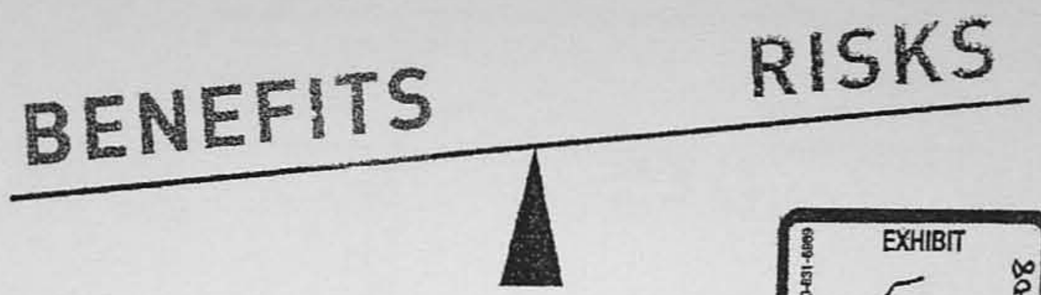
Diabetes and patients with mental illness

What do you consider when choosing medications?

What benefits do you associate with ZYPREXA® (olanzapine)?

What risks do you associate with it?



Diabetes is common.

- As many as 6.2% of American adults have diabetes.[1]
- One half of them may not know it.[1]
- 6.9% more have fasting blood glucose levels that are above normal.[1]

But your patients are at an even greater risk.

- People with serious mental illness are 2 to 4 times more likely to develop diabetes.[2-5]
- There have been reports linking antipsychotics and certain mood stabilizers with hyperglycemia since the 1950s.[6-9]

For additional safety profile and other important prescribing considerations for ZYPREXA, see insice and the full Prescribing Information.

The Adverse Reactions section of the full Prescribing Information for ZYPREXA includes hyperglycemia (infrequent), glycosuria (infrequent), diabetes mellitus (infrequent), diabetic acidosis (rare), and ketosis (rare) as well as postintroduction reports of diabetic coma.

Lilly

ars Thar[illegible]er.

Study methodology

Studies included patients aged 18 to 65 years, with a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, or acute bipolar mania. Diagnosis of treatment-emergent diabetes was based on the clinical discretion of the investigator. For this analysis, all randomized patients were considered.

ZYPREXA vs haloperidol: Three randomized, double-blind studies compared ZYPREXA (5 to 20 mg/day) with haloperidol (5 to 20 mg/day). After the initial 6-week phase, further double-blind observations were conducted following exposure for up to 52 weeks.

Comparisons also include a haloperidol-controlled study of 33 subjects receiving ZYPREXA (1 mg/day).

ZYPREXA vs risperidone: One 28-week, double-blind study compared ZYPREXA (5 to 20 mg/day) with risperidone (4 to 12 mg/day).

ZYPREXA vs divalproex: One 47-week, double-blind study compared ZYPREXA (5 to 20 mg/day) with divalproex (500 to 2500 mg/day).

