, 2000)

3) Adult:
a) Olanzapine was found to be a safe and effective alternative to other antipsychotics for the treatment of To olanzapine was initiated at 10 milligrams daily with a maximum dose of 20 milligrams daily. The mean dose a Yale Global Tic Severity Scale (YGTSS) and the Clinical Global Impression Severity Scale (CGI) scores sign day 0 (p less than 0.005). The definition of treatment success (60% reduction in YGTSS score) was achieved observed between the groups. The only side-effect observed was mild sedation which resolved as treatment The data suggests that olanzapine is safe and effective for the treatment of Tourette's disorder but more doul (Stamenkovic et al, 2000).

4.5.W Headache, Chronic, refractory

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:
Effectively treated patients with chronic refractory headache who had failed previous therapies (Silberste

3) Adult:
a) The results of a retrospective review indicate that olanzapine was effective in the treatment of patients wit

unblinded review of 50 patient charts was conducted to assess the effectiveness of olanzapine treatment in p
had failed at least 4 previous preventative medication trials. Olanzapine doses ranged from 2.5 to 35 milligra
mg (n=19) or 10 mg (n=17) per day. The mean number of headache days was significantly reduced from 27.
following treatment (p less than 0.001). Average headache severity scores were also significantly lower after
8.7, respectively; p less than 0.001). The most common adverse events were weight gain and somnolence. C
findings (Silberstein et al, 2002).

4.5.X 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:

Lessens involuntary movements (Bonelli et al, 2002; Dipple, 1999)
Decreases agitation, aggression, and delusions (Grove et al, 2000)

3) Adult:

a) High dose olanzapine (30 milligrams (mg) per day) greatly improved chorea in a 30-year-old woman with
6 years and in 2 days had a severe worsening of her chorea. She could not eat or dress without help and did
dysfunction or psychiatric abnormality. Her major deficits were in fine motor tasks, oral functions, chorea, and
first day and 30 mg/day thereafter. The chorea nearly stopped in the next 2 days, and she was able to eat an
improvement in fine motor tasks and gait. Her mild parkinsonism was not improved. Four months later, her im
2002).

b) Olanzapine improved cognition and function as measured by the Abnormal Involuntary Movement Scale (
in a 49-year-old man with dementia resulting from Huntington's disease. Prior to admission, treatment with ha
10 mg/d, and tiapride 200 mg/d had been unsuccessful. Olanzapine 5 mg/d decreased the patient's impulsivi
10 mg/d was associated with improvement in chorea movements and ability to perform activities of daily living
score dropped from 40 to 22, MMSE improved from 20 to 26. At 5 months, the cessation of irritability and agg
movement disorders, cognitive ability and functional ability suggested therapeutic benefit was related to olanz
serotonergic or dopaminergic receptor is theorized as a reason for these effects (Bogelman et al, 2001).

c) Olanzapine was used in combination with valproate in a 39-year-old man and 52-year-old woman to treat
with Huntington's disease of 8 and 13 years duration, respectively. In the year prior to hospitalization, the pat
severe neither could walk or assist in their care. Prior haloperidol treatment had been unsuccessful. Initially b
milligrams (mg) daily and valproate 125 mg twice daily. Subsequently, the olanzapine dose was reduced to 5
valproate was increased to 500 mg three times daily (plasma concentrations from 60 to 80 micrograms per m
discharged to nursing homes, able to walk with assistance, cooperative with eating, bathing, and social activi
movements decreased (Grove et al, 2000).

d) A man in his early 50's had marked improvement of his movement disorder associated with Huntington's
been treated with sulpiride, which was ineffective, and risperidone, which caused hypotension. Olanzapine 5
improvement in his involuntary movements within 1 week. He experienced slowed thinking but adjusting the t
maintained his improvement in involuntary movements over the next 6 months. The authors hypothesized tha
associated with Huntington's disease, the D2 antagonist properties of olanzapine may be beneficial in the imp

4.5.Y Obsessive-compulsive disorder, Refractory

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:

Partially effective as an augmentation strategy with serotonin-reuptake inhibitors in studies with small nu
1999)
One study showed no additional benefit in the addition of olanzapine to fluoxetine therapy in the treatme
compulsive disorder (Shapira et al, 2004)
Adjunctive therapy of risperidone or olanzapine with serotonin-reuptake inhibitors (SRI) were equally effe
in SRI monotherapy-resistant outpatients, according to an 8-week, single-blind, randomized trial (Maina

3) Adult:

a) General Information

1) Information regarding the efficacy of olanzapine for the treatment of patients with refractory obsessive
studies with small numbers of patients have reported that olanzapine therapy (1.25 to 20 milligrams (mg)
strategy with selective serotonin-reuptake inhibitors (SSRI), while the findings of a controlled study indica
additional benefit when added to SSRI therapy in patients with fluoxetine-refractory obsessive compulsiv
determine the role of olanzapine as an augmentation therapy in this patient population (Shapira et al, 20
et al, 1998).

b) Adjunctive therapy of risperidone or olanzapine with serotonin-reuptake inhibitors (SRI) were equally effec
in SRI monotherapy-resistant outpatients, according to an 8-week, single-blind, randomized trial; however thi

placebo arm, single-arm design, and underpowered nature of the trial. Following a 16-week prospective, ope who were treatment-resistant (defined as less than 35% improvement in the total score of Yale-Brown Obses Global Impression Severity (CGI-S) score greater than 2, entered an 8-week single-blind phase (n=50). Patie doses of clomipramine 200 to 225 mg, citalopram 50 to 80 mg, fluoxetine 60 mg, fluvoxamine 200 to 300 mg, were randomized to receive either risperidone 1 to 3 mg/day (n=25), or olanzapine 2.5 to 10 mg/day (n=25) i personnel and assessor-blinding constituted the single-blind study design; patients were not blinded. In an int analysis of the primary endpoints, both treatments significantly improved Y-BOCS and CGI-S scores by week mean Y-BOCS total scores, CGI-S scores, and responder rates (35% or greater improvement in Y-BOCS sc was similar between groups (Maina et al, 2008).

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		

(Maina et al, 2008)

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

c) The addition of olanzapine to ongoing fluoxetine therapy did not provide additional benefit in the treatment refractory to fluoxetine. In a double-blind, placebo-controlled study, patients (n=44) with obsessive-compulsiv partial or non- responders to 8 weeks of open-label treatment with fluoxetine (up to 40 milligrams (mg)/day) re (initial, 5 mg/day, titrated up to 10 mg/day) or placebo for 6 weeks. Mean scores for the Yale-Brown Obsessiv improved for patients in both the fluoxetine-plus- olanzapine (decrease of 5.1) and fluoxetine-plus-placebo (d However, the treatment x time interaction was not significant for olanzapine (mean, 6.1 mg) versus placebo (treatment groups, 9 (41%) patients showed a 25% or greater improvement in Y-BOCS score. In addition, a 3 patients in the fluoxetine-plus-olanzapine group and in 4 (18%) patients in the fluoxetine-plus-placebo group. fluoxetine was generally well tolerated, however patients receiving add-on therapy with olanzapine gained mo placebo (mean, 2.8 kilograms vs 0.5 kilograms, respectively) (Shapira et al, 2004).

d) Olanzapine augmentation was partially effective in the treatment of 10 patients with obsessive-compulsive milligrams per day (mg/d) for at least 10 weeks). Olanzapine 2.5 mg/d was added and titrated to 10 mg daily additional 4 weeks. Patients were assessed for improvement of symptoms using the Yale-Brown Obsessive- therapy was defined as a greater than or equal to 25% decrease in Y-BOCS score. Three patients responded and 2 only minimally improved. Seven of 10 patients had comorbid conditions, including major depression, dy disorder, and schizotypal personality disorder with tics. Two patients with comorbid conditions showed improv markedly improved mood symptoms but not OCD, and another patient with dysthymia and OCD showed rapi common adverse effects were weight gain, drowsiness, dry mouth, and increased appetite (Koran, et al, 200

e) Olanzapine may be effective in augmenting selective serotonin reuptake inhibitor (SSRI) treatment for sor disorder (OCD) refractory to SSRI therapy. Ten patients diagnosed with OCD and who had completed at leas were given open- label olanzapine augmentation for a minimum of 8 additional weeks. Prior to initiating olanz at the end of SSRI treatment and only 4 demonstrated a partial response. Olanzapine augmentation was initi indicated (mean dose was 7.3 +/- 7.3 milligrams/day). Within 8 weeks, 4 patients were responders and 3 wer changes in their OCD symptoms. Symptomatic improvement generally began within the first 2 weeks of olanz tolerated with 2 patients discontinuing olanzapine due to sedation. Further studies are warranted to determine therapy in the treatment of SSRI-refractory OCD (Weiss et al, 1999).

f) A 24-year-old woman with refractory obsessive-compulsive disorder benefited from the addition of olanzap She had previously failed a trial of clomipramine with risperidone. She was being maintained on fluoxetine 80 Obsessive Compulsive Scale (Y-BOCS) score of 18. Olanzapine was titrated up to 20 mg daily over 3 months decreased to 10. She has maintained this response for 6 months, however, she has gained 18 pounds.

