
OLANZAPINE

TRADE NAMES: Zyprexa, Zyprexa Zydis

CLASSIFICATION: Antipsychotic, atypical; a thienobenzodiazepine

ACTION:

Olanzapine is structurally and pharmacologically similar to the atypical antipsychotic clozapine. The mechanism of action is not completely understood. Antipsychotic effects may be related to blockade of dopamine (D1, D2, D3, D4), serotonin (5HT2, 5HT3, 5HT6), histamine (H1), alpha-1 adrenergic and muscarinic (M1-M5, particularly M1) receptors. Typical antipsychotics such as the phenothiazines (e.g. chlorpromazine) or the butyrophenones (e.g. haloperidol) strongly block dopamine receptors. In contrast, olanzapine blocks serotonin receptors (5HT2) more strongly than dopamine (D2) receptors. Blockade of 5HT2 receptors is a proposed mechanism for effects on negative symptoms in schizophrenia. Muscarinic blocking (anticholinergic) effects and lower affinity for dopamine receptors may possibly account for the decreased incidence of extrapyramidal symptoms (EPS) seen with olanzapine. Effect on prolactin levels is minimal.

PHARMACOKINETICS:

Well absorbed after oral administration; absorption is not changed by food. Peak plasma levels occur 5-8 hours after an oral dose. Plasma levels appear to have a correlation with therapeutic effect, requiring about 23 ng/mL for an antischizophrenic effect. Onset of antipsychotic effects is seen after 1-2 weeks of treatment. Half-life ranges from 21-54 hours (mean 30 hours). Highly protein bound (about 93%) with a volume of distribution of 10-18 L/kg. Metabolized in the liver to inactive metabolites mainly by cytochrome P450 isozyme CYP1A2, flavin-containing monooxygenase (FMO) 3, and N-glucuronidation. Minor pathways involve CYP2D6 and possibly CYP2C19 isozymes. About 40% is metabolized in the first pass through the liver. Because of the number of possible routes of metabolism, inhibition of cytochrome oxidase pathways does not markedly affect elimination of olanzapine. About 57% of a dose is excreted in urine principally as metabolites (only 7% as unchanged drug) and about 30% in the feces.

In single dose studies, half-life was not affected by decreased renal function or clinically significant cirrhosis (in smokers). In general, olanzapine elimination is slower in women, the **elderly** and non-smokers. In a small single dose study, mean half-life in elderly women was 55 hours, compared to a mean of 49 hours in elderly men. Olanzapine is not removed by dialysis.

USES AND EFFICACY:

Olanzapine is a useful agent in **acute and maintenance treatment of schizophrenia and related disorders**. It has beneficial effects on both positive and negative symptoms, an early onset of antipsychotic action and a favourable side effect profile. In patients who responded to initial therapy, olanzapine maintained clinical improvement for one year in a continuation trial. Further trials are required to evaluate long-term efficacy and safety and its usefulness in patients refractory to other antipsychotics. Olanzapine is also used in the management of psychoses in the **elderly**.

In a controlled 28 week trial in 339 patients with schizophrenia and related disorders, the efficacy of olanzapine 10-20 mg per day was compared to that of risperidone 4-12 mg per day. A significantly greater number of patients in the olanzapine group (36.8%) had at least a 40% improvement in PANSS (Positive and Negative Syndrome total score) compared to those in the risperidone group (26.7%) after 28 weeks of treatment.

Olanzapine was also more efficacious in treatment of negative symptoms (e.g. avolition, self-neglect, blunted affect). More olanzapine-treated patients maintained a response at 28 weeks (87.9%) than did risperidone-treated patients (67.7%). Fewer patients in the olanzapine group reported extrapyramidal events (18.6%) compared to patients in the risperidone group (31.1%). Akathisia and dyskinesia occurred with similar incidence in both treatment groups. Weight gain was greater and elevation in liver enzymes occurred more frequently in the olanzapine group. By the end of the 28 week study, 36% of the olanzapine group had elevated prolactin levels, compared to 90.3% of the risperidone group.