C D E F G H

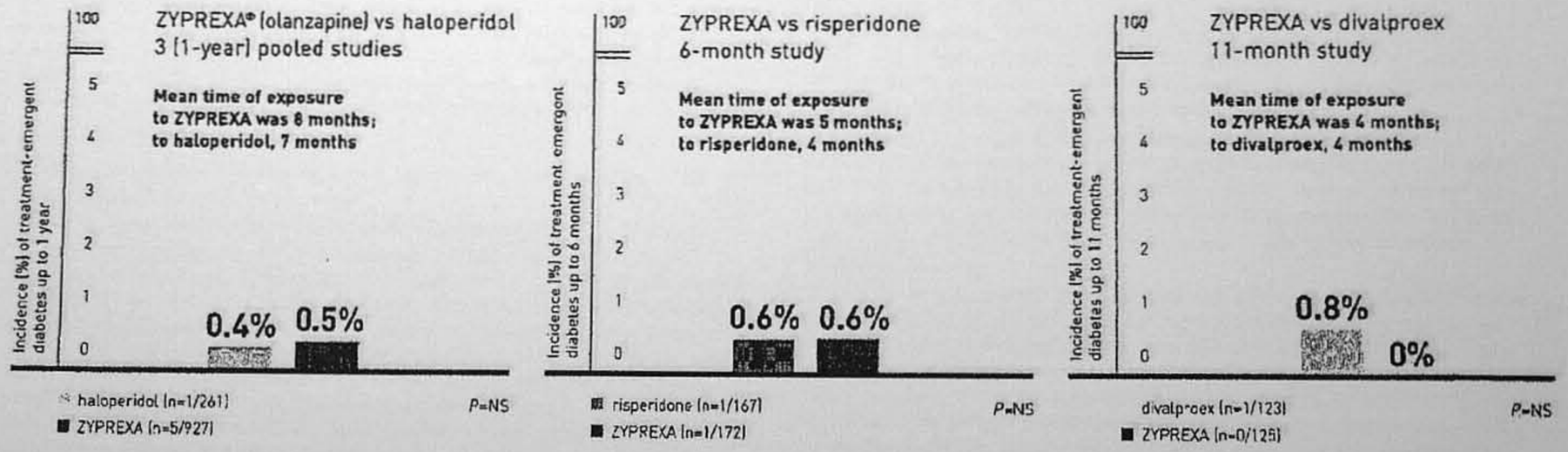
EXHIBIT 8
PAGE 2 OF 12

006095

How do the medications you use compare?

Rates of diabetes were comparable for commonly prescribed psychotropics during longer-term clinical trials.*

Incidence of diagnosed treatment-emergent diabetes in longer head-to-head schizophrenia and bipolar mania trials*



* These trials were not designed specifically to evaluate glycemic effects. Fasting glucose levels were not determined.

For safety information on haloperidol, risperidone, or divalproex, see the manufacturers' respective package inserts.
For additional safety profile and other important prescribing considerations for ZYPREXA, see inside and the full Prescribing Information.

The Adverse Reactions section of the full Prescribing Information for ZYPREXA includes hyperglycemia (infrequent), glycosuria (infrequent), diabetes mellitus (infrequent), diabetic acidosis (rare), and ketosis (rare) as well as postintroduction reports of diabetic coma.

Lilly
Answers That Matter.

C D E F G H

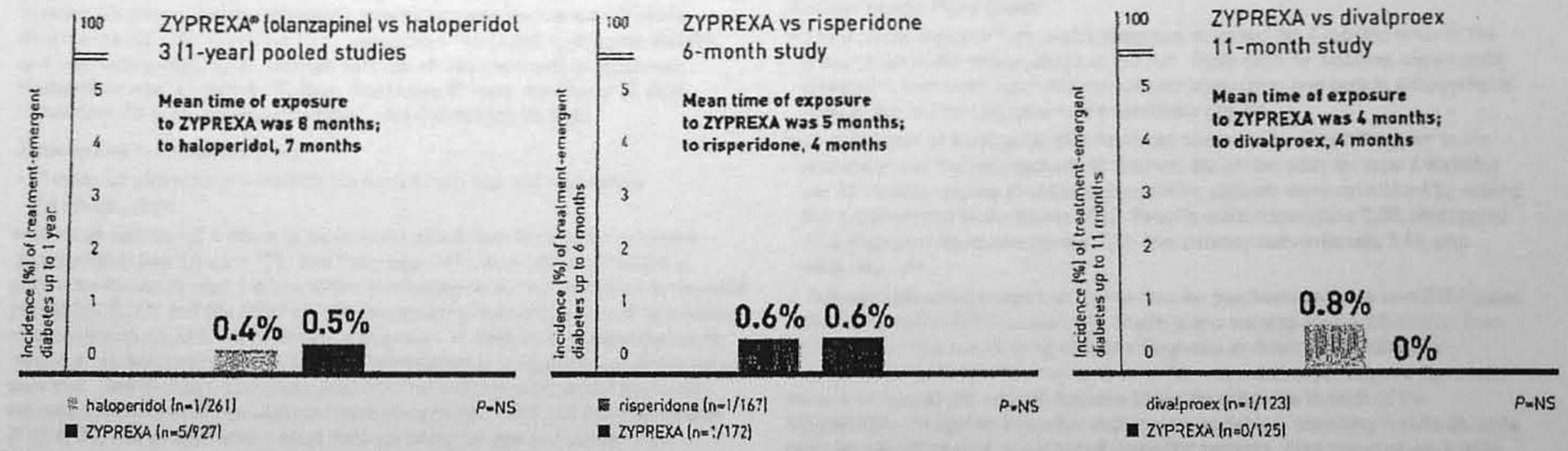
006096

EXHIBIT 8
PAGE 3 OF 10

How do the medications you use compare?