4.5.Z Parkinson's disease - 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:

Decreases psychotic symptoms in nondemented, Parkinson's patients with drug-induced psychosis

May also worsen Parkinsonian symptoms
See Drug Consult reference: THERAPY OF PSYCHOTIC DISTURBANCES IN PARKINSONIAN PATIENTS

3) Adult:

a) The results of a prospective, open-label, uncontrolled study of 21 elderly patients (mean age 74.4 +/- 6.4 y concluded olanzapine improved delusions and hallucinations while not worsening parkinsonism or cognition. milligrams/day. Due to frequent side effects (primarily drowsiness), the starting dose was reduced to 2.5 milli milligrams/day. After 8 weeks of treatment, the summed score of the Neuropsychiatric Inventory (NPI) for del 85%, and 80% of those who completed the 8 weeks were considered much or very much improved, accordin scores. Twenty-nine percent of patients withdrew due to side effects (primarily drowsiness). Larger controlled

b) In a case series of patients suffering hallucinations and vivid dreams secondary to treatment of their parki improved, however, their motor symptoms declined (Graham et al, 1998a). Five outpatients with idiopathic Pa were started on olanzapine 5 milligrams (mg) nightly. Two patients were increased to 7.5 mg. Hallucinations to discontinue olanzapine while the other 3 also had declines in their motor function and "on" time. The autho been as problematic if a smaller initial dosage form were available (less than 5 mg).

c) Olanzapine was well-tolerated and effective in an open study of 15 Parkinson's disease patients with drug Criteria) (Wolters et al, 1996a). The initial dose was 1 milligram (mg) daily, titrated up to a maximum of 15 mg Brief Psychiatric Rating Scale (BPRS), the Unified Parkinson's Disease Rating Scale (UPDRS), and a sleep s BPRS scores by 65% (p less than 0.05), significantly reduced UPDRS total scores by 21% (p less than 0.01) than 0.01).

d) In a letter to the editor, one physician's experiences with olanzapine, in patients with drug-induced psycho Parkinson's disease, were not encouraging (Friedman, 1998). He described only 9 of 19 patients remaining c other 10 all experienced worsening of their parkinsonism despite 7 patients also improving in their psychoses

4.5.AA Pervasive developmental disorder

1) Overview

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

2) Summary:

Some improvement in one small open-label study in patients with autism or pervasive developmental dis
Only 3 of 12 pediatric patients benefited in a small retrospective chart review (Demb & Roychoudhury, 2

3) Adult:

a) In a 12-week open-label pilot study of eight children, adolescents, and adults with pervasive development were rated as much improved or very much improved on the Clinical Global Impression Scale. Patients range criteria for pervasive developmental disorder (autistic disorder, n=5; not otherwise specified, n=3). Mean olan changes from baseline were observed on the Vineland Maladaptive Behavior Scale, Rivto-Freeman Real-life Questionnaire, and portions of the Clinician-Rated Visual Analog Scale (all p less than 0.001). One patient dr patients experienced weight gain, and three patients reported sedation (Potenza et al, 1999).

4) Pediatric:

a) A retrospective chart review demonstrated that olanzapine therapy (2.5 to 15 milligrams per day (mg/d)) w and hallucinations in only 3 of 12 pediatric patients (aged 5 to 17 years) with developmental disabilities or psy efficacy reporting improvement or worsening of symptoms. Ten of the 12 studied had previously failed other p mentally retarded. Eight of the 12 children discontinued olanzapine after a mean duration of 50 days due to a exacerbated target symptoms or a combination of these issues (2). The most frequent side effects were an ir tremulousness, drooling, and suicidal ideation were also reported (Demb & Roychoudhury, 2000). In another olanzapine due to weight gain despite a positive response to therapy, while adult responders continued thera groups may exhibit diverse responses to olanzapine treatment (Potenza & McDougle, 2001).

b) In a 12-week open-label pilot study of eight children, adolescents, and adults with pervasive development were rated as much improved or very much improved on the Clinical Global Impression Scale. Patients range criteria for pervasive developmental disorder (autistic disorder, n=5; not otherwise specified, n=3). Mean olan changes from baseline were observed on the Vineland Maladaptive Behavior Scale, Rivto-Freeman Real-life Questionnaire, and portions of the Clinician-Rated Visual Analog Scale (all p less than 0.001). One patient dr patients experienced weight gain, and three patients reported sedation (Potenza et al, 1999).

4.5.AB 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:

Improved all types of symptoms of PTSD in combat veterans (Petty et al, 2001)
Effective in reducing sleep disturbance and nightmares secondary to PTSD in one case report (Labbate,

3) Adult:

a) Adjunctive olanzapine therapy was more effective than placebo in the treatment of patients with selective

posttraumatic stress disorder (PTSD). In a randomized, double-blind, placebo-controlled study, patients with
responsive to at least 12 weeks of SSRI treatment received 8 weeks of adjunctive therapy with either placebo
(mg)/day then titrated to 20 mg/day as necessary; mean dose, 15 mg/day). Concurrent SSRI medications inc
paroxetine (median dose 40 mg/day), and sertraline (median dose 200 mg/day). Olanzapine-treated patients
symptoms (p less than 0.05), sleep disturbances (p=0.01), and depressive symptoms (p less than 0.03) as co
clinical global improvement were not significantly different between the two treatment groups. Patients treate
during treatment as compared with placebo (mean, 13.2 pounds (lb) vs -3 lb, respectively; p=0.001). In this re
olanzapine as an adjunctive treatment to an SSRI should be weighed against the potential health risks assoc
b) Olanzapine treatment improved all outcome measures of post- traumatic stress syndrome (PTSD) in a gro
PTSD. In an 8-week, open-label, uncontrolled study, all patients (n=46) were initially given olanzapine 5 milli
in 5 mg/week increments to a maximum of 20 mg/day. Mean dose at study end was 14 mg/day. By the end o
PTSD Scale (CAPS) decreased by approximately 30%. Symptom clusters were reduced: intrusive by 31%, a
Adverse event included increased appetite (49%), dry mouth (45%), insomnia (23%), weight gain (22%), drow
(13%), dizziness (10%), constipation (10%), and tremor (10%). Only 30 patients completed the study (Petty e
c) Nightmares and hallucinations experienced by a 58-year-old male combat veteran with posttraumatic stre
initiation of olanzapine therapy (5 milligrams at bedtime). The patient, who had a 20-year history of PTSD had
disturbances with psychotherapy and numerous psychotropics including amitriptyline, imipramine, doxepin, d
fluoxetine, bupropion, sertraline, and trazodone. Although his depression and anxiety improved, nightmares a
and anxiety were reasonably well controlled with sertraline 200 mg daily, bupropion 150 mg daily, and diazep
this regimen, sleep quality improved after 2 nights. A trial dose of 10 mg caused daytime drowsiness and har
Nightmares did not recur during the next 4 months (Labbate, 2000).

4.5.AC Repetitive self-excoriation

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 self-induced dermatoses in isolated cases (Gupta & Gupta, 2000)

3) Adult:

a) Self-excoriation of acne lesions was significantly reduced in a 28-year-old high school teacher by treatmer
14 and had begun excoriating her acne at age 16. At age 18 her acne was successfully treated with isotretino
of stress, and she resumed self- excoriation. Under stress at age 28 and performing excoriation, she was give
Improvement in her excoriating behavior was evident in 2 weeks, with further improvement at 4 weeks. She c
psychotherapy. As of 4 months after the discontinuation of olanzapine, she had maintained the improvement
b) Three patients with self-inflicted dermatoses were successfully treated with olanzapine 2.5 to 5 milligrams
acne, self-induced skin ulcers, and trichotillomania within 2 to 4 weeks of initiating olanzapine therapy. Durati
Improvement was maintained in 1 patient by taking 2.5 mg once or twice weekly as required (Gupta & Gupta,

4.5.AD Schizophrenia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (oral formulations only); Pediatric, no
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:

Indicated for the management of schizophrenia (Prod Info ZYPREXA(R) oral tablets, IM injection, ZYPRI
2006).
Produced significant reductions in both positive and negative symptoms in schizophrenic and schizophre
Effective for positive and negative symptoms of schizophrenia in Japanese patients (Ishigooka et al, 200
Olanzapine and quetiapine were both effective in reduction of symptomatology, but a significant weight g
population, according to a 6-month, randomized, open-label study in 51 patients with first episode psych

3) Adult:

a) General Information

1) Oral olanzapine has produced significant reductions in both positive and negative symptoms in schizo
uncontrolled and placebo-controlled studies, with a low propensity for extrapyramidal effects (Prod Info Z
al, 1996)(Anon, 1995; Anon, 1994b; Anon, 1994aa). The drug has been more effective than haloperidol f
(Beasley et al, 1996)(Anon, 1995). In one review of medical records, olanzapine was more likely to be ef
also have a diagnosis of bipolar disorder (Zarate et al, 1998). In 1 case, it was successfully used for the s
associated with coproporphyria (Strauss & DiMartini, 1999).

b) Short-term Treatment

1) Olanzapine and risperidone were equally safe and effective therapies in the treatment of schizophren
multicenter, double-blind study, 175 elderly patients (mean age, 71 years) were randomized to receive e
(mg)/day) or olanzapine (mean dose, 11.1 mg/day) for 8 weeks following a 1 week washout period of all

was 36.5 years and Positive and Negative Syndrome Scale (PANSS) scores were between 50 and 120 a decrease of at least 20% in the total PANSS score. Both treatment groups showed significant reductions points (p less than 0.005) and significant differences were not observed between groups. Fifty-eight perc olanzapine-treated patients achieved clinical improvement as defined by the study. Both groups also exh PANSS factor scores (p less than 0.001). The greatest mean change in the total PANSS score occurred antipsychotic medications in the thirty days prior to entering the study (p less than 0.001). The rate of ext the risperidone and olanzapine treatment groups (9.2% vs 15.9%, respectively, p=ns). The severity of EP baseline to endpoint with no significant difference between groups. A 7% or higher increase in weight oc patients as compared with those who received risperidone (14.8% vs 5.1%, p=0.043). No new cardiovas population and mean QT-c changes were not considered clinically relevant (Jeste et al, 2003a).