In short-term controlled clinical trials, olanzapine has been shown to be more efficacious than placebo and as effective or more effective than haloperidol in the treatment of schizophrenia and related disorders. In a 6 week trial in 335 patients, olanzapine in the dosage range of 15 ± 2.5 mg per day was more effective than haloperidol 15 ± 5 mg per day in the treatment of negative symptoms but was equally efficacious in overall improvement of symptom score. The percent of patients showing above 40% improvement in the Brief Psychiatric Rating Scale on olanzapine was 48%, and on haloperidol, 47%. In a large 6 week trial (1996 patients) primarily in treatment-resistant patients, the response to a mean modal dose of 13.2 mg per day of olanzapine was greater than the response to a mean modal dose of 11.8 mg per day of haloperidol. Overall efficacy was lower than in the previous trial possibly due to the fact that 77% of patients were resistant to prior antipsychotic treatment (excluding haloperidol). More patients in the haloperidol group discontinued therapy due to lack of efficacy (32.1%) than in the olanzapine group (20.7%); 7.3% of haloperidol-treated patients discontinued therapy due to adverse events, compared to 4.5% of olanzapine-treated patients. The only side effects that occurred with a higher incidence in the olanzapine group were excessive appetite (24%) and dry mouth (22.2%). The incidence of extrapyramidal events was 19.2% in the olanzapine group compared to 45.2% in the haloperidol group. Of the patients who responded to olanzapine or haloperidol in these comparative trials and subsequently continued therapy, it is estimated that 72% of haloperidol-treated patients and 80.3% of olanzapine-treated patients maintained response for at least a year.

Olanzapine has been used in the management of **acute mania in bipolar disorder**. Olanzapine, like other antipsychotics, is sometimes used as an adjunct to selective serotonin reuptake inhibitors (SSRIs) in the management of obsessive compulsive disorder.

Investigations are underway for the use of olanzapine in autism, Gilles de la Tourette's syndrome and in treatment of behavioural problems such as aggression in children with pervasive developmental disorder.

Although olanzapine has been used to treat psychotic symptoms of Parkinson's disease, its use remains controversial as it may worsen parkinsonian symptoms.

CONTRAINDICATIONS AND PRECAUTIONS:

Postural hypotension resulting in reflex tachycardia, dizziness and even syncope has been reported during the initial dose titration period. This is believed to result from alpha-1 adrenergic blocking effects. Use cautiously in patients with cardiovascular or cerebrovascular disease, in dehydrated or hypovolemic patients, in the elderly, and in patients taking antihypertensive medications. To minimize risk, use an initial dose of 2.5-5 mg and more gradual dose titration in patients prone to hypotension or in whom hypotension would pose a risk. Olanzapine has not been studied in patients with recent myocardial infarction or unstable heart disease.

Seizures occurred in a few patients during clinical trials, and conventional antipsychotics are known to lower the seizure threshold. Use cautiously in patients with a history of seizures, or who have conditions associated with seizures, or take concomitant medication that lowers seizure

threshold or have a lowered seizure threshold. There has also been a report of fatal status epilepticus .

Elevation in hepatic transaminases, primarily ALT, has occurred in some patients mainly in the first six weeks of treatment. In most cases, elevations were transient and levels fell while therapy was continued. No clinical signs or symptoms of hepatic impairment were seen. Use cautiously in patients with hepatic disorders or in those taking medication with possible hepatotoxic effects. Clinical assessment and baseline transaminase measurement are recommended in these patients.

Prolactin levels may be increased although this occurs to a lesser extent than with typical antipsychotics. Use caution in patients with a history of breast cancer which may be prolactin dependent. Also, consider risk-benefit ratio in patients with pituitary tumours.

Antipsychotics impair **hypothalamic thermoregulatory mechanisms**, which can result in hypothermia or hyperthermia, depending on environmental temperature and physical activity. Dehydration and use of anticholinergic medications may also lead to an increase in body temperature. Hyperthermia has been reported with olanzapine.

