

**Olanzapine:**  
Implications for the Primary Care  
Physician Treating the Symptoms of  
Bipolar Mania and Schizophrenia



ZY 4021 6

## A Chronology of Primary Care Prescribing of Psychotropic Medications

1970s	Benzodiazepines
1980s	SSRIs and other new antidepressants
1990s	Cholinesterase inhibitors
Present	Atypical antipsychotics

As recently as 30 years ago, primary care physicians (PCPs) would rarely venture into the domain of "psychiatric disorders." With the advent of newer and safer medications, PCPs have increasingly recognized psychiatric disorders and begun to use this increased armamentarium to safely and effectively help their patients for a variety of disorders and symptoms. PCP management often allows these patients to avoid the expense and delay associated with referral to a specialist.

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## Case Study: Outpatient—Martha

- ◆ Widow, has been your patient for several years, owns a home near her family
- ◆ Becoming more complicated to manage with increasing agitation
- ◆ Dozes during the day, has trouble sleeping at night
- ◆ Family is concerned, reports she is easily confused and forgetful, calls at all hours, just "not herself" anymore

### Goals of treatment may include:

- ◆ Reduce behavioral disturbances without impairing cognition

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## Case Study: Outpatient—Michael

- ◆ Male in his mid-30s, highly functional, has been your patient for years, is in good general health
- ◆ Reports a decreased need for sleep
- ◆ Wife reports his mood swings, spending money he doesn't have
- ◆ No evidence of substance abuse or organic causes
- ◆ He strongly resists attempts to refer him for psychiatric treatment

### Goals of treatment may include:

- ◆ Stabilize mood and reduce agitation

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## Case Study: Outpatient—Kelly

- Single female in her early 20s
- Has gradually become socially isolated and fearful
- Difficult to draw out, but eventually tells you that she believes she is worthless
- Family reports that she never sees friends anymore, can't make up her mind about the simplest things, thinks people are talking behind her back

### Goals of treatment may include:

- Improve mood and ability to think clearly
- Reduce suspiciousness

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## Postulated Roles of Neurotransmitters in Bipolar Disorder<sup>1</sup>

System	Relevance to Bipolar
Dopamine	DA antagonists reduce psychotic symptoms
Serotonin	5HT may affect mood, violence, suicide
Acetylcholine	Cholinomimetics may reduce mania, improve cognition
GABA	Mood stabilizing anticonvulsants pro-GABA, sedating effects
Glutamate	Lithium and certain anticonvulsants may enhance glutamate

1 Goodwin FK, Jamison KR. *Manic-Depressive Illness*. 1st edition. New York: Oxford University Press; 1990.

The pathophysiology of bipolar disorder is unclear. Current research is focused on several neural processes, including a range of intracellular factors and neurotransmitter systems. This slide presents some of the more familiar neurotransmitters and their postulated relationship to bipolar disorder. These hypotheses are continuously being refined as more data become available.

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## Olanzapine: Effects Across Multiple Neurotransmitter Systems<sup>1</sup>

System	Olanzapine Action
<b>Dopamine</b>	Direct DA receptor antagonist
<b>Serotonin</b>	Multiple, balanced 5HT receptor effects
<b>Acetylcholine</b>	May indirectly enhance ACh release
<b>GABA</b>	May indirectly enhance GABA release
<b>Glutamate</b>	May enhance and stabilize glutamatergic transmission

1. Bymaster FP, et al. *J Clin Psychiatry*. 1997;58(suppl 10):28-36

While knowledge is not conclusive regarding the mechanism of action of any medication for bipolar disorder, the effects of olanzapine on several neurotransmitter systems correspond to those that are postulated to be beneficial in bipolar disorder.

Olanzapine has a broad binding profile and is active at a number of neuronal receptors including dopamine (D1-5), serotonin (many receptors, prominently including 5HT2A, B, C, and 5HT6), muscarinic acetylcholine (M1-5), and histamine and norepinephrine receptors. Preliminary evidence is accruing for a variety of indirect effects on glutamate-NMDA neurotransmission and stimulation of increased release of both acetylcholine and gamma-amino butyrate (GABA).

The package insert for olanzapine notes: "Olanzapine's antagonism of muscarinic M1-5 receptors may explain its anticholinergic effects. Olanzapine's antagonism of histamine H1 receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic alpha-1 receptors may explain the orthostatic hypotension observed with this drug."

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## What Is Bipolar Disorder?<sup>1,2</sup>

- ◆ An episodic disorder of mood
  - ◆ Involves the presence or history of manic, mixed, hypomanic, and/or major depressive episodes
- Four types**
- ◆ Bipolar I
    - ◆ Manic, mixed, depressed
  - ◆ Bipolar II
    - ◆ Hypomanic, depressed
  - ◆ Cyclothymic disorder
    - ◆ Hypomanic, depressed
  - ◆ Bipolar disorder not otherwise specified (NOS)

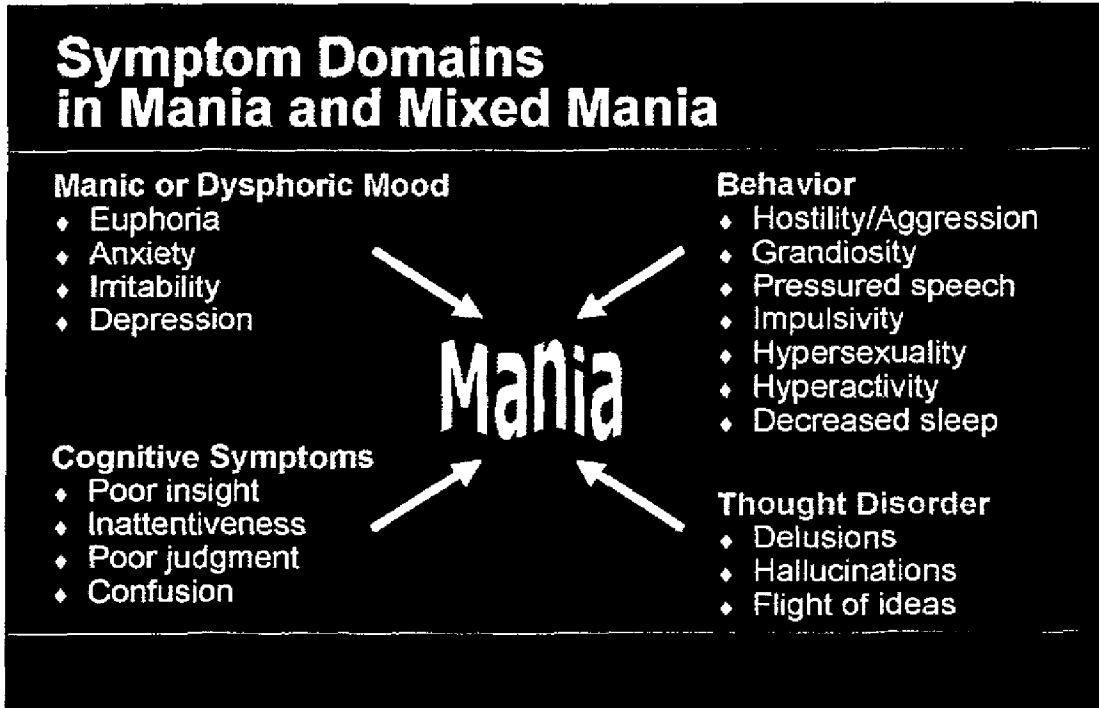
1 Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Washington, DC: American Psychiatric Association, 1994.  
2 Goodwin FK, Jamison KR. *Manic-Depressive Illness*. 1st edition. New York: Oxford University Press, 1990.

As we begin the discussion, it is important to have an understanding of bipolar disorder—an episodic disorder of mood involving the presence or history of manic, mixed, hypomanic, and/or major depressive symptoms. Bipolar disorder has commonly been referred to as “manic-depressive” disorder because of unpredictable swings in mood from mania to depression; however, at least four types of bipolar disorder have been described:

- Bipolar I (manic, mixed, depressed)
- Bipolar II (hypomanic, depressed)
- Cyclothymic disorder (hypomanic, dysthymic)
- Bipolar disorder not otherwise specified (NOS)

According to the DSM-IV definition, patients with bipolar I disorder have had at least one episode of mania. Some patients will have had previous depressive episodes, and most patients will experience subsequent manic and/or depressive episodes. Hypomanic and mixed episodes may also occur. Bipolar II disorder is characterized by major depressive episodes alternating with episodes of hypomania that do not fully meet the criteria for mania as in bipolar I disorder. Cyclothymic disorder is characterized by multiple hypomanic symptoms that do not meet full criteria for a manic episode, as well as multiple periods of depressive episodes that do not meet full criteria for a major depressive episode. Patients with bipolar I or bipolar II disorder who have four or more episodes of either mania or depression in a year have a pattern referred to as “rapid cycling.”

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Bipolar mania has effects on all four domains of a patient's behavior, mood, cognition, and thought. This can be quite devastating for the patient, the family, the caretakers, and anyone who comes close to the patient in any capacity.

Inadequately treated, the patient may become increasingly exhausted, physically ill, and the illness may then become life-threatening.

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## Clinical Features of Bipolar Disorder: Depressive Episodes<sup>1</sup>

- ◆ Depressed (sad, anxious, or empty) mood
- ◆ Reduced interest or pleasure in all, or nearly all, activities
- ◆ Fatigue or loss of energy
- ◆ Feelings of hopelessness, pessimism, guilt, worthlessness, or helplessness
- ◆ Reduced ability to think or concentrate or make decisions
- ◆ Change in body weight or appetite
- ◆ Thoughts of death or suicide

1. Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Washington, DC: American Psychiatric Association, 1994.

Depressive episodes of bipolar disorder are identified by the same signs and symptoms that characterize unipolar major depressive episodes. Symptoms of depression may include depressed (sad, anxious, or empty) mood; reduced interest of pleasure in all or nearly all activities; fatigue or loss of energy; feelings of hopelessness, pessimism, guilt, worthlessness, or helplessness. Many patients experience a reduced ability to think or concentrate or make decisions. Changes in sleep patterns (insomnia/hypersomnia) may be evident. Changes in body weight or appetite are also associated with depressive episodes. Some patients experience psychomotor agitation or retardation. Persistent thoughts of death or suicide represent a particularly dangerous symptom of a depressive episode.

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## Attributes of "Ideal" Mood Stabilizer for Mania<sup>1</sup>

- ◆ Rapid efficacy for mania
- ◆ Treats psychotic symptoms of mania
- ◆ Broad efficacy (e.g., mixed, rapid cycling)
- ◆ Reduces depressive elements in mania
- ◆ Favorable cognitive effects
- ◆ Long-term usefulness
- ◆ Safety and tolerability
- ◆ Ease of use

<sup>1</sup> Keck PE Jr, McElroy SL. Pharmacological treatment of bipolar disorders. In: Nathan PE, Gorman JM, eds. *A Guide to Treatment That Works*. New York: Oxford University Press, 1997.