2) Olanzapine was safe and effective for the treatment of schizophrenia in Japanese patients. Eighty-on of Diseases, 9th edition, criteria for schizophrenia were given olanzapine 1 milligram (mg) per day to a m optional 4 week extension. The mean dose during the study was 7.9 mg/day. Prior to the study, 67% of p medications, whereas during the study, only 14% used anticholinergics, suggesting that the frequency o with olanzapine than with their prior antipsychotic medications. Moderate and remarkable improvement v Psychiatric Rating Scale showed statistically significant improvement (p less than 0.05) from week 1 to w anergia; from week 2 to week 9 on activation and thought disturbances; and from week 4 to week 8 on h effects were insomnia, weight increase, excitement, sleepiness, and anxiety. Serum prolactin levels, whi endpoint (Ishigooka et al, 2001a).

3) In one case report, high doses (40 milligrams/day) of olanzapine appeared to be more effective for tre milligrams/day (Alao, 2000). The patient, who had a history of schizophrenia, initiated olanzapine therapy was continued for 3 weeks with no significant clinical improvement. The dose was then increased to 40 r improvements in thought process, agitation, and behavior. Additionally, there was no evidence of extrapy dose. Complete blood counts, liver function tests, electrocardiogram, vital signs, and clinical evaluations distinguish the benefits and weaknesses of high-dose olanzapine therapy in treatment- resistant schizop

4) Olanzapine combined with sulpiride, a selective dopamine-2-receptor blocker, significantly improved s schizophrenia (n=5) and acute psychosis (n=1). Olanzapine doses were titrated to 20 milligrams (mg) da Sulpiride doses ranged from 60 to 600 mg daily. Treatment response, defined by improvement in the Bri and Negative Syndrome Scale (PANSS), and the Clinical Global Impression Scale (CGI), occurred betw adverse effects were reported (Raskin et al, 2000).

5) Five patients who experienced refractory psychosis attributed to noncompliance with clozapine therap to tolerate olanzapine therapy (Weiss, 1999). On admission, all patients were drug-free, highly symptom (BPRS) score of 47. At discharge, all patients were responding well to olanzapine treatment (10 to 20 mi Upon interview, 2 patients reported mild dizziness and weight gain, while 1 patient reported akathisia. M olanzapine in patients with treatment-refractory psychosis who are intolerant of clozapine.

6) A successful transition from clozapine to olanzapine was attained in 8 out of 19 schizophrenic or schi clozapine (Henderson et al, 1998). In an open study, olanzapine 5 milligrams (mg) daily was added to ea weekly to a maximum of 30 mg/day. After the first week, clozapine doses were gradually decreased by ir transition was defined as maintaining a stable clinical status on olanzapine treatment alone for at least 2 and mean final olanzapine dose was 17.1 mg/day. Eight patients successfully transitioned, 7 patients de hospitalization, and an additional 4 patients showed worsening of clinical status. Scores on the Brief Psy increases for the negative symptoms subscale (p=0.002) and the depressive symptoms subscale (p=0.0 clinical status stabilize after 4 to 8 weeks. Those that responded had been treated for a significantly shor receiving a lower dose of clozapine (p=0.05).

7) In an open study, some patients with refractory schizophrenia or schizoaffective disorder responded t (mg)/day (Fanous & Lindenmayer, 1999). Seven treatment-refractory patients received olanzapine titrate Brief Psychiatric Rating Scale was achieved at a dose of 25 mg in 3 of 7 patients; they had only achieved was achieved by a fourth patient at 30 mg/day while only attaining a 14% reduction at lower doses. Only mg/day. Three of the 4 responders were also receiving typical neuroleptics. The 2 nonresponders were r were well-tolerated with only weight gain and diarrhea reported as adverse effects.

8) In an open trial of olanzapine in 16 patients with treatment-refractory psychosis, only two patients sho Improvement score of 1 to 3) over the 12 week study period. Patients were between 31 and 49 years old patients had failed therapy with at least 2 antipsychotics previously and were taken off all psychotropics, patient taking valproic acid. Two patients were taken off olanzapine after one week; one due to mania an behavior and paranoia. Two additional patients did not finish 12 weeks of treatment. Based on the Positiv Global Impression scale, no significant changes were seen over the 12 week period. Mean daily benzodi period; however, benztropine use decreased (p less than 0.05). No patient discontinued olanzapine due

9) Olanzapine showed a superior and broader spectrum of efficacy over haldol in the treatment of schizo profile (Tollefson et al, 1998a; Tollefson et al, 1997b). In a large international, multicenter double-blind tri haloperidol (n=660) over 6 weeks. Starting doses were 5 milligrams (mg) for both drugs which could be i discretion to a maximum of 20 mg/day. Olanzapine was significantly superior to haldol on the Brief Psych and Negative Syndrome Scale (p=0.05), the Clinical Global Impression severity score (p less than 0.03), Scale total score (p=0.001). Significant advantages were also seen in the extrapyramidal profiles and eff subsequently criticized (Capehart & Holsinger, 1998; Barbui, 1998; Mattes, 1998). Some of the criticisms participants, mismatched doses of haloperidol and olanzapine, and questionable blinding procedures.

10) In an open, pilot study, olanzapine was effective and well-tolerated in neuroleptic-resistant patients ((subtypes: 18 paranoid type, 4 disorganized, 3 undifferentiated) with a documented lack of response to 2 week study with olanzapine 15 to 25 milligrams. At the end of the study, the patients showed a statistical

positive and negative symptoms (p less than 0.05). Overall 35% of the patients met the criteria for treatm total score of less than 18 on the Brief Psychiatric Rating Scale and a rating of less than 3 on the Clinica report also documents the effectiveness of olanzapine in a patient that was treatment-resistant to typical clozapine due to tachycardia (Thomas & Labbate, 1998).

11) With olanzapine in mean doses of 11.6 and 16.3 milligrams daily for a period of 6 weeks, reductions scores by 13 and 15 (from baseline of approximately 42), respectively, were reported in schizophrenic pa exacerbation) in a relatively large trial (n=335). For positive symptoms (BPRS-positive), such as concept suspiciousness, both doses were of similar efficacy (decreased by 4.5 points), whereas the higher dose (BPRS-negative) (-3 versus -1.4 points), including emotional withdrawal and motor retardation. The Scal also revealed trends for the superiority of the higher dose. Although decreases in the BPRS-total and BP compared to placebo, significance was achieved for negative symptoms on both SANS and BPRS-negat A lower dose of olanzapine (mean, 6.6 milligrams/day) did, however, result in significant reductions in ne flaw in the trial or the need for additional dose-ranging studies. The percentage of patients demonstrating improvement, 80% improvement) did not always reach a level of significance for olanzapine over placeb

12) In a placebo-controlled study (n=152), olanzapine 10 milligrams (mg) daily was significantly superior Psychiatric Rating Scale total and Positive and Negative Syndrome Scale (PANSS) total scores) in chron refractory to prior therapy. Some patients had shown refractoriness to clozapine (Beasley et al, 1996aa). also superior to placebo with regard to core psychotic symptoms (PANSS positive scores and PANSS ne was comparable to placebo on all measures of efficacy.

c) Long-term Treatment

1) Olanzapine is also approved for long-term therapy and maintenance treatment of schizophrenia. Auth concluded that olanzapine demonstrated efficacy and long-term safety in the maintenance treatment res stable schizophrenia or schizoaffective disorder were randomized to receive olanzapine (10 to 20 milligra olanzapine improved on all quality of life measures while the patients receiving placebo worsened. Olanz 15 or 20 milligrams daily) (Anon, 2000).

2) Two other studies were presented that demonstrated olanzapine's superiority to placebo and to a sub maintenance therapy of schizophrenia (Dellva & Tran Tollefson, 1997). In a 46 week double-blind, multic schizophrenia with an acute exacerbation and who had previously responded to acute therapy were enro olanzapine (n=45) or placebo (n=13), and in the second study patients received either olanzapine (n=48) the first study, patients in the olanzapine group experienced a significantly lower relapse risk (p equal to study, patients in the olanzapine group again experienced a significantly lower relapse risk (p equal to 0. dose of olanzapine.