In clinical trials, dose-related **weight gain** occurred in 29% of patients, tending to level off after 6-8 months of treatment with a mean weight gain of 5.4 kg.

Anticholinergic effects (dry mouth, tachycardia, blurred vision, constipation) caused by muscarinic blocking effects have occurred in less than 15% of patients. Use with caution in patients with narrow angle glaucoma, urinary retention, symptomatic prostatic hypertrophy or history of paralytic ileus.

The **neuroleptic malignant syndrome (NMS)** occurs rarely with conventional antipsychotics and has also been reported with olanzapine. Symptoms include hyperthermia, muscle rigidity, changes in mental status, blood pressure changes, tachycardia, arrhythmias and sweating. The fatality rate with conventional antipsychotics is about 20%. Early diagnosis of the syndrome with discontinuation of the drug and appropriate treatment is vital.

Hematological toxicity manifested as leukopenia and neutropenia has been reported with olanzapine. As well, patients who developed clozapine-induced granulocytopenia and were then switched to olanzapine therapy before granulocyte counts recovered, have experienced an appreciable delay in return of granulocyte counts to normal. It is recommended that granulocyte counts be allowed to normalize before olanzapine therapy is begun. Periodic monitoring would be recommended.

Diabetes mellitus has been reported with the use of olanzapine in schizophrenic patients; hyperglycemia has resulted in fatal hyperosmolar nonketotic diabetic coma. Glycemic control usually improves after discontinuation of olanzapine.

The extrapyramidal symptom of **tardive dyskinesia** has been reported with olanzapine. Tardive dyskinesia caused by antipsychotic agents is usually a late-appearing neurological syndrome characterized by involuntary movements, particularly of the lips and tongue, but sometimes of the fingers, toes, trunk and respiratory muscles. Risk of tardive dyskinesia appears to be greater in elderly patients receiving high doses, especially women. Tardive dyskinesia symptoms may be masked by antipsychotic use and unmasked if the drug is discontinued. Symptoms may persist indefinitely after discontinuation of the medication although occasionally they will subside with time. Numerous drugs have been tried in an attempt to alleviate symptoms but none has been found consistently effective. To help prevent development of tardive dyskinesia, therapy with antipsychotics should be limited to those cases where it is clearly indicated. The lowest effective dose should be given and, where it is being used long-term, evaluation for signs or symptoms of tardive dyskinesia, preferably using a rating instrument for abnormal involuntary movements, should be made every three months. If signs or symptoms of tardive dyskinesia appear, the continued need for the antipsychotic should be assessed.

Somnolence may occur; patients should be advised to avoid driving motor vehicles or operating hazardous machinery until their response to olanzapine is known.

There may be occurrence of a **withdrawal** syndrome; symptoms of myoclonic jerking, piloerection, headache, nightmares, restlessness, depression and blurred vision have been reported and were also described as serotonergic rebound. Caution is advised.

PREGNANCY AND LACTATION:

With single dose administration of olanzapine, an estimated 5-14% of the dose crosses the placenta. No teratogenic effects were found in limited animal studies. Early experience with olanzapine exposure in pregnancy and lactation is promising but published reports/studies are sparse. There are a few case reports of patients taking olanzapine throughout pregnancy with no obvious adverse effect on the neonate. More information is required.

There is one report of the breast-fed infant of a mother taking 10 mg/day having negligible plasma levels of less than 2 ng/mL while the mother's were 32-39 ng/mL. In animal studies, levels in breast milk were three times higher than plasma levels. The decision to breast-feed must be a risk/benefit decision.

SIDE EFFECTS:

Side effects occurring more than double that in the placebo group with an incidence of at least 5% include: somnolence, dizziness, weight gain, constipation, akathisia (restlessness), and increased ALT.

Cardiovascular: Postural hypotension (5%), tachycardia (4%), chest pain (4%), hypotension (2%).