If there were an "ideal" mood stabilizer, what might it look like? In essence, this medication would quickly treat symptoms such as hostility, suicidality, and agitation in order to reduce immediate threat to the patient and others. It would also help stabilize the patient's manic and depressive symptoms without inducing the symptoms associated with the opposite pole. As symptoms resolve, the patient should not only be able to resume normal levels of functioning, but live with a reduced risk of future symptom relapse. To provide this level of efficacy with a reduced risk of serious medical complications and interference in a patient's daily routine...this would be "ideal."

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## Olanzapine for Acute Mania: 2 Placebo-Controlled Studies

- ◆ Both double-blind, multicenter, placebo-controlled, parallel group
  - ◆ 3 weeks<sup>1</sup>
  - ◆ 4 weeks<sup>2</sup>
- ◆ Olanzapine dosage: 5-20 mg/day
  - ◆ Starting daily dose:
 

3-week study	10 mg
4-week study	15 mg
  - ◆ Mean modal daily dose:
 

3-week study	14.9 mg
4-week study	16.4 mg
- ◆ DSM-IV bipolar I disorder, manic or mixed
- ◆ Lorazepam use limited to initial study phase

1. Tohen MF, et al. *Am J Psychiatry*. 1988;145(5):702-709

2. Tohen MF, et al. Presented at XI World Congress of Psychiatry, Aug 6-11, 1999, Hamburg, Germany

The efficacy of olanzapine for bipolar mania was demonstrated in two placebo-controlled registration trials. Both trials enrolled patients diagnosed with an acute manic or mixed episode, with or without psychotic features. Minor differences in study designs were as follows:

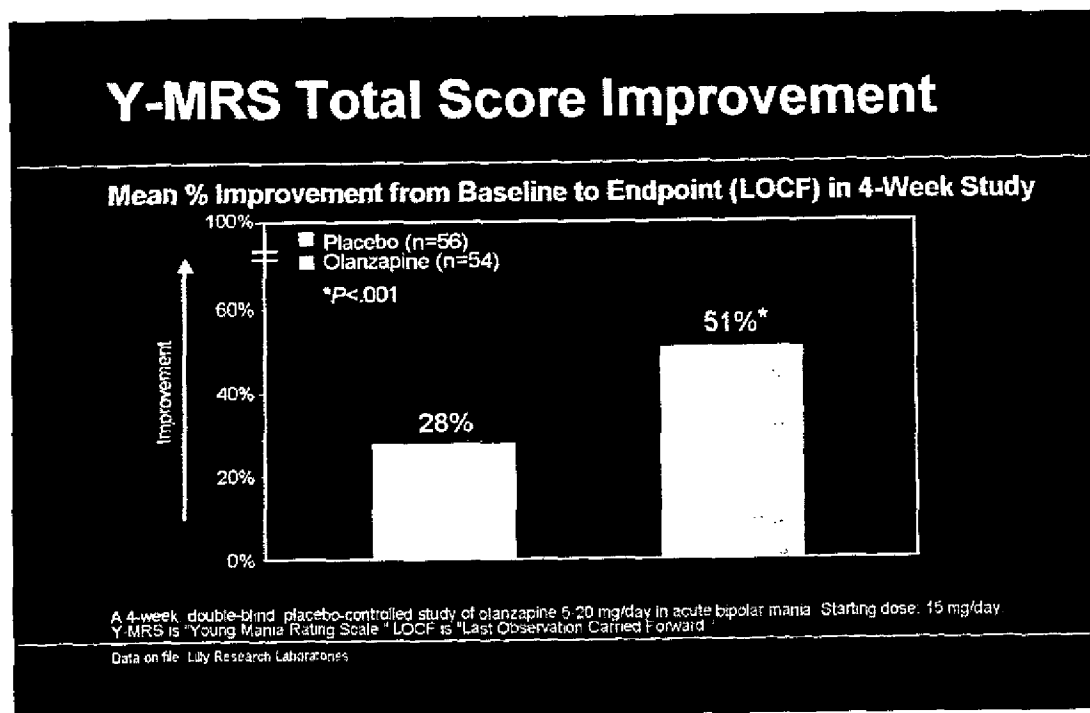
- Duration: three weeks versus four weeks
- Starting dose: 10 mg in the three-week study;  
15 mg in the four-week study

More robust results were seen with the 15 mg starting dose (four-week study). Both studies were double-blind, placebo-controlled, parallel group studies. Subjects were initially hospitalized, but responders could be discharged after one week. Medically unstable, organically impaired, or substance-dependent subjects were excluded. Patients in their first episode of mania were excluded from the four-week study.

After a two- to four-day screening period, qualified patients were randomly assigned to either olanzapine or placebo. Following the first day of treatment, the daily dose could be adjusted upward or downward, as clinically indicated, by one tablet (olanzapine 5 mg or placebo) within the allowed range of one to four tablets/day.

Limited use of adjunctive lorazepam was allowed. The four-week study was the more restrictive: lorazepam max 2 mg/day for the first four days, max 1 mg/day for the next six days, none after day 10.

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The primary efficacy measure in both mania studies was the Young Mania Rating Scale (Y-MRS),<sup>1</sup> a scale of 11 items that measures mania symptoms. The studies demonstrated that olanzapine is effective for treating manic or mixed episodes associated with bipolar disorder.

The Y-MRS includes: elevated mood, increased motor activity/energy, sexual interest, sleep, irritability, speech (rate and amount), language/thought disorder, thought content, disruptive/aggressive behavior, appearance, and insight. To enroll in either study, subjects had to score at least 20 on the Y-MRS, a moderately severe score that generally reflects the need for hospitalization. "Response" was defined for both studies as improvement of  $\geq 50\%$  from baseline Y-MRS score. "Euthymia" was defined in the four-week study as a final Y-MRS score of  $\leq 12$ .

In the four-week study, patients treated with olanzapine improved by 51% (14.8 points) from baseline to endpoint, versus 28% (8.1 points) in the placebo group ( $P < .001$ ).

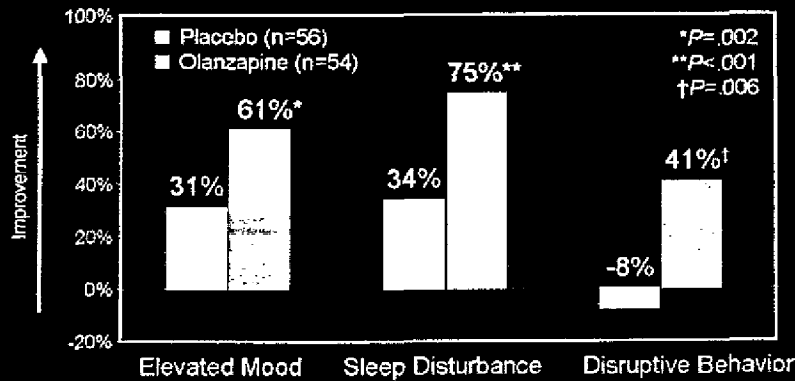
In the three-week study, patients treated with olanzapine improved by 37% from baseline to endpoint, versus 18% in the placebo group ( $P = .054$ ).

1. Young RC, et al. *Br J Psychiatry*. 1978;133:429-435.

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## Improvement in Several Y-MRS Individual Items

Mean % Improvement from Baseline to Endpoint in 4-Week Study



A 4-week, double-blind, placebo-controlled study of olanzapine 5-20 mg/day in acute bipolar mania. Starting dose: 15 mg/day. Y-MRS is "Young Mania Rating Scale."

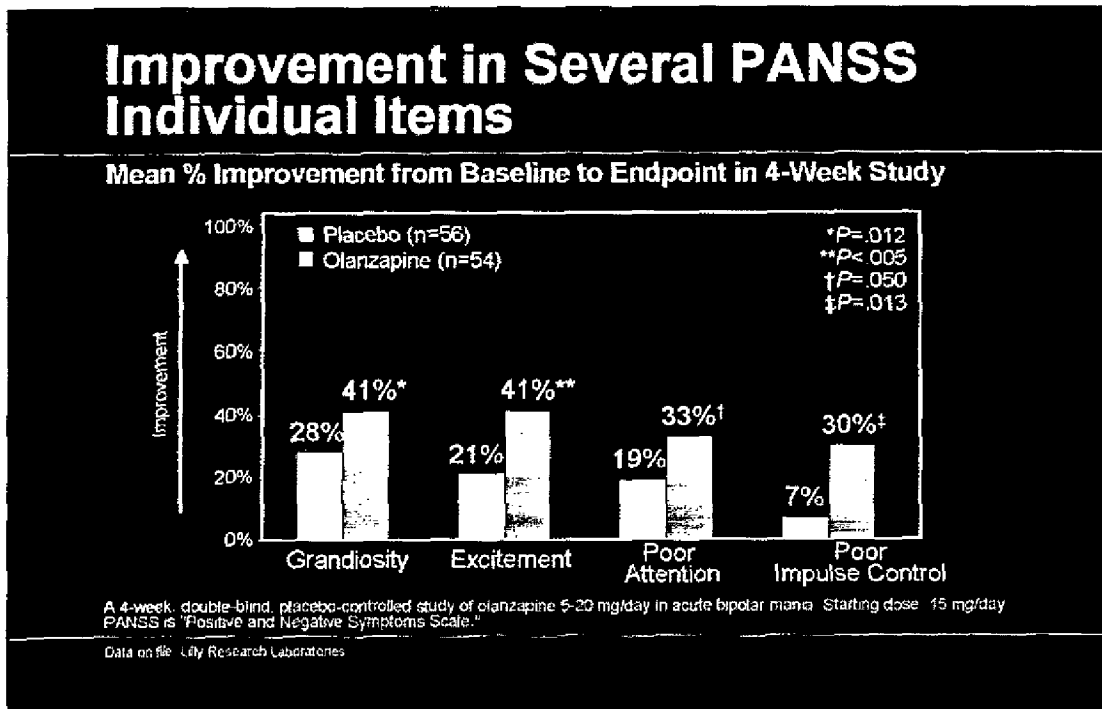
Data on file. Lilly Research Laboratories

In the four-week study, olanzapine demonstrated statistically significant improvement in several Y-MRS individual item scores as compared with placebo. Olanzapine showed improvement compared with placebo in terms of elevated mood, sleep disturbance, and disruptive behavior.