4) Pediatric:

a) Olanzapine and quetiapine were both effective in reducing the symptomatology of first episode psychosis, olanzapine in the adolescent population, according to a 6-month, prospective, randomized, open-label study 1.25 years (range 12 to 18 years), a diagnosis of schizophrenia or any other psychotic disorder according to before the age of 18, lasting less than 1 year were included in the study. Patients were randomized to receive milligrams/day (mg/day), n=24), or olanzapine (mean dose 9.7 +/- 6.5 mg/day, n=26) for 6 months (mean, 14 antipsychotics, such as benzodiazepines, antidepressants, antiepileptics, were permitted. The results of the p published. Based on the intent-to-treat analysis of secondary outcomes, both the olanzapine and quetiapine g months from baseline in the Positive and Negative symptoms scale (PANSS) total score (-2.201, p=0.028 an positive subscale (-2.366; p=0.018 and -2.028, p=0.042, respectively). The negative PANSS subscale scores p=0.011), but the reduction did not reach statistical significance in the olanzapine arm (-0.21, p=0.833). Patie the Strengths and Difficulties Questionnaire (SDQ), but the improvements did reach statistical significance ex between-group comparisons of improvement in secondary endpoints were nonsignificant except patient-repo 15.5 kilograms (kg) (p less than 0.001) was seen in the olanzapine group, and a 5.4 kg gain was seen in the adverse events associated with quetiapine and olanzapine throughout the study included concentration difficu fatigability (79% vs 73%), and sleepiness/sedation (79% vs 84%). At the study conclusion at 6 months, 16 pa study. The results were limited by the open-label study design, small sample size, variety of concomitant med 2009).

4.5.AE Schizophrenia, Refractory

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Improved symptoms sufficiently for hospital discharge in about half of patients in small study (Dinakar et
May be effective in the treatment of children with drug-resistant childhood-onset schizophrenia (Mozes e

3) Adult:

a) Among patients who had been hospitalized for schizophrenia for longer than 5 years and who were consid showed sufficient clinical improvement after 3 months of treatment with olanzapine or risperidone to be disch suited to treatment with clozapine either because of medical contraindications or because of unwillingness to were given olanzapine 10 to 30 milligrams (mg) per day or risperidone 4 to 10 mg/day. Treatments were titrat continued for 3 months. Mean scores on the Brief Psychiatric Rating Scale decreased from 67 to 53 for the o risperidone group (n=47) (p less than 0.001 for both groups). Of the 34 patients who were discharged from th

the 90-day follow-up. No significant side effects (such as weight change) were observed during the 3 months

4) Pediatric:

a) Olanzapine seemed to be effective in the treatment of children with drug-resistant schizophrenia. In an op (mean age, 12.5 years), with childhood-onset schizophrenia refractory to previous treatment with at least two 2.5 milligrams (mg)/day, titrated to doses of 10, 15, or 20 mg per day; mean dose, 15.56 mg/day) for 12 week reductions were observed at week 12 as compared with baseline in the mean scores for the Brief Psychotic R p=0.03) and the Clinical Global Impression scale (decreased from 6.09 to 4.7; p less than 0.005). The Positiv mean score was reduced from 123.56 at baseline as compared with 96.7 at week 12 (p=0.026). In addition, t significant reductions at week 12 as compared with baseline (p=0.048 and p=0.05, respectively). The most co and weight gain (100%; mean weight gain, 6.1 kilograms). No extrapyramidal side effects, dystonias, elevate electrocardiogram or electroencephalogram abnormalities were observed. Larger, controlled studies are neec olanzapine for the treatment of childhood-onset schizophrenia (Mozes et al, 2003).

4.5.AF Schizophrenic prodrome

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:

May be effective in the treatment schizophrenic prodromal syndrome (Woods et al, 2003)

3) Adult:

a) The results of one study suggest that olanzapine may be effective in the treatment of patients experiencin randomized, double-blind, placebo-controlled, multicenter study, patients with prodromal syndrome received mean dose, 8 mg/day) or placebo (n=29) for 8 weeks. Results of the study were inconsistent across analyses olanzapine-treated patients showed a significant improvement from baseline to endpoint in total score for the x time interaction), as compared with placebo (p less than 0.005). However, when a last observation carried f favored olanzapine but did not reach statistical significance. Significantly more patients taking olanzapine exp baseline body weight as compared with placebo (56.7% vs 3.4%, respectively, p less than 0.001). Larger, lon clinical efficacy (Woods et al, 2003).

4.5.AG Senile dementia of the Lewy body type

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in low doses (5 milligrams/day) but not at high doses (15 mg/day) (Cummings et al, 2002)

3) Adult:

a) Olanzapine at low doses significantly reduced delusions and hallucinations in patients with dementia with were a subset of patients with Alzheimer's disease being treated for psychosis with various doses of olanzapi controlled trial. Within the DLB subset, 10 patients were treated with placebo, 5 with olanzapine 5 milligrams with olanzapine 15 mg/day. In comparison to scores with placebo treatment, final scores on the delusions sul Home (NPI/NH) after 12 weeks of olanzapine treatment were significantly better for the 5 mg group (p=0.009) mg group. Scores on the hallucinations subscale were significantly better for the 5 mg group only. Olanzapine symptoms of parkinsonism or any decrease in cognition. The 5-mg dose also diminished disruptiveness of pa

b) Olanzapine (2.5 to 7.5 milligrams daily) showed little advantage over conventional neuroleptics in 8 patien (DLB). Only 2 patients demonstrated clear improvement in psychotic and behavioral symptoms. Three patien remaining 3 patients could not tolerate olanzapine, even at the lowest dose. The data suggests that benzodia methods should be considered prior to olanzapine for treatment of DLB (Walker et al, 1999).

4.5.AH Severe major depression with psychotic features

See Drug Consult reference: PSYCHOTIC DEPRESSION - DRUG THERAPY

4.5.AI Tardive dyskinesia

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:

Improvements seen in tardive dyskinesias after switching to olanzapine in case reports (Soutullo et al, 19

See Drug Consult reference: TARDIVE DYSKINESIA - DRUG THERAPY

3) Adult:

a) Tardive dyskinesia improved in 2 patients after being switched to olanzapine (Soutullo et al, 1999a). The f
Abnormal Involuntary Movement Scale (AIMS) which improved after 4 weeks. His AIMS score was 9 at 2 mo
maintained on olanzapine 15 milligrams (mg). The second had a score of 31 which improved to 3 after 1 wee
a score of 9. Other cases of significant improvement have been reported (Almeida, 1998).
b) Four cases of patients with tardive dyskinesias showing marked improvements on the Abnormal Involunta
al, 1998). All cases involved patients on long-term neuroleptic therapy that were switched to olanzapine and t
therapy tardive dyskinesias had decreased.

4.5.AJ Trichotillomania

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 several cases, either alone or as adjunct therapy with fluoxetine or citalopram (Gupta & Gupt
Effectively reduced symptoms of hair pulling during small, open-label trial (Stewart & Nejtek, 2003)

3) Adult:

a) Olanzapine therapy reduced symptoms of hair pulling, depression, and anxiety in patients with trichotillom
(n=17) diagnosed with trichotillomania received 12 weeks of treatment with olanzapine (initial, 2.5 milligrams
mg at bedtime by week 8; mean dose at week 12, 8.5 mg/day). A significant reduction in the mean score for t
Scale (MGH) was observed from baseline to weeks 4, 6, 8, and 12 (weeks 4 and 6, p less than or equal to 0.
From baseline to endpoint, hair pulling was reduced by 66% (MGH), anxiety levels decreased by 63% as mea
less than or equal to 0.05) and depressive symptoms shrunk by 43% as measured by the Hamilton Rating Sc
events were sedation and weight gain. Randomized, controlled trials are needed to confirm these findings (St
b) In 3 of 4 patients with trichotillomania as well as other psychiatric disorders, olanzapine in addition to citalo
trichotillomania had failed to respond to various regimens of SSRIs (selective serotonin reuptake inhibitors). E
milligrams (mg) per day. The dose used by the patient whose trichotillomania did not respond was 1.25 mg/d
mg/day (Ashton, 2001).
c) Three patients with self-inflicted dermatoses were successfully treated with olanzapine 2.5 to 5 milligrams
acne, self-induced skin ulcers, and trichotillomania within 2 to 4 weeks of initiating olanzapine therapy. Durati
Improvement was maintained in 1 patient by taking 2.5 mg once or twice weekly as required (Gupta & Gupta,
d) A 22-year-old woman with trichotillomania improved when olanzapine was added to her fluoxetine regime
trichotillomania and obsessive-compulsive disorder. She had failed trials with multiple selective serotonin reu
perphenazine. She did have a response to fluvoxamine with risperidone but developed severe hyperprolactin
milligrams (mg)/day and then had olanzapine 10 mg added. After 7 weeks, her Massachusetts General Hosp
and the Yale-Brown Obsessive Compulsive Scale compulsion subscale from 13 to 4. Due to sedation, her ola
Thereafter, she tolerated olanzapine well but gained 8 pounds.

4.6 Comparative Efficacy / Evaluation With Other Therapies

Aripiprazole

Chlorpromazine

Clozapine

Haloperidol

Lithium

Olanzapine/Fluoxetine Hydrochloride

Perphenazine

Quetiapine

Risperidone

Valproic Acid

Ziprasidone

4.6.A Aripiprazole

4.6.A.1 Schizophrenia

a) A trend toward greater improvement in some areas of neurocognitive function (eg, verbal learning, workin daily compared to olanzapine 15 mg daily in a randomized study (n=256) (Kern et al, 2001). However, a plac unavailable (unpublished).