CNS: Somnolence (26-35% and dose-related), agitation (23%), insomnia (20%), headache (17%), nervousness (16%), hostility (15%), dizziness (11-15%, dose-related), anxiety (9%), personality disorder (8%), akathisia (5%), hypertonia (4%), speech disorder (4%), tremor (4-6%, dose-related), amnesia (2%), drug dependence (2%), euphoria (2%), neurosis (1%), seizures (0.9%), aggression, mania.

Dermatologic: Vesiculobullous rash (2%), dermatitis (2%).

Endocrine/Metabolic: Weight gain (29%), increased appetite (2%), fever (5%), edema (2%), peripheral edema (2%), prolactin elevation (mild, usually transient), menstrual disorder (2%), hyperglycemia, diabetes mellitus. Uric acid may also increase. Non-NMS hyperthermia.

Gastrointestinal: Abdominal pain (4%), constipation (9%, dose-related), dry mouth (7%).

Hematologic: Leukopenia (1%), neutropenia, transient eosinophilia (5.7%). Agranulocytosis and pancytopenia have been reported.

Hepatic: Increased levels of ALT (8%), AST, GGT (2%). Periodic monitoring is recommended.

Neuromuscular: Arthralgia (3%), joint disorders (5%), twitching (2%), neck rigidity (2%), back pain (4%), increased creatine kinase (1%). Extrapyramidal symptoms (15%), tardive dyskinesia (0.5%), neuroleptic malignant syndrome (NMS) (rare).

Other: Rhinitis (10%), increased cough (5%), pharyngitis (5%, dose-related), amblyopia (5%), blepharitis (2%), corneal lesions (1%), pancreatitis (rare), priapism.

OLANZAPINE

INTERACTIONS:

DRUG	EFFECT	MECHANISM	IMPORTANCE
Antihypertensives	Increased antihypertensive effect	Additive	Monitor blood pressure initially
Carbamazepine	Decreased olanzapine levels	Increased olanzapine metabolism	Caution
CNS depressants (alcohol, anesthetics, barbiturates, benzodiazepines, opiates, sedatives, tranquilizers)	Increased CNS depression	Additive	Caution (theoretical)
Dopamine agonists (bromocriptine, pergolide, pramipexole, ropinirole)	Decreased dopamine agonist effect	Possible blockade of dopamine receptors	Caution
Fluvoxamine	Increased olanzapine levels	Inhibition of olanzapine metabolism	Caution
Levodopa	Decreased levodopa effect	Possible blockade of dopamine receptors	Caution
Omeprazole	Possible decreased olanzapine levels	Increased olanzapine metabolism	Caution
Quinolone antibiotics	Increased olanzapine levels	Inhibition of olanzapine metabolism	Caution
Valproic acid	Possible increased valproic acid levels	Possible decreased valproate clearance	Caution; monitor valproic acid levels

In single dose studies, metabolism of the following drugs was not inhibited by olanzapine: diazepam, desipramine, imipramine, warfarin. Sertraline does not affect the metabolism of olanzapine. No interaction was seen with lithium. Single doses of aluminum and magnesium antacids, or cimetidine did not affect bioavailability of olanzapine. Smoking decreases olanzapine half-life possibly by inducing CYP1A2.

DOSAGE:

Adults:

Oral: Initially, 5-10 mg once daily without regard to meals. After one week, the dose can be increased to the usual target dose of 10 mg daily. Dose adjustments should occur at intervals of a minimum of seven days. If response is not adequate, the patient should be clinically assessed before increasing the dose to 15 mg daily or greater. Doses greater than 20 mg/day are not generally recommended. Steady state serum levels are reached one week after starting therapy or after a dose increase or decrease.

Acute mania in bipolar disorder: 5-15 mg/day.

Elderly or debilitated: Initially, 2.5-5 mg once daily. "As required" dosing is not recommended as the time to action is quite slow. Increase dose with caution, observing for hypotensive effects. Experience is limited in this group of patients.