In the three-week study, olanzapine showed statistically significant superiority over placebo in sleep disturbance and a numerical advantage that did not separate from placebo on other items mentioned.

These data suggest that olanzapine is effective in manic symptoms not normally associated with psychosis.

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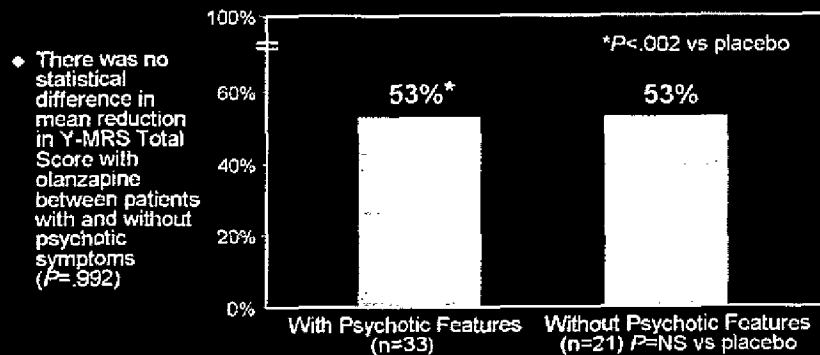
A secondary rating scale used in both studies was the Positive and Negative Symptoms Scale (PANSS). In addition to measures of psychosis, the PANSS includes general psychopathology measures, including several individual items that may shed light on how olanzapine affects nonpsychotic symptoms of mania. The graphed items are from the four-week study and generally reflect manic symptoms without psychotic features. On these items—grandiosity, excitement, poor attention, and poor impulse control—olanzapine produced superior improvement that was significantly greater than that with placebo. In the three-week study, olanzapine showed statistically significant superiority to placebo in sleep disturbance and a numerical advantage that statistically did not separate from placebo for other items mentioned.

The PANSS individual items include: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, hostility, blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking, somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance.

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## Y-MRS Total Score Improvement With/Without Psychotic Features

Manic Patients With/Without Psychotic Symptoms:  
Mean % Improvement from Baseline to Endpoint (LOCF) in 4-Week Study

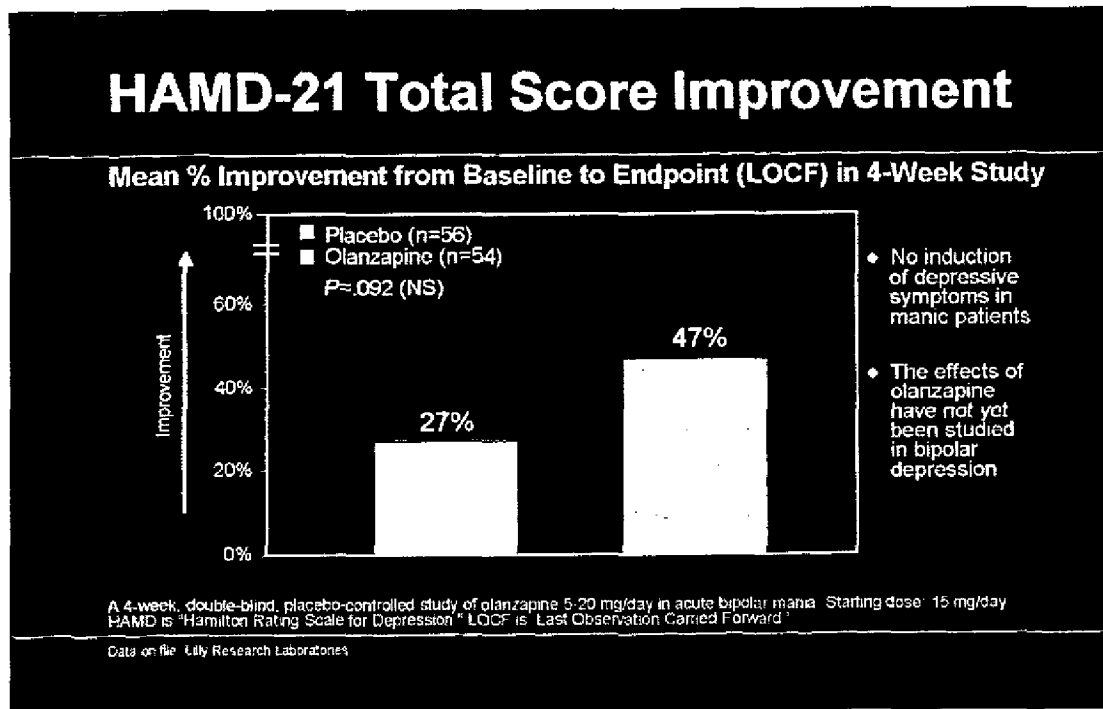


A 4-week, double-blind, placebo-controlled study of olanzapine 5-20 mg/day in acute bipolar mania. Starting dose: 15 mg/day. Y-MRS is "Young Mania Rating Scale." LOCF is "Last Observation Carried Forward."

Data on file. Lilly Research Laboratories

Another way of looking at the effects of olanzapine on nonpsychotic aspects of mania is to explore results in those patients not diagnosed as having psychotic features. This slide compares improvement in the four-week study between subjects with and without baseline psychotic features. Improvement with olanzapine was statistically similar across the two groups, suggesting that olanzapine is not limited in usefulness to psychotic patients. There was no statistically significant difference in mean reduction in Y-MRS Total Score with olanzapine between patients with and without psychotic symptoms.

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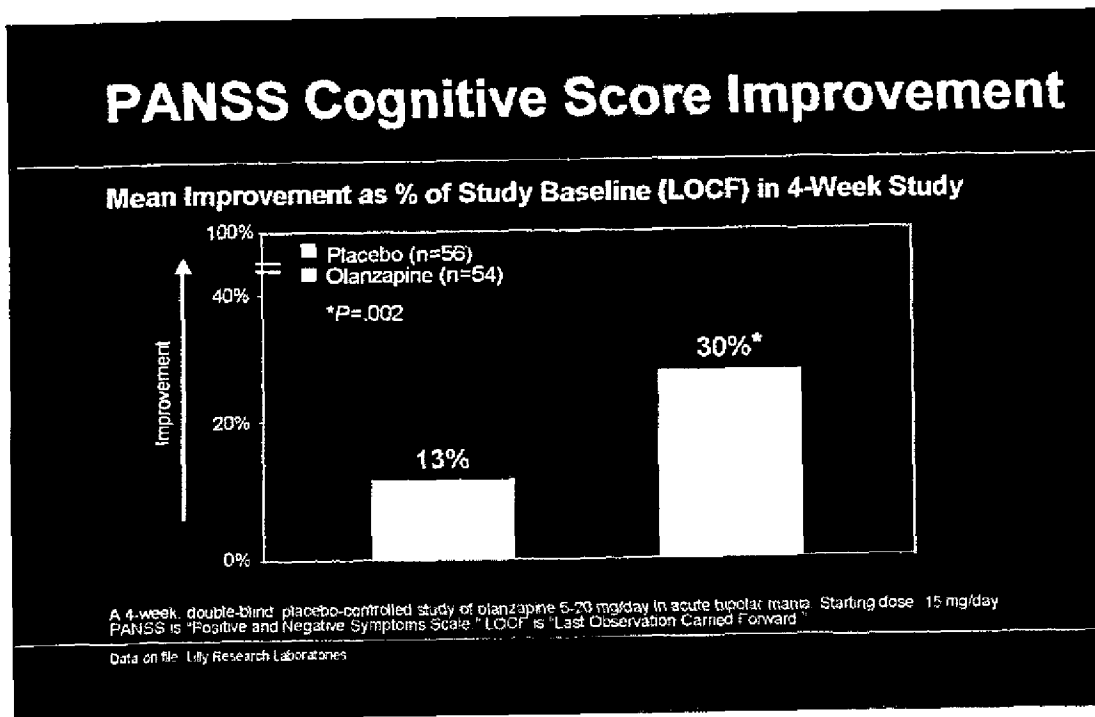


Among the reasons that some clinicians avoid conventional antipsychotic drugs for treating bipolar mania is the possibility that they may worsen depressive symptoms. This effect does not seem to occur with olanzapine. In both placebo-controlled trials, the 21-item Hamilton Depression Rating Scale (HAMD-21) was used as a secondary measure. Though the studies were not primarily designed to assess depressive symptoms, patients treated with olanzapine had beginning-to-endpoint reduction in depression ratings.

Does improvement in overall ratings in both treatment groups mask worsening in some individuals? In both studies, some subjects had HAMD score increases, but the number of subjects with baseline-to-endpoint worsening in HAMD scores was not lower with placebo than with olanzapine. Therefore, olanzapine does not appear to be associated with worsening of depression during short-term treatment of mania.

The HAMD-21 individual items include: depressed mood, guilt, suicide, early insomnia, middle insomnia, late insomnia, work and activities, retardation, agitation, anxiety (psychological), anxiety (somatic), somatic symptoms (gastrointestinal), somatic symptoms (general), genital symptoms, hypochondriasis, loss of weight (history), loss of weight (actual), insight, diurnal variation (present), diurnal variation (severity), depersonalization and derealization, paranoid symptoms, and obsessive and compulsive symptoms.

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This slide illustrates changes on the cognitive component of the PANSS.

In the four-week study, patients treated with olanzapine showed mean improvement in the PANSS Cognitive Score that was statistically significantly superior to placebo. In the three-week study, improvement in the PANSS Cognitive Score with olanzapine was 17% (n=34) versus 14% with placebo (n=33), which was not statistically different.

These data from placebo-controlled trials suggest that olanzapine does not cause cognitive impairment, and may actually benefit cognition in mania.