4.6.B Chlorpromazine

Schizophrenia

Schizophrenia, Treatment-resistant

4.6.B.1 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo-controlled, fixed-dose and fi schizophrenic patients, the minimum effective dose of olanzapine was 10 milligrams/day (equivalent to chlorp

4.6.B.2 Schizophrenia, Treatment-resistant

a) Olanzapine 25 milligrams (mg) daily and chlorpromazine 1200 mg daily plus benztropine 4 mg daily show randomized trial of 84 patients with treatment-resistant schizophrenia. No significant differences were seen b Scale (BPRS), Scale for the Assessment of Negative Symptoms, or the Clinical Global Impression (CGI) Sco of the chlorpromazine patients met response criteria of at least a 20% reduction in baseline BPRS score and post-treatment BPRS score of less than 35. Dry mouth, orthostatic changes, and unsteady gait were more co 0.01), as was extrapyramidal symptoms (p less than 0.05) (Conley et al, 1998).

4.6.C Clozapine

Bipolar disorder

Drug-induced psychosis

Hostile behavior

Schizophrenia

Schizophrenia - Suicidal intent

4.6.C.1 Bipolar disorder

a) In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic r and risperidone (n=25), along with standard mood stabilizers, showed similar efficacy. Overall, 68% of patien Clinical Global Impressions assessment over the 12-week study. Mean dosages were 210 milligrams (mg) pe and 1.7 mg day for risperidone. The only serious adverse event to occur during the study was a seizure in a p (EPS) were reported in 12 of 42 subjects (28.6%). Parkinsonism occurred in 4 of 25 patients taking risperidor clozapine. Weight gain was more extreme in patients taking clozapine and olanzapine than in those taking ris reported in other studies, may have been affected by concurrent mood enhancing medications (Guille et al, 2

4.6.C.2 Drug-induced psychosis

a) In a small (n=18), open study, clozapine and olanzapine were both effective in reducing symptoms of dop Parkinson's disease. However, olanzapine and not clozapine caused worsening of Parkinsonian symptoms. T milligrams (mg) per day and was increased at weekly intervals as necessary to optimize clinical status. The fi week study was 16.9 mg /day (range: 6.25 to 37.5 mg/day). Olanzapine was started at 2.5 to 5 mg/day. The f completing the study was 4.7 mg/day (range: 2.5 to 10 mg/day). Three patients dropped out of the study after for 2 patients, 5 mg for 1 patient) because of worsening of parkinsonism. All patients in the clozapine group c somnolence, falls, orthostatic hypotension, and syncope. Neuropsychiatric symptoms markedly improved with Neuropsychiatric Inventory global scores for clozapine and olanzapine, respectively). Parkinsonian motor scc group and worsened by 25% in the olanzapine group. It is possible that the differences observed were due to of olanzapine was excessive (Gimenez-Roldan & Mateo D Navarro, 2001).

4.6.C.3 Hostile behavior

a) Clozapine reduced hostility in patients with schizophrenia and was superior to haloperidol and risperidone with a diagnosis of schizophrenia or schizoaffective disorder and a history of poor response to drug treatmen

olanzapine, risperidone, or haloperidol in cross-titration with the antipsychotic drug used prior to the start of th antidepressants had been phased out earlier. Daily doses of olanzapine, risperidone, and haloperidol were es 20, 8, and 20 milligrams (mg), respectively. Patients receiving clozapine were scheduled to achieve the targe fixed for the remainder of the initial 8-week period. In a second (6-week) period, doses were allowed to vary: olanzapine, 4 to 16 mg for risperidone, and 10 to 30 mg for haloperidol. Hostility, measured by the hostility ite (PANSS), improved significantly (in comparison to baseline) in the clozapine group only (p=0.019). This effec symptoms (delusional thinking, hallucinations) or on sedation. The effect of clozapine on hostility was superic (p=0.012) but not to that of olanzapine (Citrome et al, 2001).

4.6.C.4 Schizophrenia

a) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in pat that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients we (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 1(treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was adverse effects). Improvement over time in global neurocognitive score was seen for olanzapine and risperid organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, p ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improv

4.6.C.5 Schizophrenia - Suicidal intent

a) In the International Suicide Prevention Trial (InterSePT), clozapine was shown to be more effective than o adult, patients with schizophrenia or schizoaffective disorder. Men and women between the ages of 18 to 65 recruited to participate in this 2-year, prospective, randomized, international, parallel group, study. The endpo attempts (including completed suicides) or hospitalization due to imminent suicide risk (type 1 events) or ratin Clinical Global Impression of Suicide Severity (CGI-SS) scale (type 2 events). Of the total sample of 980 pati diagnosed as having schizophrenia and 38% (371) were diagnosed with schizoaffective disorder. Twenty-sev treatment resistant. The patients were divided into two treatment groups (clozapine or olanzapine) and did no diagnosis, treatment resistance, number of previous suicide attempts, or baseline concomitant medications. E Dropout rates for the two groups were similar with 192 discontinuing treatment with clozapine and 187 with ol (95% CI, 0.58-0.97) for type 1 events (p=.03) and 0.78 (95% CI, 0.61-0.99) for type 2 events (p=.04) compare adverse events for the olanzapine group were weight gain, somnolence, dry mouth, and dizziness, while saliv dizziness were the most frequently reported adverse events reported for the clozapine group. The overall nur between the two groups. Decreased white blood cell counts occurred in 5.8% of clozapine-treated patients ar were no reports of agranulocytosis or deaths due to granulocytopenia in either group. There was a total of 8 s olanzapine). The mean daily olanzapine dosage was 16.6 +/- 6.4 mg and the mean daily clozapine dosage w

4.6.C.6 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) c identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications cl as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most p months after initiation of treatment (Koller et al, 2003b).

b) Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rate of but was similar to rates occurring with risperidone and clozapine therapy. In a pooled analysis of 23 randomiz schizophrenia, frequency and severity of EPS associated with olanzapine therapy (2.5 to 20 milligrams (mg)/(mg/day), risperidone (4 to 12 mg/day), clozapine (25 to 625 mg/day), and placebo. Dystonic events (ie, dysto occurred in significantly fewer patients during olanzapine treatment as compared with haloperidol (0.5% vs 5. (1% vs 3.2%, respectively; p=0.047) treatment, while no significant difference was found between olanzapine olanzapine-treated patients, a significantly higher percentage of haloperidol-treated patients experienced parl extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no signific olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to the occurrence occurred in significantly more patients treated with haloperidol as compared with olanzapine (44.4% vs 16.2% patients treated with clozapine as compared with olanzapine (2.6% vs 6.8%, respectively; p=0.047). The over and risperidone groups as compared with olanzapine. Significantly fewer patients received anticholinergic me with the haloperidol (p less than 0.001) or risperidone (p=0.018) groups. No difference was found between ol placebo or clozapine in regard to percentage of patients given anticholinergic drugs during therapy (Carlson e

c) In an open-label trial (n=24), olanzapine-treated patients had significantly lower levels of serum anticholine to enrollment, subjects were stabilized on therapeutic doses, averaging 15 milligrams (mg)/day and 444 mg/d mean serum anticholinergic levels were 0.96 and 5.47 picomoles/atropine equivalents in the olanzapine and (Scores assessing clinical anticholinergic effects were significantly higher for salivation, constipation, micturitic clozapine versus olanzapine recipients (p less than 0.05). Dry mouth was more problematic with olanzapine t differ cognitively with respect to Mini Mental State Exam scores. Although efficacy was not a primary endpoin clozapine (p=0.002), with no statistical difference in Clinical Global Impression Scale, Severity subscale score due to adverse effects (Chengappa et al, 2000).

4.6.D Haloperidol

Adverse reaction to cannabis - Drug-induced psychosis

Mania

Schizophrenia

Tardive dyskinesia

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

a) Olanzapine was as effective as haloperidol in the treatment of cannabis-induced psychotic disorder (Berk
a psychotic episode associated with cannabis use were randomized to receive either olanzapine 10 milligram
weeks there was a significant improvement in both groups as compared to baseline measured on the Brief Ps
p=0.0001 for haloperidol). There was no significant difference between the 2 groups. Olanzapine was associa

4.6.D.2 Mania

a) Olanzapine and haloperidol therapies were similarly effective in the treatment of acute mania in patients w
study, patients with bipolar I disorder, mixed or manic episode and a Young-Mania Rating Scale (Y-MRS) sco
milligram (mg)/day) or haloperidol (3 to 15 mg/day) at flexible doses for 6 weeks. Patients showing symptom
in which they received ongoing treatment. Symptomatic remission was defined as a Y-MRS score of 12 or les
score (HAM-D) of 8 or less at week 6. Symptomatic remission rates for patients in the olanzapine group were
at week 6 (52.1% vs 46.1%, respectively; p=NS) and week 12 (51.7% vs 43.8%, respectively; p=NS). Howev
improvements in health- related quality of life factors as compared with haloperidol treatment (Shi et al, 2002)