Rates of diabetes were comparable for commonly prescribed psychotropics during longer-term clinical trials.*

Incidence of diagnosed treatment-emergent diabetes in longer head-to-head schizophrenia and bipolar mania trials*



* These trials were not designed specifically to evaluate glycemic effects. Fasting glucose levels were not determined.

For safety information on haloperidol, risperidone, or divalproex, see the manufacturers' respective package inserts.
For additional safety profile and other important prescribing considerations for ZYPREXA, see inside and the full Prescribing Information.

The Adverse Reactions section of the full Prescribing Information for ZYPREXA includes hyperglycemia (infrequent), glycosuria (infrequent), diabetes mellitus (infrequent), diabetic acidosis (rare), and ketosis (rare) as well as postintroduction reports of diabetic coma.

Answers T Lilly er.

006097

EXHIBIT B
PAGE 4 OF 10

Lilly Advance PCS Study

- Incidence among all patients combined on typical antipsychotics was 1.6% (307/19,782)
- Hazard ratio was significantly elevated for all treatment groups vs control patients not receiving antipsychotic medications

A 3-year retrospective, pharmacoepidemiological study of an independent prescription claims database (Advance PCS) containing over 50 million members. Patients who had been prescribed a diabetes medication at any point during the 12-month period prior to enrollment or who had been prescribed an antipsychotic during the 6-month period prior to enrollment were excluded. Diabetes mellitus was identified by oral hypoglycemic or insulin prescription claims in both the study and control groups. Patients in the antipsychotic study group were prescribed a single typical or atypical antipsychotic during the 6 months of follow-up. Out of this database, 5.8 million patients receiving a prescription medication that was not an antipsychotic served as the reference group. Hazard ratio was determined by Cox proportional hazard regression controlling for age, gender, and accounting for time to event. Incidence of new antidiabetic prescription was haloperidol 133/8476, thioridazine 62/3133, clozapine 7/277, olanzapine 194/13,863, quetiapine 40/4196, and risperidone 400/20,633. Average duration of treatment with antipsychotic medications was: clozapine 137 days, olanzapine 89 days, quetiapine 89 days, risperidone 90 days, haloperidol 68 days, and thioricazine 76 days

Janssen Quebec Medicare Study

- *P*-value for olanzapine vs risperidone hazard ratio was not reported by the investigators

A Janssen-sponsored analysis of patients identified from the Quebec Medicare database between January 1997 and December 1999. One cohort consisted of patients who had at least 1 prescription for olanzapine but not clozapine during that period (n=19,153) and the other of patients receiving risperidone but not olanzapine or clozapine (n=14,792). Patients with a diagnosis of diabetes or a prescription for insulin or an oral hypoglycemic agent before beginning antipsychotic therapy were excluded. New diabetes diagnoses after the first antipsychotic prescription were tabulated. Incidence of new diabetes were olanzapine 319/19,153 and risperidone 217/14,792. Cox proportional hazard ratio adjusting for age and gender was calculated and reported relative to risperidone group. Duration of treatment with antipsychotic medicines was not reported by the investigators.

Lilly IMS Study

- Odds ratio for olanzapine- and risperidone-treated patients was not significantly different vs patients receiving typical antipsychotic medication

A retrospective analysis of the IMS LifeLink™ claims database identified patients aged 18-65 initiated on antipsychotic medicine between October 1996 and December 1998. The study included only patients with no antipsychotic use for 6 months prior and no diagnosis of diabetes or receipt of any diabetic medication for 1 year prior to antipsychotic initiation. Observed diabetes incidences were typical antipsycholics 68/3208, olanzapine 32/1530, and risperidone 43/1598. Logistic regressions were used to estimate odds ratios (OR) of a diagnosis of diabetes or use of any diabetic medication in the 1-year post-initiation compared to patients on typical antipsychotics; controlling for age, gender, mental health comorbidities, and regional differences. This analysis tabulated all diabetes incidences during 1 year subsequent to antipsychotic prescription irrespective of duration of the treatment episode.