PANSS Cognitive Score assesses cognitive disorganization, difficulty in abstract thinking, stereotyped thinking, tension, mannerisms and posturing, poor attention, and lack of judgment and insight. (Score validation described by Bell et al.<sup>1</sup>)

1. Bell MD, et al. *Psychiatry Res.* 1994;54:51-58.

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## Safety Profile of Olanzapine in Bipolar Mania

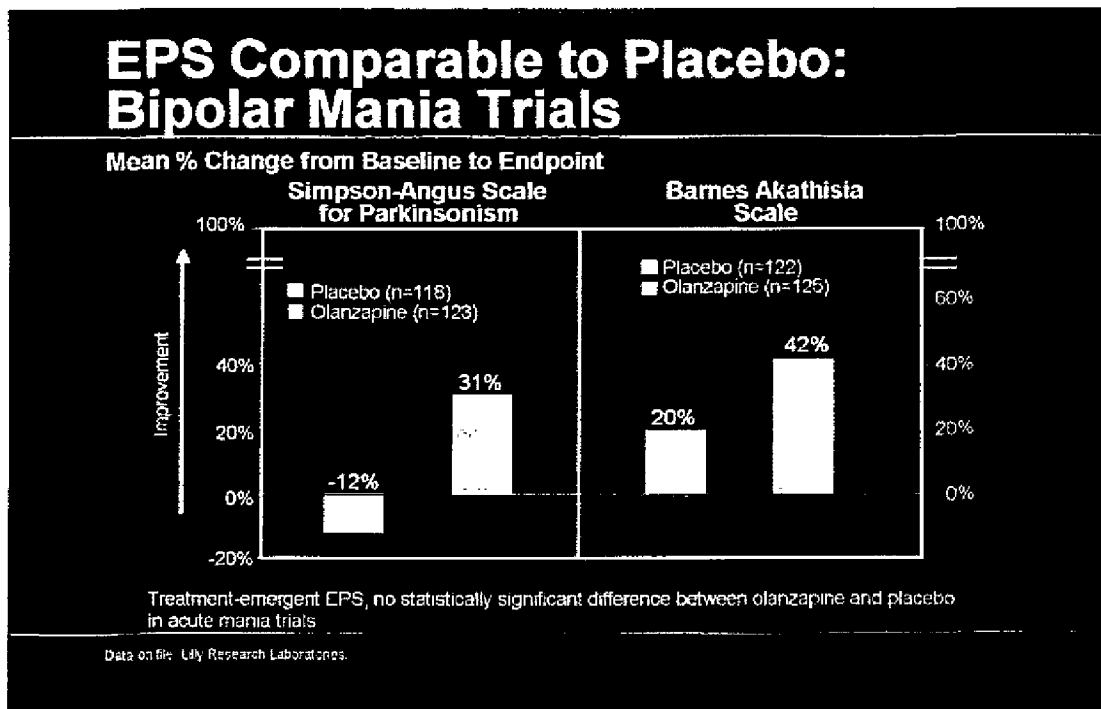
### Low Risk of Certain Serious Medical Complications

- ◆ Low potential for drug interactions
- ◆ No clinically significant hepatic, renal, hematologic, or cardiac changes in acute mania trials
- ◆ No black-box or bolded warnings
- ◆ Avoids routine blood monitoring
- ◆ Pregnancy Category C

Safety and tolerability are important considerations in the treatment of bipolar mania, even more so because so many patients discontinue their therapy prematurely due to adverse events. Olanzapine has demonstrated a low potential for drug interactions, including effects on pharmacokinetics of commonly used medications for bipolar disorder (imipramine, lithium, desipramine, diazepam). Coadministration of diazepam or ethanol with olanzapine may potentiate orthostatic hypotension.

Olanzapine does not have any black-box or bolded warnings in its label and is rated Pregnancy Category C. Olanzapine has not been studied in pregnant women; however, there are no known teratogenic effects in humans.

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Extrapyramidal side effects were not observed during acute mania trials. On both the Simpson-Angus scale for parkinsonism and the Barnes Akathisia Scale, the olanzapine-treated group had beginning-to-endpoint improvement in mean scores. In both cases, this was numerically better and not statistically distinguishable from the placebo group. On the Simpson-Angus Scale, patients treated with olanzapine had a 31% improvement from baseline versus 12% worsening with placebo. On the Barnes Akathisia Global Scale, patients treated with olanzapine had a 42% improvement from baseline, versus 20% with placebo.

In only one analysis of a placebo-controlled study in schizophrenia patients, only one specific form of EPS, akathisia, was reported significantly more often with olanzapine at any specific dose ( $10 \pm 2.5$  or  $15.0 \pm 2.5$  mg/day) compared with placebo.

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## Olanzapine (ZYPREXA®): Ease of Use

- ◆ Compatible with patient's daily routine
- ◆ Once-daily dosing with or without food
- ◆ No titration required
- ◆ Flexibility in dosing, 5-20 mg
  - ◆ Available tablet strengths  
2.5, 5, 7.5, 10, 15, and 20 mg

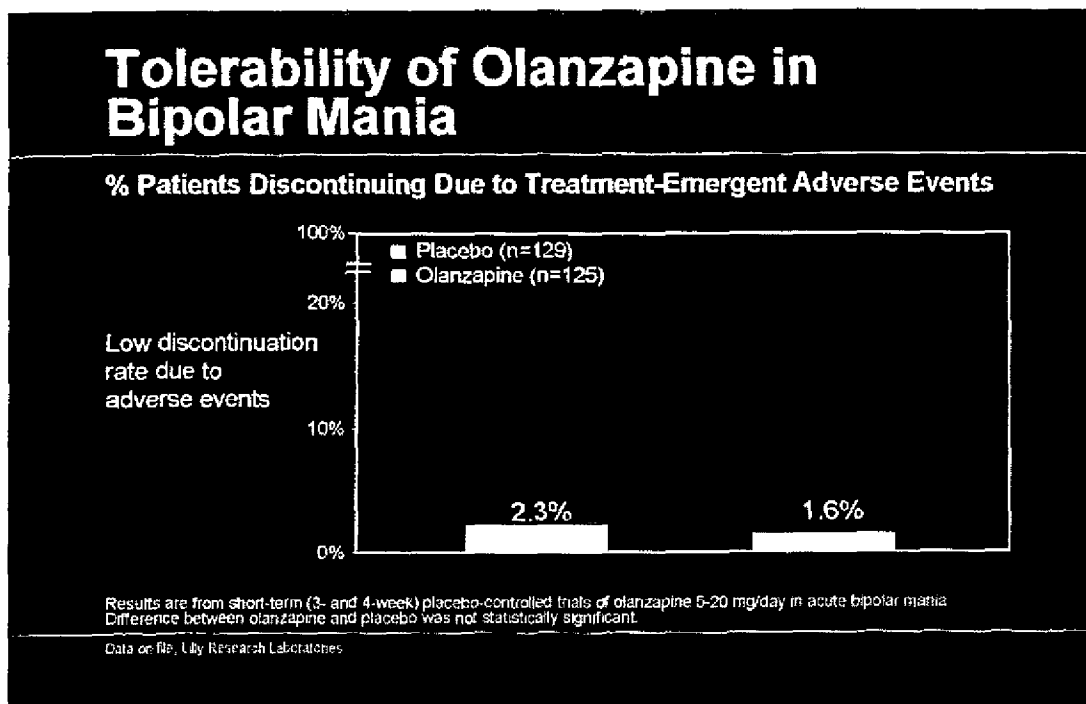
The image shows six tablets arranged in two rows. The top row contains four round tablets with the following strengths below them: 2.5 mg, 5 mg, 7.5 mg, and 10 mg. The bottom row contains two oval tablets with the following strengths below them: 15 mg and 20 mg.

Zyprexa is a registered trademark of Eli Lilly and Company.

In general, olanzapine is convenient to use. For most patients, therapy can begin immediately at a dose that is within the therapeutic range. In most cases, once-daily dosing is appropriate, and this can be scheduled with or without food to maximize convenience for the patient.

The available tablet strengths offer flexibility in dosing from 5-20 mg.

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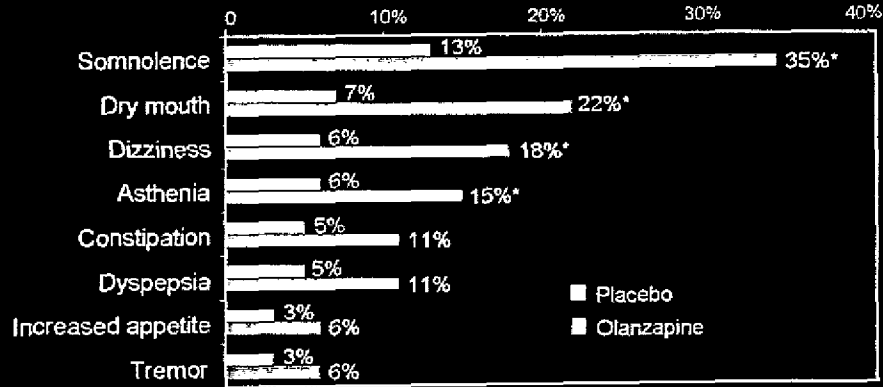
Olanzapine was well tolerated in placebo-controlled, bipolar mania trials. Dropout rates due to adverse events were comparable to placebo. In clinical trials, only 2 of 125 patients treated with olanzapine discontinued due to adverse events (one case of rash and one of unintended pregnancy). The difference between olanzapine and placebo was not statistically significant.<sup>1</sup>

1. Data on file, Lilly Research Laboratories.

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# Most Common Treatment-Emergent Adverse Events in Bipolar Mania Trials

% Patients With Treatment-Emergent Adverse Events



\*In bipolar mania trials, 4 adverse events occurred with statistically significantly higher incidence with olanzapine than with placebo—none of these resulted in discontinuation

Data on file. Lilly Research Laboratories

In controlled, short-term trials of olanzapine in acute bipolar mania, somnolence was the most commonly reported adverse event. Other commonly reported events were dry mouth, dizziness, asthenia, constipation, dyspepsia, increased appetite, and tremor.

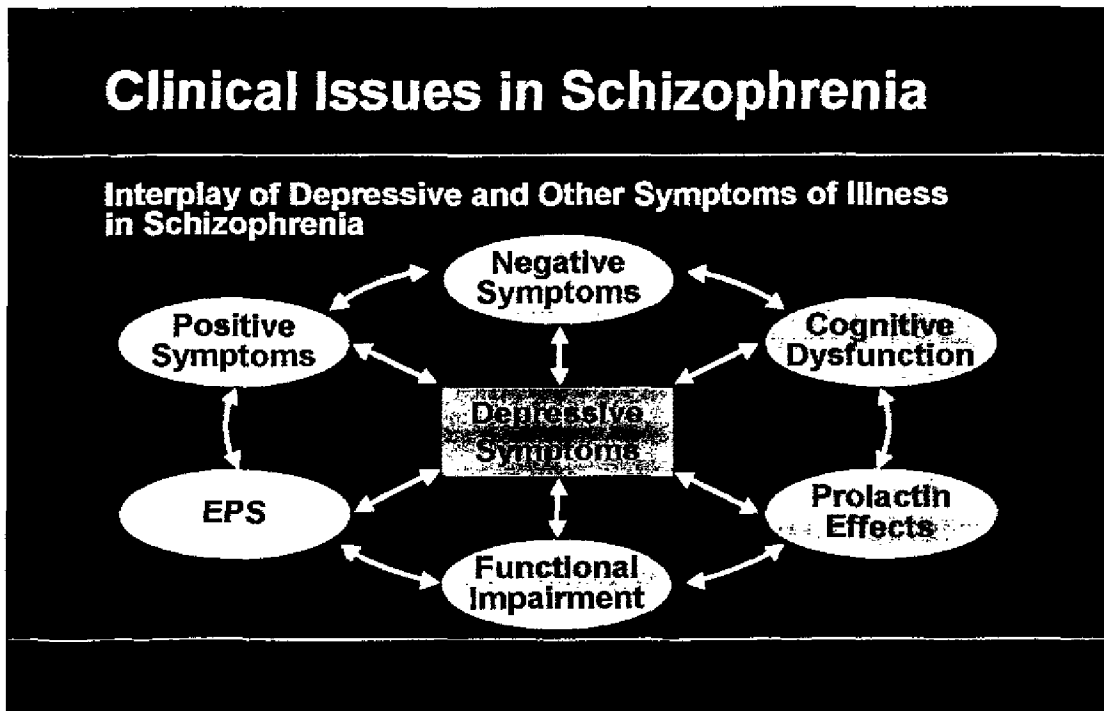
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## Summary: Olanzapine in Bipolar Mania