4.6.D.3 Schizophrenia

a) SUMMARY: Olanzapine is more effective than haloperidol for the treatment of negative symptoms of schiz
managing positive symptoms. Olanzapine is less likely to induce extrapyramidal reactions or elevation of seru
b) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in pa
that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients we
(mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 1
treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500
week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was
adverse effects). Improvement over time in global neurocognitive score was seen for olanzapine and risperid
organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor
Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (
enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, p
ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improv
c) Olanzapine was at least as effective as and safer than haloperidol for the treatment of schizophrenia in a l
and negative symptoms resistant to treatment with typical antipsychotics. In a randomized, double-blind trial,
milligrams (mg) per day and increased to a maximum of 15 mg/day, or haloperidol, starting at 4 mg/day and i
daily doses were 10.5 mg for olanzapine and 8 mg for haloperidol. The proportion of olanzapine-treated patie
improvement was 44.5%, compared to 40.5% of haloperidol-treated patients. The 95% confidence interval wa
olanzapine was not inferior to haloperidol in efficacy. Total and subscale scores on the Positive and Negative
in the olanzapine group than in the haloperidol group, but only on the negative symptoms subscale did the di
Eighty-one percent of olanzapine-treated patients and 66% of haloperidol-treated patients finished the study,
because of adverse events or abnormal laboratory values (8 vs 22). Olanzapine-treated patients showed an
whereas haloperidol-treated patients showed a worsening (p less than 0.001). Treatment-emergent parkinsor
18.8% of the haloperidol group. By the end of treatment, parkinsonism had resolved in all patients in the olan
haloperidol group. There was a significantly greater incidence of insomnia, akathisia, tremor, anorexia, increa
nausea, and weight decrease in haloperidol-treated patients than in olanzapine-treated patients. Only weight
kilogram vs -0.71 kilogram, p less than 0.001). Thirty-two percent of olanzapine-treated patients showed no a
abnormality, compared to 15.5% of haloperidol-treated patients (p=0.008) (Ishigooka et al, 2001).
d) Olanzapine has been at least as effective as haloperidol, each given for six weeks, in the treatment of sch
1996)(Anon, 1996; Anon, 1995). Overall improvement, based on Brief Psychiatric Rating Scale (BPRS) total s
reached significance in the largest trial (Anon, 1996). Both agents have produced similar decreases in positiv
with olanzapine is attributed to a greater reduction in negative symptoms in these patients, particularly in high
negative symptoms have been significantly greater with olanzapine on the Scale for the Assessment of Nega
Syndrome Scale (PANSS), although significance was not achieved on the BPRS-negative scale in one study
have demonstrated greater than 80% improvement in BPRS-total scores with olanzapine, whereas the perce
always differed significantly between drugs.
e) Intramuscular (IM) olanzapine successfully treated acutely agitated patients with schizophrenia in 3 clinica
evaluated 108 patients receiving fixed or variable doses of 2.5, 5.0, 7.5, or 10.0 milligram (mg) given as 1 to 4
20 mg orally (PO) QD for 2 days. Response was assessed using the Brief Psychiatric Rating Scale (BPRS); t

PO Administration (no statistical analysis was performed). The third study was a multicenter, double-blind, pla with IM haloperidol in the treatment of acute agitation. Patients (n=311) received up to 3 doses of olanzapine hours. Thereafter, patients were treated with oral olanzapine (5 to 20 mg QD) or oral haloperidol (5 to 20 mg or haloperidol showed significantly greater improvement over placebo at 2 and 24 hours as measured by the observed between olanzapine- and haloperidol-treated patients. Patients treated with intramuscular olanzapi significant difference between patients treated with IM drug between baseline and day 5 (Jones et al, 2000)

f) In a study of 300 patients with schizoaffective disorder, olanzapine treated patients showed significantly gr patients on the Brief Psychiatric Rating Scale (BPRS) total (p=0.002), Positive and Negative Syndrome Scale (p=0.006), and Montgomery-Asberg Depression Rating Scale (MADRS) total (p less than 0.001). Patients we study. Patients were assessed weekly for a six week acute phase with responders followed for up to 1-year. olanzapine (5 to 20 milligrams) was superior to haloperidol (5 to 20 milligrams) in the BPRS (p=0.012), PANS MADRS (p less than 0.001); however, in depressed subtype patients, no significant differences were seen wh During the double-blind extension phase, the only significant difference between treatment groups was in the (p=0.045). Extrapyramidal symptoms were less severe among olanzapine treated patients (p=0.016), but wei al, 1997).

g) In a 6-week randomized study of 83 patients with first-episode psychosis (schizophrenia, schizophreniform receiving olanzapine showed significantly greater improvement on the Brief Psychiatric Rating Scale (BPRS) (PANSS) as compared to patients receiving haloperidol. Patients greater than 45 years of age at onset of syr years received olanzapine or haloperidol 5 milligrams (mg) per day and adjusted every 7 days within the rang olanzapine treated patients experienced a 40% or greater improvement from baseline compared to 29.2% of treated patients also improved more on the PANSS total score (p=0.02) and positive symptom score (p=0.03 the Simpson-Angus scale, olanzapine patients showed improvement in extrapyramidal symptoms, whereas h 0.001). Somnolence was more common in olanzapine treated patients, whereas akathisia and hypertonia we 1999).

h) Olanzapine showed a superior and broader spectrum of efficacy over haloperidol in the treatment of schiz profile (Tollefson et al, 1997). In a large international, multicenter double-blind trial, olanzapine (N=1336) was Starting doses were 5 milligrams (mg) for both drugs which could be increased by 5 mg increments at the inv Olanzapine was significantly superior to haloperidol on the Brief Psychiatric Rating Scale (p less than 0.02), t (p=0.05), the clinical Global Impression severity score (p less than 0.03), and the Montgomery-Asberg Depre Significant advantages were also seen in the extrapyramidal profiles and effects on prolactin levels. Further a symptoms were also better controlled with olanzapine therapy (Tollefson et al, 1998). On the Montgomery-As significantly more effective than haloperidol (p = 0.001).

i) In multiple clinical trials of olanzapine, the incidence of self-directed aggression among patients receiving o significantly different (Keck et al, 2000a). These trials indicated a significantly greater improvement in suicida with haloperidol-treated patients. Another analysis demonstrated a 2.3-fold reduction in the annual suicide att receiving olanzapine versus haloperidol.

4.6.D.4 Tardive dyskinesia

a) Olanzapine was associated with a lower incidence of tardive dyskinesia when compared to haloperidol (T and blinded studies evaluating patients with schizophrenia, schizophreniform disorder, or schizoaffective disc (n=197) were compared. Patients had no evidence of tardive dyskinesia at baseline. At any visit after baselin 16.2% of patients in the haloperidol group manifested treatment-emergent tardive dyskinesia (p less than 0.0 patients and 7.6% of haloperidol patients manifested tardive dyskinesia (p equal to 0.001). Similar results hav

4.6.D.5 Efficacy

a) Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rate of but was similar to rates occurring with risperidone and clozapine therapy. In a pooled analysis of 23 randomiz schizophrenia, frequency and severity of EPS associated with olanzapine therapy (2.5 to 20 milligrams (mg)/ mg/day), risperidone (4 to 12 mg/day), clozapine (25 to 625 mg/day), and placebo. Dystonic events (ie, dysto occurred in significantly fewer patients during olanzapine treatment as compared with haloperidol (0.5% vs 5. (1% vs 3.2%, respectively; p=0.047) treatment, while no significant difference was found between olanzapine olanzapine-treated patients, a significantly higher percentage of haloperidol-treated patients experienced par extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no signific olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to the occurrence occurred in significantly more patients treated with haloperidol as compared with olanzapine (44.4% vs 16.2% patients treated with clozapine as compared with olanzapine (2.6% vs 6.8%, respectively; p=0.047). The over and risperidone groups as compared with olanzapine. Significantly fewer patients received anticholinergic me with the haloperidol (p less than 0.001) or risperidone (p=0.018) groups. No difference was found between ol placebo or clozapine in regard to percentage of patients given anticholinergic drugs during therapy (Carlson e

b) Pooled safety results from 3 large double-blind, controlled trials in 2606 patients demonstrated that olanza extrapyramidal symptoms (EPS) occurring versus haloperidol (p less than 0.001) (Tran et al, 1997). Also stat discontinued the study because of EPS (p less than 0.001). This suggests that the use of olanzapine may be fewer adverse effects.

c) The risk of extrapyramidal adverse effects is lower with olanzapine compared to haloperidol, especially dy been significantly less with olanzapine (Tollefson et al, 1997); (Beasley et al, 1996)(Anon, 1996; Anon, 1995)

4.6.D.6 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis

dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) c
identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications cl
as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most p
months after initiation of treatment (Koller et al, 2003).