Sernyak Study

A 4-month retrospective analysis included 38,632 outpatients listed in the Veterans Health Administration database with schizophrenia who were treated with typical or atypical antipsychotics. Using the same database, patients with a diagnosis of diabetes were also identified and used to calculate the prevalence of diabetes mellitus among patients receiving prescriptions for antipsychotic agents. Of the total number of patients included in the study, 15,984 received typical neuroleptics and 22,648 received atypical neuroleptics; 1,207 received clozapine; 10,970 olanzapine; 955 quietapine; and 9,903 risperidone.

Janssen Health Plans Study*

- The analysis depicted here is of a subgroup observed for 4 months prior to the prescription of the antipsychotic of interest. Odds ratio for diabetes significantly elevated vs untreated psycholic patients for olanzapine and typical antipsychotic groups, but not for clozapine and risperidone groups.
- In an analysis of a subgroup that had been observed for 8 months prior to the prescription of the antipsychotic of interest, estimated odds for type 2 diabetes per 12 months relative to untreated psychotic patients were calculated by raising the monthly odds to the power of 12. Results were risperidone 0.88, olanzapine 3.10, high-potency conventionals 2.13, low-potency conventionals 3.46, and clozapine 7.44.

A Janssen-sponsored analysis of claims data for psychosis patients (n=4,331 treated, 3,061 untreated) within 2 unspecified health plans encompassing 2.5 million lives. Patients reporting pre-existing diabetes diagnosis or claim for antidiabetic medication up to 4 months prior to observation were excluded. Logistic regression models compared the odds of diabetes based on exposure to each of the antipsychotic categories and other explanatory variables, reporting results as odds ratio per month relative to untreated psychotic patients. Also reported were odds ratios of 1.05 high-potency typicals and 1.06 low-potency typicals. Characteristics reported for the group observed for 4 months prior to the antipsychotic treatment episode of interest were: Number of observed treatment episodes—clozapine 64, olanzapine 1,047, risperidone 1,368, high-potency typical antipsychotics 1,376, and low-potency typical antipsychotics 480. Average duration of antipsychotic treatment episodes were: clozapine 6.8 months, olanzapine 5.6 months, risperidone 6.4 months, high-potency typical antipsycholics 6.7 months, and low-potency typical antipsycholics 6.8 months. The investigators did not provide these details for the subset observed for 8 months prior to the antipsychotic treatment episode.

* Control group is psychotic patients not treated with antipsychotic medication.

Incidence and odds ratios of developing diabetes during treatment with antipsychotics.

Findings from 5 epidemiological studies show no consistent differences regardless of the agent studied.

	Lilly[10] Advance PCS Database	Janssen[11] Quebec Medicare Database	Lilly[12] IMS Database†	Sernyak[13] Veterans Database	Janssen[14] Health Plans Study
N	58,751	33,945	6,440	38,632	4,308
Control	0.8%*	–	–	–	1.00‡
Clozapine	2.5%	–	–	1.25	1.08
Quetiapine	1.0%	–	–	1.31	–
Risperidone	1.9%	1.5%	2.7%	1.05	1.02
Olanzapine	1.4%	1.7%	2.1%	1.11	1.08
Typical antipsychotics	1.6-2.0%	–	2.1%	–	1.05-1.06
	§OBSERVED INCIDENCE			‖CALCULATED ODDS RATIO/MONTH	

(–) Drug not studied or value not supplied.

N=Number of antipsychotic-treated subjects studied.

* Control group is general population patients receiving prescriptions other than antipsychotic medications.
† Data on file, Lilly Research Laboratories.
‡ Control group is psychotic patients not receiving prescriptions for antipsychotic medication.

§ Observed incidence is the percentage of patients taking the medication of interest who have new onset of diabetes mellitus. It does not control for potentially important factors such as patient age or duration of treatment.