- ◆ Efficacy for patients with manic or mixed bipolar episodes as early as week 1
- ◆ Mania improved in patients with and without psychotic symptoms, including reduction in core manic symptoms
- ◆ No induction of depressive symptoms
- ◆ Does not appear to cause cognitive dulling
- ◆ Offers low risk of certain serious medical complications
- ◆ Compatible with patient's daily routine

The acute bipolar mania trials suggest that olanzapine provides a number of benefits for patients suffering from this disorder. These benefits compare well with those offered by current mood stabilizers, suggesting that olanzapine should be counted among the first-line mood stabilizers for mania associated with bipolar disorder.

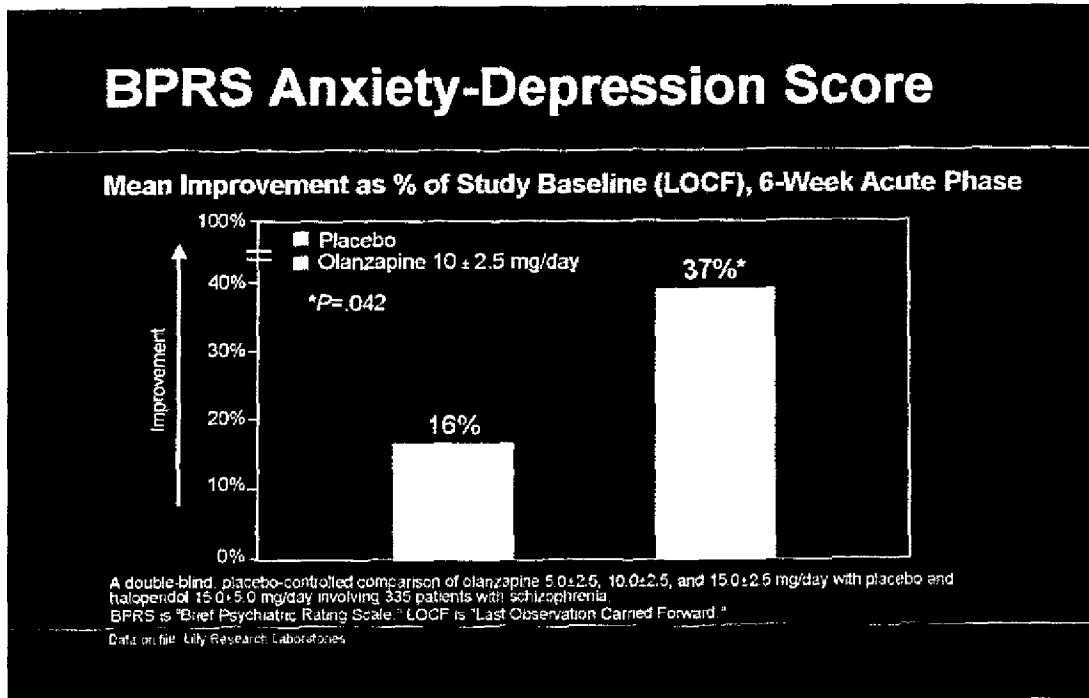
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Depressive symptoms associated with schizophrenia:

- Affect both positive and negative symptoms.
- Are interrelated with:
  - Cognitive dysfunction
  - Functional impairment
  - EPS
  - Prolactin effects

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Olanzapine has been shown to be effective in improving mood symptoms of schizophrenia in placebo-controlled, double-blind, randomized trials.

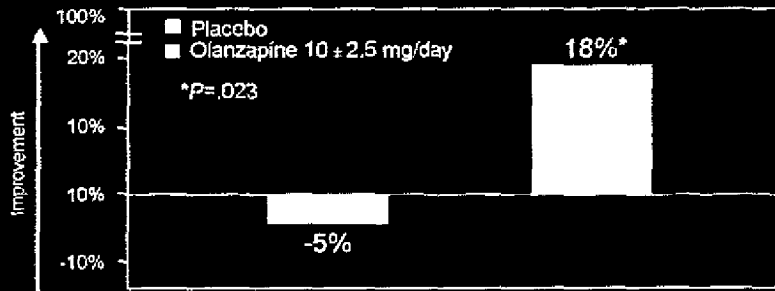
Using the BPRS Anxiety-Depression score, there was a significantly greater mean improvement from baseline with olanzapine compared with placebo at week 6 in a trial of 335 patients.<sup>1</sup>

1. Data on file, Lilly Research Laboratories.

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# BPRS Hostility Score

Mean Improvement as % of Study Baseline (LOCF), 6-Week Acute Phase



A double-blind, placebo-controlled comparison of olanzapine 5.0 ± 2.5, 10.0 ± 2.5, and 15.0 ± 2.5 mg/day with placebo and haloperidol 15.0 ± 5.0 mg/day, involving 335 patients with schizophrenia. BPRS is Brief Psychiatric Rating Scale. LOCF is Last Observation Carried Forward.  
Data on file, Lilly Research Laboratories.

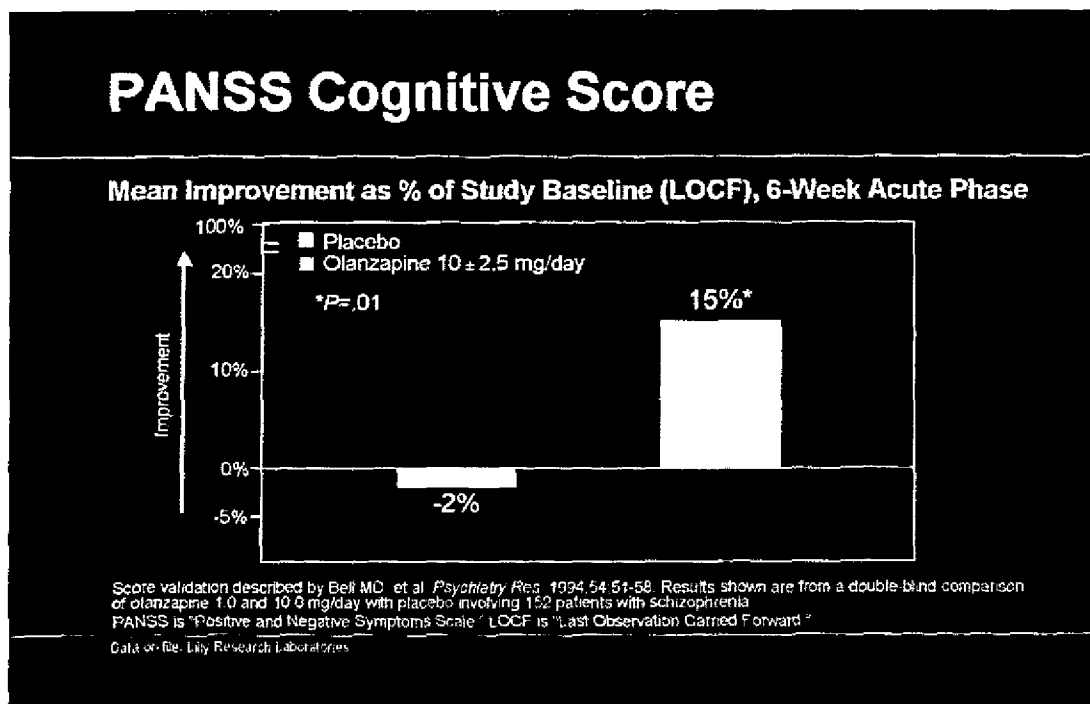
The efficacy of olanzapine for reducing hostile behavior has been demonstrated in placebo-controlled, double-blind, randomized trials of patients with schizophrenia.

The BPRS Hostility score was used to assess hostile behaviors such as anger and belligerence.

In a trial of 335 patients, there was significantly greater mean improvement from baseline in BPRS Hostility score with olanzapine compared with placebo at week 6.<sup>1</sup>

1. Data on file, Lilly Research Laboratories.

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PANSS Cognitive Score assesses cognitive disorganization, difficulty in abstract thinking, stereotyped thinking, tension, mannerisms and posturing, poor attention, and lack of judgment and insight. (Score validation described by Bell et al.<sup>1</sup>)

There was a significantly greater mean improvement in the PANSS Cognitive score from baseline with olanzapine compared with placebo at week 6 in a trial of 152 patients with schizophrenia.<sup>2</sup>

1. Bell MD, et al. *Psychiatry Res.* 1994;54:51-58.
2. Data on file, Lilly Research Laboratories.

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## Low Risk for Tardive Dyskinesia

- ◆ Low risk of TD in clinical trials; no causal relationship established
  - ◆ Includes 300 patients treated for more than 1 year
  - ◆ Prescribing should be consistent with the need to minimize the risk of TD

Olanzapine appears to have a low risk of TD as suggested by:

- Low risk of TD in clinical trials
- No established causal relationship

The evidence of the low risk of TD with olanzapine includes 300 patients treated for more than one year.<sup>1</sup>

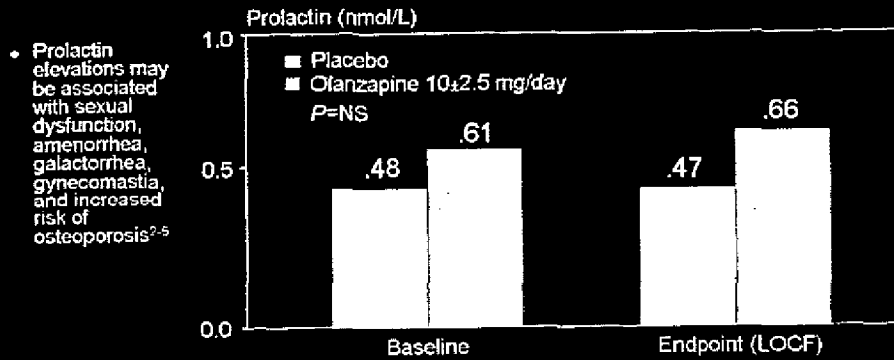
As with all antipsychotics, prescribing should be consistent with the need to minimize the risk of TD.