4.6.E Lithium

4.6.E.1 Mania

a) A review of 3 randomized, double-blinded, placebo-controlled studies concluded that a more rapid antima
loading of divalproex than with standard titration divalproex, lithium or placebo. In these short-term studies, o
30 milligrams/kilogram/day (mg/kg/day) for the first 2 days and maintained at 20 mg/kg/day or it was initiated
increased to a maximum of 20 mg/kg/day plus 1000 mg by day 6. This regimen was compared to divalproex
to serum levels of 40 to 150 micrograms/milliliter (mcg/mL), lithium (n=54) initiated at 300 mg 3 times a day a
and olanzapine (n=55) initiated at 10 mg/day and titrated to a maximum of 20 mg/day and placebo (n=72). Pa
assessed using the change from baseline measurement of the Mania Rating Scale (MRS), the Manic Syndro
Scale (BIS). Intent-to-treat analyses showed that MRS measurements from oral-loaded divalproex patients w
patients. However, it showed significant differences from standard titration divalproex and placebo by day 5 a
Similar results were found for MSS and BIS measurements. Dry mouth and increased appetite was more con
standard titration (p less than 0.05). However, standard titration divalproex was associated with an increased
(p less than 0.05). Divalproex overall was associated with greater decreases in platelet counts than other gro
greater reports of headache and fever (p less than 0.05) and olanzapine was associated with greater adverse
speech disorder, rhinitis, increases in total cholesterol and increases in serum alanine aminotransferase) ove
b) Olanzapine was found to be at least as effective as lithium in the treatment of mania. In a 4-week, double-
were randomized to receive olanzapine 10 milligrams daily or lithium carbonate 400 milligrams twice daily. Th
two treatment groups on any primary outcome measures. However, olanzapine was significantly (p equal to 0
Global Impression severity scale at week 4 (lithium 2.83, olanzapine 2.29). The two medications did not differ
symptoms (Berk et al, 1999a).

4.6.F Olanzapine/Fluoxetine Hydrochloride

4.6.F.1 Depression - Schizophrenia

a) Results of an 8-week, double-blind trial demonstrated that patients receiving both olanzapine and fluoxeti
improvement in Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI
medication alone. Twenty-eight patients with nonpsychotic treatment-refractory depression received olanzapi
60 milligrams/day). In addition, there were no significant differences in adverse events among the 3 different

4.6.G Perphenazine

4.6.G.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp
perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before
schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 3
risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients
months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for zip
to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard r
to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontin
all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients disco
(average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and trig

4.6.H Quetiapine

4.6.H.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp
perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before
schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 3
risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients
months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for zip
to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard r
to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontin
all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients disco
(average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and trig

4.6.I Risperidone

Agitation, acute - Psychotic disorder

Bipolar disorder

Chronic schizophrenia

Dementia - Problem behavior

Extrapyramidal disease

Obsessive-compulsive disorder, Refractory

Schizophrenia

4.6.I.1 Agitation, acute - Psychotic disorder

a) Olanzapine orally disintegrating tablets (ODT) and risperidone oral solution (OS) yielded similar improvem Negative Syndrome Scale (PANSS-EC) and the Clinical Global Impression (CGI) scale in 87 patients treated emergency setting, according to an open-label, flexible-dose study. Patients with a baseline PANSS-EC scor were assigned to receive initial doses of either olanzapine ODT 10 milligram (mg) (n=34) or risperidone OS 3 based on previous effective treatments, or monthly assignments to olanzapine or risperidone according to the continued agitation could be re-dosed at any time, and after 1 hour could receive adjunctive drug therapy. PA time. The mean CGI change from baseline was similar between the olanzapine and risperidone group (2.8 vs PANSS-EC score over time ANOVA (at baseline and every 15 minutes for 1 hour) revealed no significant ma treatment over time (F=2.94, p=0.09 and F=0.88, p=0.41, respectively). There was a significant mean change compared with risperidone OS group (-9.2 vs 1.1 beats/minute, p=0.03). There were no significant differences including extrapyramidal symptoms (Hatta et al, 2008).

4.6.I.2 Bipolar disorder

a) In a retrospective study of 50 consecutive patients treated for bipolar disorder with atypical antipsychotic r and risperidone (n=25), along with standard mood stabilizers, showed similar efficacy. Overall, 68% of patien Clinical Global Impressions assessment over the 12-week study. Mean dosages were 210 milligrams (mg) pe and 1.7 mg day for risperidone. The only serious adverse event to occur during the study was a seizure in a p (EPS) were reported in 12 of 42 subjects (28.6%). Parkinsonism occurred in 4 of 25 patients taking risperidor clozapine. Weight gain was more extreme in patients taking clozapine and olanzapine than in those taking ris reported in other studies, may have been affected by concurrent mood enhancing medications (Guille et al, 2

4.6.I.3 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compa perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 3 risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for zip to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard r to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontin all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients disco (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and trig

4.6.I.4 Dementia - Problem behavior

a) Risperidone and olanzapine were equally effective in the treatment of dementia-related behavioral disturb facilities. In a double-blind, parallel study, patients (mean age, 83 years) with dementia received oral olanzap titrated to maximum dose of 10 mg/day) or risperidone (n=19, initial dose 0.5 mg/day, titrated to maximum do a 3-day washout period of psychotropic drugs. Antidepressants and mood stabilizers were allowed at stable d medication at doses of 0.5 to 1 mg as needed for acute agitation. The mean daily doses for olanzapine and ri 1.47 mg (range, 0.5 to 2 mg), respectively. Lorazepam was utilized a median of 3.5 days (range 1-12 days) a mg). Primary outcome measures were the Neuropsychiatric Inventory (NPI) and the Clinical Global Impressio lowered CGI scores and total NPI scores from baseline to endpoint (p less than 0.0001, both values), howeve Adverse events were frequent in this elderly population, with the most common including drowsiness, falls, ar

4.6.I.5 Extrapyramidal disease

a) Results of a retrospective analysis showed that olanzapine treatment was associated with a lower rate of but was similar to rates occurring with risperidone and clozapine therapy. In a pooled analysis of 23 randomiz schizophrenia, frequency and severity of EPS associated with olanzapine therapy (2.5 to 20 milligrams (mg)/ mg/day), risperidone (4 to 12 mg/day), clozapine (25 to 625 mg/day), and placebo. Dystonic events (ie, dysto occurred in significantly fewer patients during olanzapine treatment as compared with haloperidol (0.5% vs 5. (1% vs 3.2%, respectively; p=0.047) treatment, while no significant difference was found between olanzapine olanzapine-treated patients, a significantly higher percentage of haloperidol-treated patients experienced parl extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, and tremor) (9.3% vs 28.3%, respectively akathisia, hyperkinesia) (6.7% vs 20.4%, respectively; p less than 0.001) during therapy. However, no signific

olanzapine group as compared with the placebo, risperidone, or clozapine groups in regard to the occurrence occurred in significantly more patients treated with haloperidol as compared with olanzapine (44.4% vs 16.2% patients treated with clozapine as compared with olanzapine (2.6% vs 6.8%, respectively; p=0.047). The over and risperidone groups as compared with olanzapine. Significantly fewer patients received anticholinergic me with the haloperidol (p less than 0.001) or risperidone (p=0.018) groups. No difference was found between ol placebo or clozapine in regard to percentage of patients given anticholinergic drugs during therapy (Carlson e

4.6.I.6 Obsessive-compulsive disorder, Refractory

a) Adjunctive therapy of risperidone or olanzapine with serotonin-reuptake inhibitors (SRI) were equally effec in SRI monotherapy-resistant outpatients, according to an 8-week, single-blind, randomized trial; however thi placebo arm, single-arm design, and underpowered nature of the trial. Following a 16-week prospective, oper who were treatment-resistant (defined as less than 35% improvement in the total score of Yale-Brown Obses Global Impression Severity (CGI-S) score greater than 2) entered an 8-week single-blind phase (n=50). Patie doses of clomipramine 200 to 225 mg, citalopram 50 to 80 mg, fluoxetine 60 mg, fluvoxamine 200 to 300 mg, were randomized to receive either risperidone 1 to 3 mg/day (n=25), or olanzapine 2.5 to 10 mg/day (n=25) i personnel and assessor-blinding constituted the single-blind study design; patients were not blinded. In an int analysis of the primary endpoints, both treatments significantly improved Y-BOCS and CGI-S scores by week mean Y-BOCS total scores, CGI-S scores, and responder rates (35% or greater improvement in Y-BOCS sco 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 p=0.016), and amenorrhea (66.7% vs 10%, p=0.02), respectively. The small sample size and the absence of to the limitations of this study (Maina et al, 2008).