Renal or hepatic impairment, hemodialysis: Dose and disposition are not affected but initiate therapy with low doses. Only single dose studies have been done.

Children:

Minimal experience; doses of 2.5-15 mg daily have been used in 5-17 year olds with developmental disabilities or psychoses. Other sources recommend 5-10 mg daily with a maximum of 20 mg daily for adolescents.

NURSING IMPLICATIONS:

- Carefully observe patient while doses are taken to prevent omissions or possible hoarding.
- May be given with or without meals.
- The orally disintegrating tablets (Zyprexa Zydis) dissolve on contact with moisture and hence in the mouth. They may also be pre-dissolved in a glass of water, milk, coffee, orange juice or apple juice and ingested immediately. Tablets must be handled with dry hands.
- Hypotension, dizziness and syncope may occur, particularly in elderly patients beginning treatment. Instruct patients to rise slowly from a lying or sitting position. Supervise ambulation. Monitor standing and lying blood pressure initially and when dose is increased.
- Observe for and report appearance of tremor, rigidity, unusual involuntary movements of the tongue or jaw, and restlessness, which are possible extrapyramidal side effects. The elderly are more likely than younger patients to develop tardive dyskinesia.
- Advise physician immediately of severe muscle stiffness, seizures, fever and tachycardia (neuroleptic malignant syndrome).
- Constipation may occur. Encourage fluids and dietary fibre.

OLANZAPINE

8. Diabetes mellitus has occurred; observe for increased thirst and urination.
9. Therapeutic benefits may include improvement in positive symptoms (delusions, hallucinations, thought disorder) and in negative symptoms (avolition, self-neglect, blunted affect) in psychotic patients.

PATIENT INSTRUCTIONS:

1. Olanzapine is used to treat schizophrenia and related psychotic disorders. It helps to relieve hallucinations (hearing or seeing things that are not there), delusions, suspiciousness, emotional withdrawal, depression, anxiety and tension. It may also be used to treat other disorders as determined by your physician.
2. Take the medication exactly as prescribed by your physician. Do not stop taking the drug unless you first discuss this with your physician. Symptoms usually relapse if medication is stopped.
3. This medication may be taken with or without food.
4. The oral disintegrating tablets (Zyprexa Zydis) dissolve immediately in the mouth. They may also be pre-dissolved in a glass of water, milk, coffee, orange juice or apple juice and ingested immediately. Tablets must be handled with dry hands.
5. If you miss a dose by a few hours, take it as soon as you remember. However, if most of the day has passed, wait until your next scheduled dose and try not to miss any more. Do not take two doses at once to make up for a missed one.
6. Dizziness, lightheadedness or fainting may occur when you first start taking this medication, especially when you get up from a sitting or lying position. Getting up slowly may help. Check with your physician if the problem continues or gets worse.
7. If this medication makes you feel drowsy, dizzy, confused, lightheaded, or causes blurred vision, do not drive a vehicle or operate hazardous machinery.
8. Other possible side effects include increased appetite, weight gain, ankle swelling, constipation, and dry mouth.
9. Check with your physician if any of the following side effects occur: muscle spasms, restlessness, shuffling walk, jerky movements of the head, face, neck and mouth, or trembling of hands and fingers. Also tell your physician if you have increased thirst and increased urination.
10. Tranquilizers, sleeping pills, medicines for seizures, some painkillers, and some cold and allergy medications may add to drowsiness. Check with your physician or pharmacist before taking any of these.
11. The effects of alcohol can be made worse while taking olanzapine. Drowsiness and dizziness may be increased; it is recommended that you not take alcohol while on this medication.
12. Tell your physician if you are pregnant, or plan to become pregnant, or if you wish to breast-feed your baby.
13. Store this medication in a tightly closed container, protected from light and in a dry place. Do not let anyone else use this medication. Keep it out of the reach of children.

PRESENTATION:

Tablets: 2.5, 5, 7.5, and 10 mg.

Orally disintegrating tablets: 5 and 10 mg.

Also see Antipsychotics monograph.