1. Data on file, Lilly Research Laboratories.

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## Low Prolactin Effects

Mean Change in Prolactin Level (nmol/L)  
No Statistically Significant Difference Between Olanzapine and Placebo



Prolactin levels were analyzed in a double-blind study comparing olanzapine 1.0 and 10.0 mg/day with placebo and involving 152 patients with schizophrenia. Results shown are for the 6-week acute phase.

1. Data on file, Lilly Research Laboratories.
2. Hamner MB, Arana GW. *CNS Drugs*. 1998;10(3):209-222.
3. Halbreich U, Palter SF. *Schizophr Bull*. 1996;22:447-454.
4. Marken PA, et al. *Clin Pharmacy*. 1992;11:851-856.
5. Ataya K, et al. *Fertil Steril*. 1988;50(6):876-881.

Elevations in prolactin may be associated with acute side effects such as sexual dysfunction, amenorrhea, galactorrhea, and gynecomastia;<sup>2-4</sup> these effects can be troublesome for the patient and may interfere with compliance.

Long-term effects of elevated prolactin may include an increased risk of osteoporosis.<sup>3, 5</sup>

There were no significant differences in mean change in prolactin levels between the group treated with olanzapine and the placebo group at week 6 in a trial of 152 patients with schizophrenia.<sup>1</sup>

1. Data on file, Lilly Research Laboratories.
2. Hamner MB, Arana GW. *CNS Drugs*. 1998;10(3):209-222.
3. Halbreich U, Palter SF. *Schizophr Bull*. 1996;22:447-454.
4. Marken PA, et al. *Clin Pharmacy*. 1992;11:851-856.
5. Ataya K, et al. *Fertil Steril*. 1988;50(6):876-881.

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## Low Prolactin Effects *(cont.)*

- ◆ Modest elevations in prolactin were seen with olanzapine in acute-phase schizophrenia trials (incidence 34% vs 13% with placebo); however, mean changes from baseline to endpoint were not statistically significantly different between olanzapine and placebo

Data on file, Lilly Research Laboratories

Modest elevations in prolactin were seen with olanzapine in acute phase trials of schizophrenia patients.

Mean changes from baseline to endpoint were not statistically different between olanzapine and placebo.<sup>1</sup>

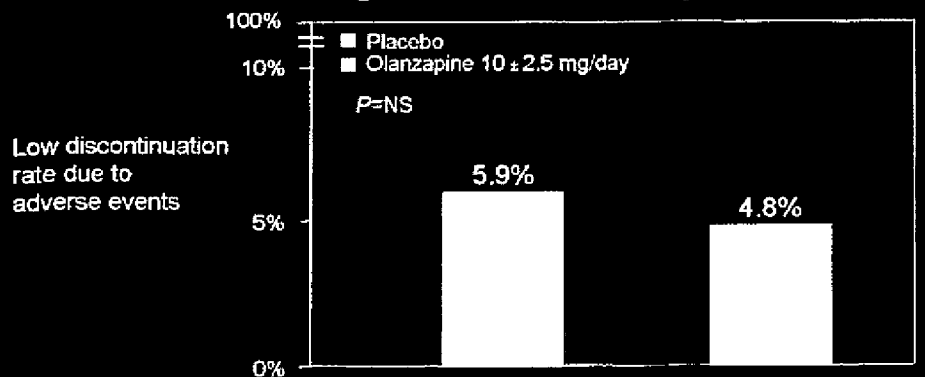
1. Data on file, Lilly Research Laboratories.

ZY 4021 36

PCP 31

## Tolerability of Olanzapine in Schizophrenia

### % of Patients Discontinuing Due to Treatment-Emergent Adverse Events



Results shown are for schizophrenic inpatients in 2 studies who had up to 6 weeks of therapy with olanzapine 2.5-17.5 mg/day or with placebo  
Data on file, Lilly Research Laboratories

In clinical trials, olanzapine was associated with a low rate of discontinuation due to adverse events.

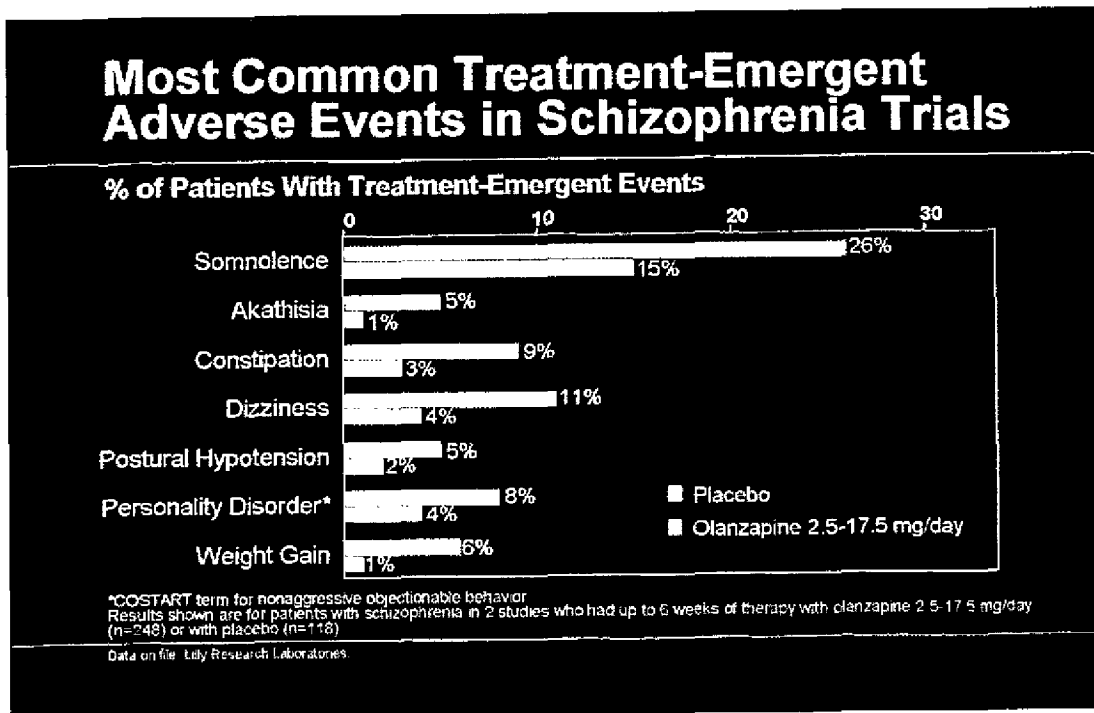
There was no statistically significant difference in rates of discontinuation of olanzapine or placebo because of adverse events.<sup>1</sup>

The rate of discontinuation due to side effects was 4.8% for olanzapine compared with 5.9% for placebo in two studies of inpatients receiving up to six weeks of therapy.<sup>1</sup>

Safety data on olanzapine were collected in 2500 patients worldwide, one of the largest premarketing patient databases for any antipsychotic agent.<sup>1</sup>

1. Data on file, Lilly Research Laboratories.

ZY 4021 37



In controlled, acute phase premarketing trials of olanzapine in schizophrenia, somnolence was the most commonly reported adverse event.<sup>1</sup>

Other commonly reported events were dizziness, constipation, personality disorder (COSTART term for nonaggressive objectionable behavior), weight gain, postural hypotension, and akathisia.<sup>1</sup>

1. Data on file, Lilly Research Laboratories.

ZY 4021 38

## Summary: Olanzapine in Schizophrenia

- ◆ Efficacy in positive, negative, depressive, and anxious symptoms
- ◆ Symptom improvement as early as week 1 in many patients in clinical trials
- ◆ EPS comparable to placebo
- ◆ Low risk of TD
- ◆ Proven safety profile
- ◆ Simple, easy-to-use, once-daily dosing

In placebo-controlled, double-blind, randomized trials, olanzapine demonstrated excellent control over positive, negative, behavioral, and affective symptoms associated with schizophrenia.

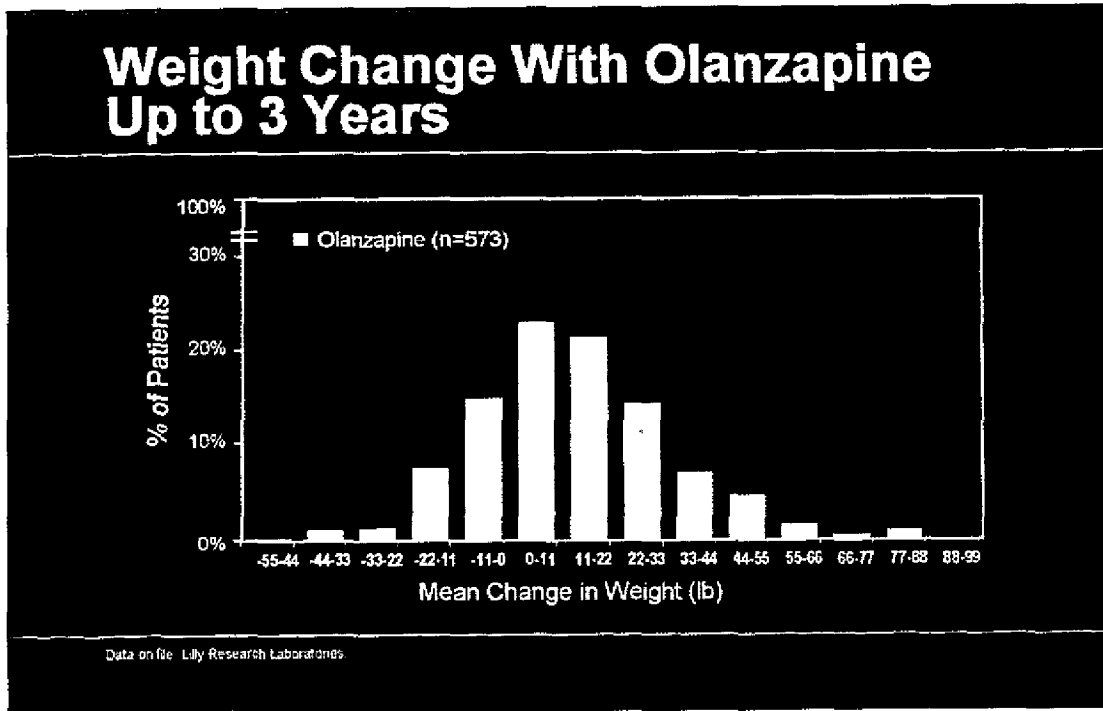
Olanzapine was shown to improve symptoms as early as one week of therapy.