‖ Odds ratio refers to probability of becoming diabetic relative to control group. An odds ratio of 1.05 means that for every 100 cases seen in the control group, no more than 105 would be expected to develop diabetes in the comparison group.

For safety information on clozapine, quetiapine, or risperidone, see the manufacturers' respective package inserts.
For additional safety profile and other important prescribing considerations for ZYPREXA, see inside and the full Prescribing Information.

The Adverse Reactions section of the full Prescribing Information for ZYPREXA includes hyperglycemia (infrequent), glycosuria (infrequent), diabetes mellitus (infrequent), diabetic acidosis (rare), and ketosis (rare) as well as postintroduction reports of diabetic coma.

Lilly
Answers That Matter.

Important safety information

The most common treatment-emergent adverse event associated with ZYPREXA® (olanzapine) in 6-week schizophrenia trials vs placebo was somnolence (26% vs 15%). Also observed (ZYPREXA vs placebo) were:

postural hypotension (5% vs 2%)
dizziness (11% vs 4%)
personality disorder* (8% vs 4%)
akathisia (5% vs 1%)
constipation (9% vs 3%)
weight gain (6% vs 1%)

The most common treatment-emergent adverse event associated with ZYPREXA in placebo-controlled bipolar mania trials was somnolence† (35% vs 13% for placebo). Also observed (ZYPREXA vs placebo) were:

dry mouth† (22% vs 7%)
dyspepsia (11% vs 5%)
constipation (11% vs 5%)
tremor (6% vs 3%)
dizziness† (18% vs 6%)
asthenia† (15% vs 6%)
increased appetite (6% vs 3%)

Transient, asymptomatic elevations of hepatic transaminase

In placebo-controlled schizophrenia studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to ZYPREXA 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.

No baseline ECG required

No difference in clinically significant QTc prolongation with ZYPREXA compared to placebo in premarketing clinical trials.

Orthostatic hypotension

In premarketing trials of oral ZYPREXA, some patients may have experienced orthostatic hypotension associated with dizziness‡; tachycardia‡; and in some cases, syncope (15/2500, 0.6%).

Low potential for drug interactions

Coadministration of diazepam or ethanol with ZYPREXA may potentiate orthostatic hypotension. Lower doses of ZYPREXA should be considered in patients receiving concomitant therapy with fluvoxamine.

Tardive dyskinesia—as with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD. If its signs and symptoms appear, discontinuation should be considered.

Seizures—occurred infrequently in premarketing clinical trials (22/2500, 0.9%). Confounding factors may have contributed to many of these occurrences. ZYPREXA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

* COSTART term for nonaggressive objectionable behavior.
† In bipolar mania trials, 4 adverse events occurred with statistically significantly higher incidence with ZYPREXA than with placebo—none of these resulted in discontinuation.
‡ In acute-phase, placebo-controlled schizophrenia trials (n=366), dizziness (11% vs 4%) and tachycardia (4% vs 1%) were reported; these events were not always associated with hypotension.