4.6.I.7 Schizophrenia

a) Olanzapine and risperidone were equally safe and effective therapies in the treatment of schizophrenia in double-blind study, 175 elderly patients (mean age, 71 years) were randomized to receive either risperidone (mean dose, 11.1 mg/day) for 8 weeks following a 1 week washout period of all psychotropic medications. Me and Negative Syndrome Scale (PANSS) scores were between 50 and 120 at baseline. Clinical improvement total PANSS score. Both treatment groups showed significant reductions from baseline in the total PANSS sc significant differences were not observed between groups. Fifty-eight percent of risperidone-treated patients clinical improvement as defined by the study. Both groups also exhibited significant improvement in four of th The greatest mean change in the total PANSS score occurred in the 93 patients who had received conventio to entering the study (p less than 0.001). The rate of extrapyramidal symptoms (EPS) was similar between th (9.2% vs 15.9%, respectively, p=ns). The severity of EPS symptoms was reduced in both groups from baseli between groups. A 7% or higher increase in weight occurred in significantly more olanzapine-treated patients (14.8% vs 5.1%, p=0.043). No new cardiovascular events were observed in this patient population and mean relevant (Jeste et al, 2003).

b) Olanzapine and risperidone improved neurocognitive deficits more than did haloperidol or clozapine in pa that was refractory to treatment with typical antipsychotics. In a randomized, double-blind study, inpatients we (mg) per day, olanzapine (n=26) 10 to 40 mg/day, risperidone (n=26) 4 to 16 mg day, or haloperidol (n=25) 1 treatment (target doses: olanzapine 20 mg/day, risperidone 8 mg/day, haloperidol 20 mg/day, clozapine 500 week study; during the last 6 weeks, dosages were adjusted individually (generally increased if response was adverse effects). Improvement over time in global neurocognitive score was seen for olanzapine and risperid organization and in processing speed and attention, improvement was seen with olanzapine. In simple motor Changes in global neurocognitive performance with olanzapine and risperidone were of medium magnitude (enough to be clinically significant. Beneficial changes with clozapine were modest. Despite cognitive gains, p ability and social/vocational functioning. Improvements in neurocognitive deficits were associated with improv

c) In a prospective, multicenter, double-blind trial, olanzapine was more cost-effective than risperidone in pa or schizophreniform disorder. One hundred fifty patients were randomized to either olanzapine (10 to 20 milli mg/d) (n=75) treatment for a period of 28 weeks. During the study, olanzapine- treated patients were significa

throughout the course of therapy than risperidone- treated patients (p=0.048). However, the proportion of pat
significantly different between groups. Overall, the incidence of side effects was similar between groups, but
required an anticholinergic to control treatment-emergent extrapyramidal effects than did those receiving olar
costs were significantly higher for olanzapine-treated patients than those treated with risperidone ($2513 vers
52% reduction 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
6 months, risperidone was more effective for treatment of psychotic symptoms. However, olanzapine was ass
At discharge the average doses of olanzapine and risperidone were 14.4 and 5.7 milligrams (mg) daily, respe
risperidone was significantly greater than with olanazapine. The dose of drug was uncontrolled and adjusted
response, tolerability of side effects, and manufacturer recommendations. Measures of effectiveness include
(BPRS), Global Assessment Scale (GAS) and quality of life measures. (Ho et al, 1999). Larger studies are ne

e) Olanzapine (10 to 20 milligrams (mg) daily) was superior to risperidone (4 to 12 mg daily) in the treatment
international, multicenter, double-blind, parallel-group 28-week prospective study of 339 patients with DSM-iv
disorder, or schizoaffective disorder, the olanzapine group had a significantly better overall response rate (gre
Negative syndrome Scale) and was significantly superior to risperidone in the treatment of negative symptom
curves, a significantly greater number of the olanzapine patients maintained their response at 28 weeks com
reactions were significantly less with olanzapine, in particular extrapyramidal side effects, hyperprolactinemia
weight gain; suicide attempts occurred significantly less in the olanzapine group (Tran et al, 1997a). The use
been subsequently criticized (Schooler, 1998; Gheuens & Grebb, 1998).

4.6.I.8 Adverse Effects

a) The results of one study suggest that patients receiving atypical antipsychotics have a higher incidence of
conventional antipsychotic medication. In a retrospective, pharmacovigilance study, 192 cases of pancreatitis
dose, 306.7 milligrams (mg)/day), olanzapine (mean dose, 15 mg/day), risperidone, (mean dose, 4 mg/day) c
identified cases, 40%, 33%, and 16% were related to treatment with the atypical antipsychotic medications cl
as compared with 12% of the cases which were related to the conventional neuroleptic, haloperidol. In most p
months after initiation of treatment (Koller et al, 2003a).

4.6.J Valproic Acid

4.6.J.1 Mania

a) A review of 3 randomized, double-blinded, placebo-controlled studies concluded that a more rapid antima
loading of divalproex than with standard titration divalproex, lithium or placebo. In these short-term studies, o
30 milligrams/kilogram/day (mg/kg/day) for the first 2 days and maintained at 20 mg/kg/day or it was initiated
increased to a maximum of 20 mg/kg/day plus 1000 mg by day 6. This regimen was compared to divalproex
to serum levels of 40 to 150 micrograms/milliliter (mcg/mL), lithium (n=54) initiated at 300 mg 3 times a day a
and olanzapine (n=55) initiated at 10 mg/day and titrated to a maximum of 20 mg/day and placebo (n=72). Pa
assessed using the change from baseline measurement of the Mania Rating Scale (MRS), the Manic Syndro
Scale (BIS). Intent-to-treat analyses showed that MRS measurements from oral-loaded divalproex patients w
patients. However, it showed significant differences from standard titration divalproex and placebo by day 5 a
Similar results were found for MSS and BIS measurements. Dry mouth and increased appetite was more con
standard titration (p less than 0.05). However, standard titration divalproex was associated with an increased
(p less than 0.05). Divalproex overall was associated with greater decreases in platelet counts than other gro
greater reports of headache and fever (p less than 0.05) and olanzapine was associated with greater adverse
speech disorder, rhinitis, increases in total cholesterol and increases in serum alanine aminotransferase) ove

b) Olanzapine was superior to divalproex for the treatment of acute mania in a 3-week, randomized, double-
bipolar I disorder, manic or mixed episode, and with or without psychotic features, were given flexibly dosed c
divalproex (500 to 2500 mg/day). Modal doses were 17.4 mg/day for olanzapine and 1401 mg/day for divalpr
(mcg/L) or greater (the targeted therapeutic range) was attained by approximately 87% of divalproex-treated
Mania Rating Scale total score was 13.4 points for the olanzapine group and 10.4 points for the divalproex gr
difference was significant (in favor of olanzapine) among patients without psychotic features (p=0.06), but the
patients with psychotic features. Clinical response (50% or greater improvement in they Young Mania Rating
treated patients and 43% of divalproex-treated patients (p=0.058). Time-to- remission was significantly shorte
0.04). There were more adverse events with olanzapine, mainly somnolence, dry mouth, and weight gain. Na
group (Tohen et al, 2002).

4.6.K Ziprasidone

Chronic schizophrenia

Schizophrenia

4.6.K.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were comp
perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before
schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 3

risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for zip to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard r to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontin all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients disco (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and trig

4.6.K.2 Schizophrenia

a) In a randomized, double-blind trial (n=269), six-week courses of OLANZAPINE and ZIPRASIDONE had c or schizoaffective disorder (DSM-IV), while the side effects profile of ziprasidone appeared to be more favora favorable related to QT interval prolongation. Enrollees were acutely ill, recently admitted inpatients. During th study drugs: olanzapine 5 milligrams (mg) on days 1 and 2 and 10 mg/day on days 3 to 7 (n=133); ziprasidon twice daily on days 3 to 7 (n=136). Dosing was flexible over weeks 2-6 (olanzapine 5 to 15 mg/day; ziprasido doses were 12.4 mg for olanzapine and 138.6 mg for ziprasidone (the latter in 2 divided doses daily). Efficacy Scale (BPRS), Clinical Global Impression (CGI) severity and improvement scales, Positive and Negative Syn for Schizophrenia. At study end, there were no significant differences on any rating scale between improveme ziprasidone group. At endpoint, 36.8% of the olanzapine group and 48.5% of the ziprasidone group had disco olanzapine and ziprasidone groups, respectively, had experienced adverse events that were considered treat seen related to dyskinesia, dystonia, or extrapyramidal symptoms. Weight gain amounted to approximately 3 ziprasidone-treated patients, respectively (p less than 0.0001). Total cholesterol, low- density lipoprotein chol approximately 10%, 13%, and 25%, respectively, in the group receiving olanzapine; all the same measures d than 0.0001; p=0.0004; p less than 0.003, respectively). Fasting serum insulin increased by median 3.3 and 0 ziprasidone groups, respectively (p=0.051). Prolongation of the QTc interval amounted to 0.52 and 6.08 millis than 0.05) (Simpson et al, 2004).

b) A multicenter, randomized, double-blind, parallel-group, 28 week study (n=548) found that olanzapine the psychopathology improvement and higher response and completion rates compared to ziprasidone, while zip and lipid profile. Patients with schizophrenia were randomized to receive olanzapine (n=277) 10 to 20 mg/day primary efficacy measure, the Positive and Negative Syndrome Scale total score, showed that the olanzapine the ziprasidone group (p less than 0.001). The olanzapine group also showed significant improvement from b Positive and Negative Syndrome subscales: positive symptoms, negative symptoms, general psychopatholog except for negative symptoms p=0.003). Patients were allowed to take benzodiazepines or hypnotic monothe study if they required more than two concurrent benzodiazepine hypnotic medications. Significantly more pati dose of a benzodiazepine compared to the olanzapine group (53.5% versus 40.4%; p=0.003). Response was Negative Syndrome Scale total score at endpoint, and the rate was significantly higher for the olanzapine gro versus 42.5%) (p less than 0.001). There was no significant difference in exacerbation of symptoms between in the Positive and Negative Syndrome Scale total score by 20% or more and a decrease in the Clinical Glob more after week 8 (14.6% olanzapine and 25.3% ziprasidone; p=0.06). Significantly more patients in the olan group (42.4%) completed the study (p less than 0.001). Reasons for discontinuation were only significant for ziprasidone 13.7%; p=0.02) and aggravation of psychosis (olanzapine 1.4% versus ziprasidone 4.4%; p=0.05 body weight and levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides (all p less tha high-density lipoprotein cholesterol (p=0.001) in the olanzapine group than in the ziprasidone group (Breier et

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