Olanzapine has a proven safety profile:

- Incidence of EPS comparable to placebo
- Low risk of TD

Olanzapine offers simple, easy-to-use, once-daily dosing.

ZY 4021 39



The majority of patients taking olanzapine in this study experienced modest or no weight gain after treatment for up to three years. During this period, 9% of patients gained more than 20 kg (44 lb).

ZY 4021 40

## Weight Gain Stabilized Over Time

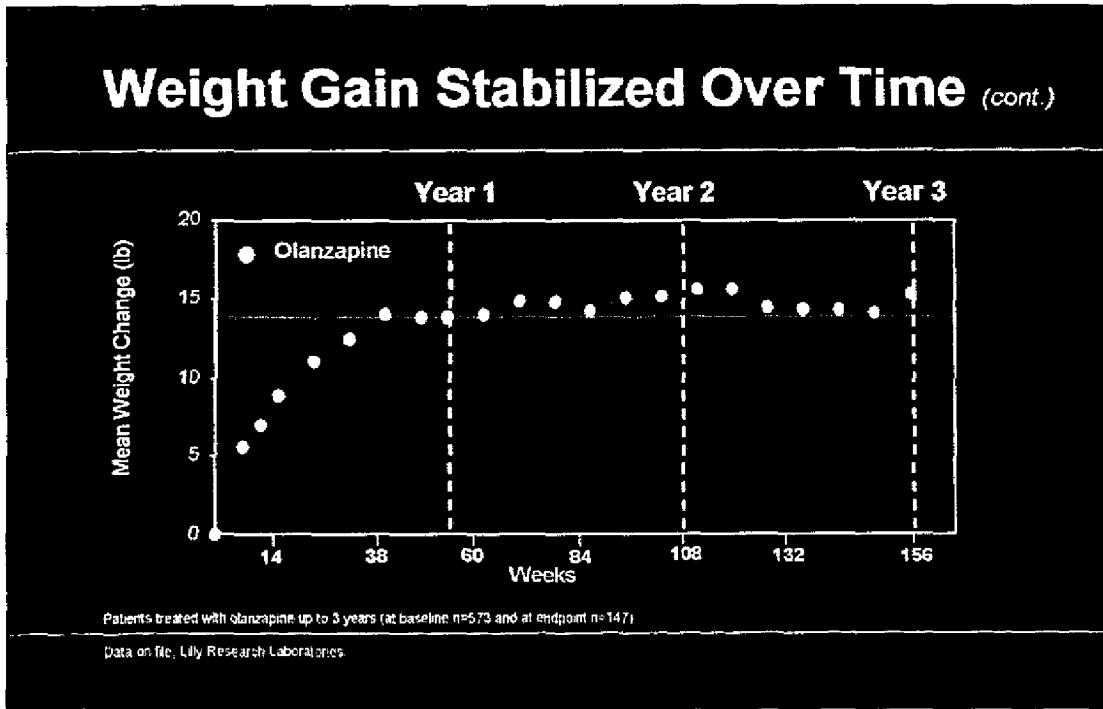
- ◆ For patients who gained weight while taking olanzapine:
  - ◆ Mean weight gain plateaued after the first 39 weeks of treatment
  - ◆ Mean long-term (LOCF) weight change with olanzapine plateaued at 6.26 kg (13.8 lb)

Data on file. Lilly Research Laboratories

In the three-year schizophrenia study, weight gain with olanzapine slowed over time and reached a plateau after the first 39 weeks of treatment.

The mean long-term weight change with olanzapine plateaued at 6.26 kg (13.8 lb).

ZY 4021 41



For those patients who gained weight while taking olanzapine in this study, the weight gain plateaued after 39 weeks of therapy.

ZY 4021 42

## Weight Change and BBMI

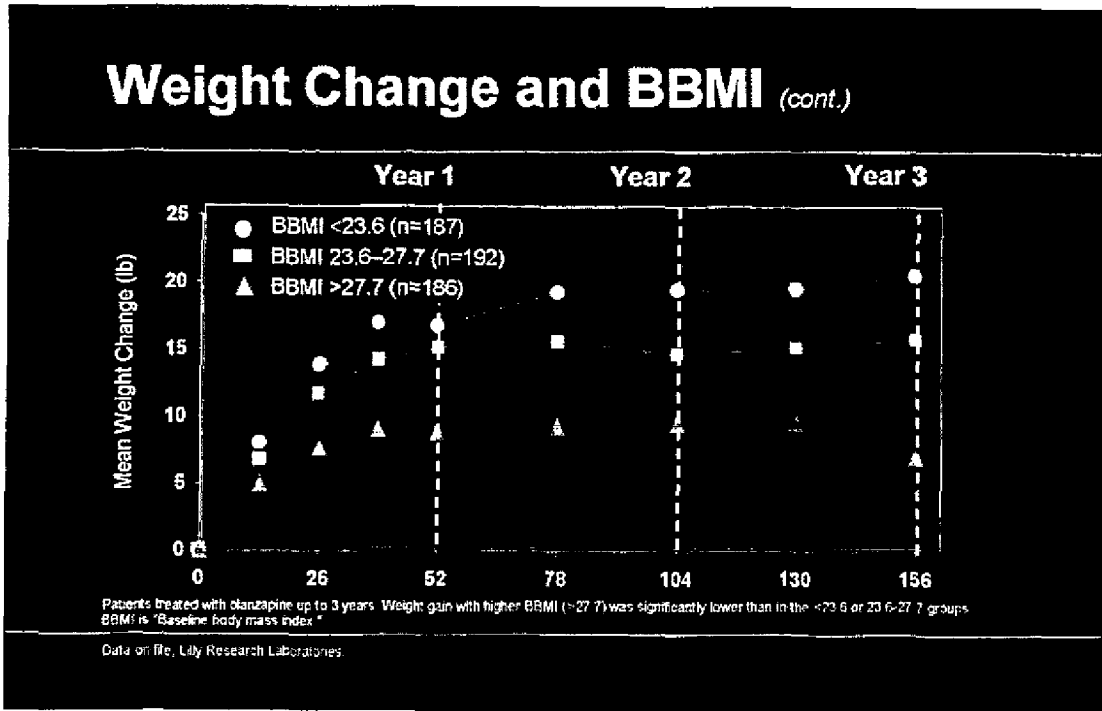
- ◆ Baseline body mass index (BBMI) as predictor of weight change in clinical trials
  - ◆ Body mass index = weight (kg) / height (m)<sup>2</sup>
- ◆ For patients who gained weight while taking olanzapine:
  - ◆ Patients with higher BBMI values (>27.7) gained significantly less weight than patients with lower BBMI values (≤27.7)

Body mass index (BMI) = weight (kg)/height(m)<sup>2</sup>.

Baseline BMI was evaluated as a predictor of weight change in clinical trials. This analysis allowed a determination of whether thinner individuals tended to gain more weight while taking olanzapine than heavier persons.

Patients with a lower initial BMI (thinner persons) gained the most weight while being treated with olanzapine. Patients who had a higher initial BMI (heavier persons) gained significantly less weight than their thinner counterparts.

ZY 4021 43



In treatment with olanzapine for schizophrenia for up to three years, weight gain was significantly lower in patients with baseline BMI (BBMI)  $>27.7$  than in patients with  $BBMI \leq 27.7$ .

ZY 4021 44

## Weight Change and Dosage

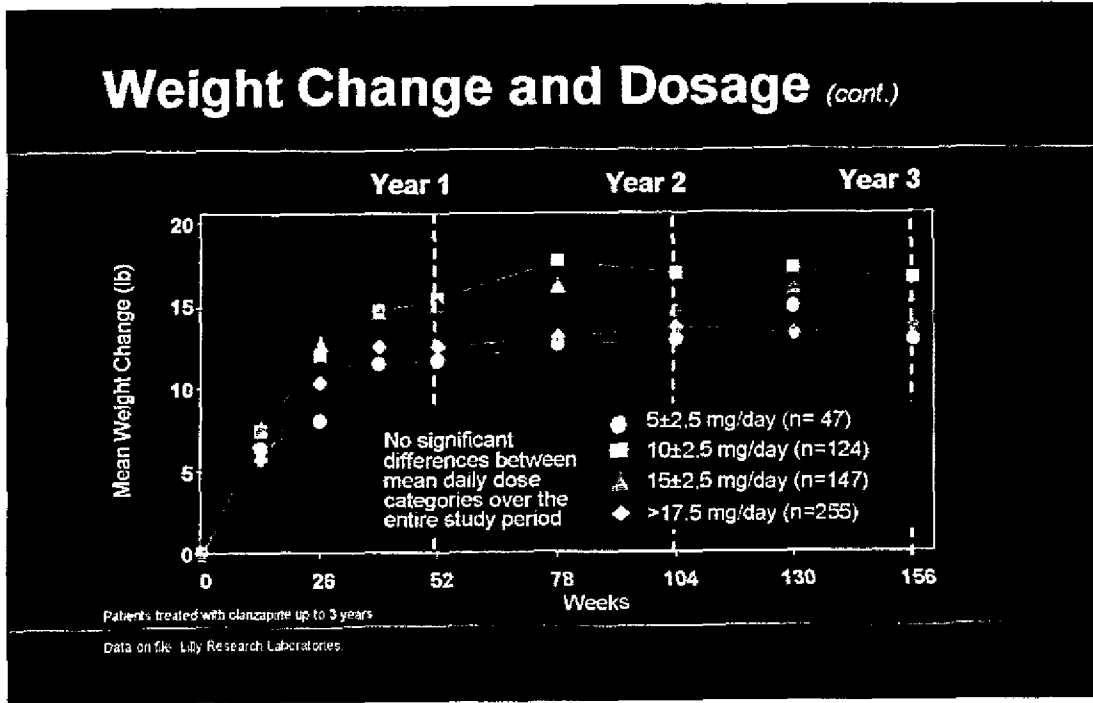
- ◆ For patients who gained weight while taking olanzapine:
  - ◆ Effect of dose on weight was not significant
  - ◆ This suggests that the most effective dose of olanzapine for a given patient may be administered without affecting weight gain

The relationship between weight gain and dose was also evaluated in this trial.

In patients treated up to three years, there were no significant differences in mean change in body weight between different dosage groups.

This suggests that the most effective dose of olanzapine may be administered without affecting the potential for weight gain.

ZY 4021 45



In the three-year study, individuals were divided into four categories based on the mean daily doses of olanzapine they received: 5 mg, 10 mg, 15 mg, or greater than 17.5 mg.