References

1. NHS Direct. Diagnosis, risk factors for diabetes. Available at: http://www.psychiatry.ox.ac.uk/diabetes/patient/diagnosis/risk.html. Accessed March 7, 2003.
2. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry.* 1996;37:68-73.
3. McKee HA, D'Arcy PFD, Wilson PJK. Diabetes and schizophrenia: a preliminary study. *J Clin Hosp Pharm.* 1986;11:297-299.
4. Keskiner A, Tcumi AE, Bousquet T. Psychotropic drugs, diabetes, and chronic mental patients. *Psychosomatics.* 1973;16:176-181.
5. Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. *Am J Psychiatry.* 1999;156:1417-1420.
6. Charatan FBE, Bartlett NG. The effect of chlorpromazine ("Largactil") on glucose tolerance. *J Mental Sci.* 1955;101:351-353.
7. Isojarvi JI, Laatikainen TJ, Knip M, et al. Obesity and endocrine disorders in women taking valproate for epilepsy. *Ann Neurol.* 1996;39:579-584.
8. Garland EJ, Remick RA, Zis AP. Weight gain with antidepressants and lithium. *J Clin Psychopharmacol.* 1988;8:323-330.
9. Mellerup ET, Dam H, Wildschiodtz G, Rafaelsen OJ. Diurnal variation of blood glucose during lithium treatment. *J Affective Dis.* 1983;5:341-347.
10. Buse JB, Cavazzoni P, Hornbuckle K, et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiol.* 2003;56:164-170.
11. Caro JJ, Ward A, Levinton C, Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry.* 2002;63(12):1135-1139.
12. Lage MJ, Karmer J, Loosbrock D, Hill AL. Use of atypical antipsychotics and the incidence of diabetes: evidence from a claims database. Presented at: 53rd IPS Annual Meeting; Oct 10-14, 2001;Orlando, Florida.
13. Sernyak MJ, Leslie DL, Alarcon RD, et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry.* 2002; 159:561-566.
14. Gianfrancesco FD, Grogg AL, Mahmoud RA, et al. Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on Type 2 diabetes: findings from a large health plan database. *J Clin Psychiatry.* 2002;63(10):920-930.
15. American Diabetes Association Screening for type 2 diabetes. *Diabetes Care.* 2000;23 (suppl 1).
16. Rewers M, Hamman RF. Risk Factors for non-insulin dependent diabetes. *Diabetes in America* 2nd Ed; Natl Inst of Health. 1995:179-220.
17. Foss MC, Paula FJ, Paccola GM, et al. Peripheral glucose metabolism in human hyperprolactinaemia. *Clin Endocrinol.* 1995;43:721-726.

Important safety information

The most common treatment-emergent adverse event associated with ZYPREXA® (olanzapine) in 6-week schizophrenia trials vs placebo was somnolence (26% vs 15%). Also observed (ZYPREXA vs placebo) were:

postural hypotension (5% vs 2%)	akathisia (5% vs 1%)
dizziness (11% vs 4%)	constipation (9% vs 3%)
personality disorder* (8% vs 4%)	weight gain (6% vs 1%)

The most common treatment-emergent adverse event associated with ZYPREXA in placebo-controlled bipolar mania trials was somnolence† (35% vs 13% for placebo). Also observed (ZYPREXA vs placebo) were:

dry mouth† (22% vs 7%)	dizziness‡ (18% vs 6%)
dyspepsia (11% vs 5%)	asthenia† (15% vs 5%)
constipation (11% vs 5%)	increased appetite (6% vs 3%)
tremor (6% vs 3%)	

Transient, asymptomatic elevations of hepatic transaminase

In placebo-controlled schizophrenia studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to ZYPREXA 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.

No baseline ECG required

No difference in clinically significant QTc prolongation with ZYPREXA compared to placebo in premarketing clinical trials.

Orthostatic hypotension

In premarketing trials of oral ZYPREXA, some patients may have experienced orthostatic hypotension associated with dizziness‡; tachycardia‡; and in some cases, syncope (15/2500, 0.6%).

Low potential for drug interactions

Coadministration of diazepam or ethanol with ZYPREXA may potentiate orthostatic hypotension. Lower doses of ZYPREXA should be considered in patients receiving concomitant therapy with fluvoxamine.

Tardive dyskinesia—as with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD. If its signs and symptoms appear, discontinuation should be considered.

Seizures—occurred infrequently in premarketing clinical trials (22/2500, 0.9%). Confounding factors may have contributed to many of these occurrences. ZYPREXA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

* COSTART term for nonaggressive objectionable behavior.

† In bipolar mania trials, 4 adverse events occurred with statistically significantly higher incidence with ZYPREXA than with placebo—none of these resulted in discontinuation.

‡ In acute-phase placebo-controlled schizophrenia trials (n=266), dizziness (11% vs 4%) and tachycardia (4% vs 1%) were reported; these events were not always associated with hypotension.

References

1. NHS Direct. Diagnosis, risk factors for diabetes. Available at: http://www.psychiatry.ox.ac.uk/diabetes/patient/diagnosis/risk.html. Accessed March 7, 2003.
2. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry*. 1996;37:68-73.
3. McKee HA, D'Arcy PFD, Wilson PJK. Diabetes and schizophrenia: a preliminary study. *J Clin Hosp Pharm*. 1986;11:297-299.
4. Keskiner A, Toumi AE, Bousquet T. Psychotropic drugs, diabetes, and chronic mental patients. *Psychosomatics*. 1973;16:175-181.
5. Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. *Am J Psychiatry*. 1999;156:1417-1420.
6. Charatan FBE, Bartlett NG. The effect of chlorpromazine ["Largactil"] on glucose tolerance. *J Mental Sci*. 1955;101:351-353.
7. Isojarvi JI, Laatikainen TJ, Knip M, et al. Obesity and endocrine disorders in women taking valproate for epilepsy. *Ann Neurol*. 1996;39:579-584.
8. Garland EJ, Remick RA, Zis AP. Weight gain with antidepressants and lithium. *J Clin Psychopharmacol*. 1988;8:323-330.
9. Mellerup ET, Dam H, Wildschiodtz G, Rafaelsen OJ. Diurnal variation of blood glucose during lithium treatment. *J Affective Dis*. 1983;5:341-347.
10. Buse JB, Cavazzoni P, Hornbuckle K, et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiol*. 2003;56:164-170.
11. Caro JJ, Ward A, Levinton C, Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry*. 2002;63(12):1135-1139.
12. Lage MJ, Kemner J, Loosbrock D, Hill AL. Use of atypical antipsychotics and the incidence of diabetes: evidence from a claims database. Presented at: 53rd IPS Annual Meeting; Oct 10-14, 2001;Orlando, Florida.
13. Sernyak MJ, Leslie DL, Alarcon RD, et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry*. 2002; 159:561-566.
14. Gianfrancesco FD, Grogg AL, Mahmoud RA, et al. Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on Type 2 diabetes: findings from a large health plan database. *J Clin Psychiatry*. 2002;63(10):920-930.
15. American Diabetes Association Screening for type 2 diabetes. *Diabetes Care*. 2000;23 (suppl 1).
16. Rewers M, Hamman RF. Risk Factors for non-insulin dependent diabetes. *Diabetes in America* 2nd Ed; Natl Inst of Health. 1995:179-220.
17. Foss MC, Paula FJ, Paccola GN, et al. Peripheral glucose metabolism in human hyperprolactinaemia. *Clin Endocrinol*. 1995;43:721-726.

The diabetes risk your patients face may be even greater if they:[15-17]

- ☑ Are African American, Native American, Asian American/Pacific Islander, or Hispanic.
- ☑ Are 45 years of age or older.
- ☑ Have a body mass index ≥25 kg/m².
- ☑ Have dyslipidemia.
- ☑ Do not get enough exercise.
- ☑ Are hypertensive.
- ☑ Have polycystic ovary syndrome.
- ☑ Have a previous history of glucose intolerance.
- ☑ Have a family history of diabetes.
- ☑ Have a history of gestational diabetes or delivered a baby weighing >9 lbs.

For additional safety profile and other important prescribing considerations for ZYPREXA, see inside and the full Prescribing Information.

The Adverse Reactions section of the full Prescribing Information for ZYPREXA includes hyperglycemia (infrequent), glycosuria (infrequent), diabetes mellitus (infrequent), diabetic acidosis (rare), and ketosis (rare) as well as postintroduction reports of diabetic coma.

Lilly
Answers That Matter.

C D E F G H

0061102

EXHIBIT 8
PAGE 9 OF 10

Page 9 of 10

Consider the whole story.

- Diabetes is **common**, and people with serious **mental illness** are at an even **greater risk**

- Among patients treated with different antipsychotics, clinical trial and epidemiological data show **no consistent differences** in rates of diabetes

- **Assess** patients for **risk factors** of diabetes, irrespective of which psychotropic is prescribed

- Treatment selection should be based on the patient's underlying **psychiatric condition** and the overall **risk/benefit profile** of the medication

For additional safety profile and other important prescribing considerations for ZYPREXA, see inside and the full Prescribing Information.

The Adverse Reactions section of the full Prescribing Information for ZYPREXA includes hyperglycemia (infrequent), glycosuria (infrequent), diabetes mellitus (infrequent), diabetic acidosis (rare), and ketosis (rare) as well as postintroduction reports of diabetic coma.

Lilly
Answers That Matter.