There were no differences in the mean change in body weight based on dose.

ZY 4021 46

## Summary: Weight Change

- ◆ Weight gain can often be associated with psychotropic medications
- ◆ Only 7 patients out of 2500 discontinued therapy due to weight gain in premarketing clinical trials of olanzapine
- ◆ For patients in whom weight gain may be a concern, advise and discuss in relation to clinical improvement
  - ◆ Consider interventions such as diet and moderate exercise as part of a healthy lifestyle
- ◆ Weight gain, like all unwanted side effects, should be evaluated in the context of overall efficacy, safety, and ease of use

It is important to recognize that weight gain is often associated with psychotropic medications.

Weight gain was an infrequent reason for discontinuation of olanzapine during clinical trials; among patients who received olanzapine in premarketing schizophrenia trials, only 7 of 2500 discontinued therapy due to weight gain.<sup>1</sup>

As with any potential unwanted side effect, weight gain should be evaluated in the context of efficacy, safety, and ease of use.

Counseling on nutrition and exercise may be offered to help patients manage changes in weight.

1. Data on file, Lilly Research Laboratories.

ZY 4021 47

## Cardiac Safety: QTc

- ◆ QTc is the measure of the QT interval on the ECG corrected for heart rate
- ◆ Lengthening of the QT interval can be associated with a potentially fatal ventricular arrhythmia known as *torsade de pointes*
- ◆ QT prolongation may be associated with various ventricular arrhythmias, syncope, and sudden death
- ◆ Medications like terfenadine, cisapride, and astemizole have been removed from the market due to fatalities caused by QTc prolongation<sup>1</sup>

1. Welch R, Chue P. *J Psychiatry Neurosci*. 2000;25(2):154-160.

Lengthening of the QT interval, or QTc prolongation, may be associated with potentially fatal effects.

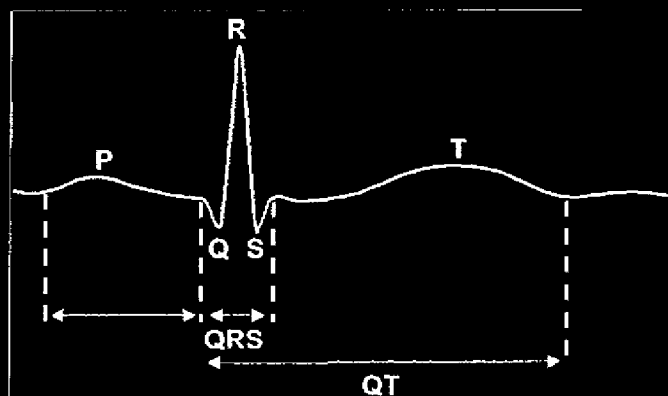
Medications such as terfenadine, cisapride, and astemizole have been withdrawn from the market due to fatalities attributed to QTc prolongation.<sup>1</sup>

QTc prolongation has been associated with some antipsychotics, such as thioridazine, which recently received a black box warning regarding its effects on QTc, and sertindole, which was pulled from the European market in December 1999.

1. Welch R, Chue P. *J Psychiatry Neurosci*. 2000;25(2):154-160.

ZY 4021 48

## QTc Interval



QTc interval is the length of time it takes the electrical system in the heart to repolarize adjusted for heart rate

An electrocardiogram records the electrical events in the myocardium.

The QT interval reflects the electrical signals from depolarization to repolarization of the heart—this stage prepares the ventricles for the next beat.

The depolarization/repolarization process occurs more rapidly as the heart rate increases.

The corrected QT interval, QTc, adjusts for this difference.

ZY 4021 49

## Cardiac Safety of a Drug

- ◆ The cardiac ion channel flow, which ensures the synchrony of action of individual cardiac cells, can be affected by some drugs in these classes:
  - ◆ Antihistamines
  - ◆ Antibiotics
  - ◆ Antiarrhythmics
  - ◆ Antipsychotics
- ◆ Several medications known to prolong the QTc interval have been reported to cause *torsade de pointes*; many of these are metabolized by the cytochrome P450-3A4 (CYP-3A4) enzyme system
- ◆ A patient taking a medication known to prolong the QTc interval and metabolized at the CYP-3A4 may face an even higher risk for sudden death due to increased serum concentrations
- ◆ QTc prolongation greater than 500 msec may be associated with a higher risk of sudden death

Some antihistamines, antibiotics, antiarrhythmics, and antipsychotics may affect cardiac ion channel flow, thus influencing the synchrony of action of individual cardiac cells.

Risk of sudden death may be increased by drugs that both prolong the QTc interval and are metabolized by the cytochrome P450-3A4 (CYP-3A4) enzyme system.

ZY 4021 50

## Known Cardiac Risks

- ◆ Several CYP-3A4 metabolized products withdrawn from market due to numerous reports of *torsade de pointes*
- ◆ Most cases occurred in patients taking other meds also metabolized by CYP-3A4
  - ◆ Terfenadine (Seldane®), an antihistamine
    - ◆ Voluntarily withdrawn from market in 1998 after 13 years
  - ◆ Astemizole (Hismanal®), an antihistamine
    - ◆ Voluntarily withdrawn from market in 1999 after 11 years
  - ◆ Cisapride (Propulsid®), a prokinetic agent (GI motility)
    - ◆ Voluntarily withdrawn from market in 2000 after 7 years

Product names are the property of their respective owners.

Reports of *torsade de pointes*, often occurring in patients taking multiple drugs metabolized by the CYP-3A4 enzyme system, have recently caused a number— of products to be taken off the market:

- The antihistamine terfenadine (Seldane®) was withdrawn in 1998<sup>1</sup>
- The antihistamine astemizole (Hismanal®) was withdrawn in 1999<sup>2</sup>
- The GI motility agent cisapride (Propulsid®) was withdrawn in 2000<sup>3</sup>

1. FDA news release. Available at:

<http://news.medscape.com/govmt/FDA/1998/02.98/FDA.seldane.html>. Feb 28, 1998.

2. AP press release. Available at: <http://www.wwwlawyer.com/articles/article2414.cfm>. June 21, 1999.

3. FDA news release. Available at: <http://www.fda.gov/medwatch/safety/2000/propul1.html>. Apr 12, 2000.

ZY 4021 51

## Known Cardiac Risks *(cont.)*

- ◆ Thioridazine (Mellaril®)
  - ◆ July 2000; black box warning added to package insert reporting dose-related prolongation of QTc interval (mean change 23 msec)
  - ◆ Use now restricted to refractory schizophrenia (after failure on other antipsychotics)
  - ◆ Contraindicated for use with other drugs known to inhibit CYP-2D6
  - ◆ Baseline ECG and serum potassium levels advised prior to starting therapy; periodic monitoring recommended
  - ◆ If QTc is >500 msec, therapy should be stopped

Product names are the property of their respective owners

The antipsychotic thioridazine (Mellaril®) received a black box warning in its package insert in July 2000 because of reports of dose-related QTc prolongation.

The use of thioridazine is now restricted to patients who have failed repeatedly on other antipsychotics.

Thioridazine is contraindicated for use with other drugs that inhibit the CYP-2D6 enzyme system.

ZY 4021 52

## Summary: Cardiac Issues

- ◆ QTc prolongation can lead to sudden death
- ◆ Clinicians may need to ask more questions regarding cardiac safety and antipsychotics
- ◆ Patients with schizophrenia may be at a higher risk for QTc prolongation than the general public because of:
  - ◆ Overdose risk
  - ◆ Multiple concomitant meds
  - ◆ Lifestyle
- ◆ Drug-drug interactions may put patients at an increased risk for QTc prolongation
- ◆ No difference in potentially clinically significant changes in ECG with olanzapine compared with placebo in clinical trials

QTc prolongation is a potentially fatal condition.

Patients with schizophrenia may be at greater risk for QTc prolongation than the general population because of such factors as the general risk of overdose, use of multiple concomitant medications, treatment with drugs that prolong QTc, electrolyte imbalance, a past history of ischemic disease, and lifestyle.

Physicians need to be confident of safety profiles when prescribing psychotropics.

There was no difference in potentially clinically significant changes in ECG with olanzapine versus placebo in premarketing trials.

ZY 4021 53

## Additional Prescribing Considerations for Olanzapine

### Orthostatic hypotension

- Reported in premarketing trials; may have been associated with dizziness, tachycardia, or syncope (15/2500 patients, 0.6%)

### Transient, asymptomatic elevations of hepatic transaminase

- Clinically significant ALT (SGPT) elevations were observed in 2% of patients in placebo-controlled schizophrenia trials (vs 0% with placebo); these patients did not develop jaundice. Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

### Seizures

- Occurred infrequently in premarketing clinical trials (22/2500 patients, 0.9%). Olanzapine should be used cautiously in patients ages 65 years or older and in patients with a history of seizures or with conditions that lower the seizure threshold.

The next two slides present additional prescribing considerations for olanzapine.

### Orthostatic hypotension

In premarketing trials, some patients taking olanzapine may have experienced orthostatic hypotension associated with dizziness, tachycardia, and, in some cases, syncope (15/2500, 0.6%). In acute-phase schizophrenia trials (n=366), dizziness (11% vs 4%) and tachycardia (4% vs 1%) were reported; these events were not always associated with hypotension.

### Transient, asymptomatic elevations of hepatic transaminase

In placebo-controlled studies involving schizophrenia patients, clinically significant ALT (SGPT) elevations ( $\geq 3$  times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

**Seizures** occurred infrequently in premarketing clinical trials (22/2500, 0.9%). Confounding factors may have contributed to many of these occurrences. Olanzapine should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Such conditions may be more prevalent in patients aged 65 years or older.

ZY 4021 54

## Additional Prescribing Considerations for Olanzapine *(cont.)*

### **Tardive dyskinesia**

- ◆ Prescribing should be consistent with the need to minimize the risk of TD. If its signs and symptoms appear, discontinuation should be considered.

### **Patients with concomitant illness**

- ◆ Adverse events occurring more often with olanzapine than placebo in a clinical study of Alzheimer's patients with various psychiatric symptoms: somnolence, abnormal gait, fever, dehydration, back pain. Use olanzapine with caution in elderly patients with dementia.

### **Tardive dyskinesia (TD)**

Prescribing should be consistent with the need to minimize the risk of TD. If its signs and symptoms appear, discontinuation should be considered.

### **Use in patients with concomitant illness**

In a clinical study involving nursing home patients having various psychiatric symptoms in association with Alzheimer's disease, somnolence, abnormal gait, fever, dehydration, and back pain were observed more often with olanzapine than with placebo. As with other CNS-active drugs, olanzapine should be used with caution in elderly patients with dementia.

ZY 4021 55