

On behalf of Eli Lilly and Company, I would like to address important questions about one of our medications, Zyprexa[®] (olanzapine), which is approved in the US for treating the devastating disorders of schizophrenia and bipolar mania. More than 11 million patients have been treated with Zyprexa, and a substantial body of scientific evidence supports its overall efficacy and safety profile. Questions have arisen whether there is an increased risk of diabetes in patients treated with Zyprexa or other atypical antipsychotics. We believe it's in the best interest of patients to set the record straight.

Is there an increased rate of diabetes among patients with schizophrenia and bipolar illness? Yes. There is an epidemic of diabetes in the US population,^{1,2} with a two- to four-fold greater rate of diabetes among patients with serious mental illness, irrespective of drug treatment.^{3,4} Thus, it is not surprising that diabetes has been reported during treatment with the most commonly prescribed atypical antipsychotics and mood stabilizers.⁵⁻¹²

Does Zyprexa cause diabetes? The available data do not establish a causal link between diabetes and Zyprexa—or any other antipsychotic, for that matter. We have been intensively investigating this question for several years from multiple vantage points: preclinical studies, head-to-head clinical trials, epidemiological surveys,^{14,15} and endocrinological challenge or “clamp” studies.^{16,17} Our conclusions have been confirmed by studies conducted by others from around the world.¹⁸⁻²⁰ Two clamp studies conducted by Lilly found that Zyprexa did not decrease pancreatic insulin release¹⁶ or, unlike other medicines (e.g., prednisone, protease inhibitors), have a direct effect on insulin sensitivity.¹⁷ It is clear that this important area requires more research, and Lilly is committed to staying on the forefront of this scientific inquiry.

Are my overweight patients at increased risk for diabetes? Yes. Being overweight (BMI > 25) is a long-term risk factor for diabetes in the general population.^{21,22} Many other factors also influence diabetes risk (eg, genetic predisposition, diet, exercise, comorbid conditions), so diabetes frequently affects non-overweight individuals. That said, most people who are overweight do not develop diabetes. Being overweight should be considered a modifiable risk factor and managed appropriately.

Given the weight gain profile of Zyprexa, how can Lilly claim “no consistent differences” for treatment-emergent diabetes among patients treated with atypicals? If weight gain were the only relevant factor, it might seem reasonable to predict more cases of diabetes with Zyprexa than with drugs less associated with weight gain. But we know there are a number of risk factors. The fact is, head-to-head clinical studies and epidemiology studies show no consistent or clinically significant difference in the risk of diabetes among patients treated with different atypical antipsychotics, despite differences in their respective weight gain profiles.^{14,15,23-34} In an analysis of clinical studies (most a year long, involving thousands of patients), elevated baseline random glucose levels and presence of multiple risk factors for diabetes were significant predictors of treatment-emergent diabetes, whereas weight gain and antipsychotic drug assignment were not.¹³

Answers That Matter.

What are the clinical implications of the diabetes “debate”? Risk for diabetes should be considered among patients with serious mental illness regardless of medication choice. A negative outcome would be the perception that choosing a particular psychotropic will determine diabetes risk. This can be harmful to patients if it leads clinicians to avoid the most appropriate treatment for a patient’s core psychiatric illness in the mistaken belief that it is an unsafe drug, or if it leads clinicians to a mistaken belief that they can avoid diabetes concerns by choosing a “safe” drug. A positive outcome of this debate would be if all caregivers who are responsible for the care of the persistently mentally ill understand the facts about the high rate of diabetes in their patients, and familiarize themselves with the risk factors and how and when to assess their patients.

We at Eli Lilly and Company are committed to the welfare of patients who take our medications. We are proud of the safety and efficacy that Zyprexa provides and welcome your questions or comments to our Medical Division at 1-800-LillyRX. For your convenience, important safety information and full prescribing information for Zyprexa accompany this letter.

Alan Breier, MD
Vice President, Pharmaceutical Products

Important Safety Information for ZYPREXA[®] (olanzapine)

ZYPREXA is indicated for the short- and long-term treatment of schizophrenia and for the treatment of acute mania associated with bipolar I disorder in patients displaying a manic or mixed episode.

The Adverse Reactions section of the Prescribing Information includes the following events—infrequent: hyperglycemia, glycosuria, diabetes mellitus; rare: diabetic acidosis, ketosis—as well as postintroduction reports of diabetic coma.

In 6-week acute-phase schizophrenia trials, the most common treatment-emergent adverse event associated with ZYPREXA was somnolence. Other common events were dizziness, weight gain, personality disorder (COSTART term for nonaggressive objectionable behavior), constipation, akathisia, and postural hypotension.

In short-term (3- and 4-week) acute bipolar mania trials, the most common treatment-emergent adverse event associated with ZYPREXA was somnolence. Other common events were dry mouth, dizziness, asthenia, constipation, dyspepsia, increased appetite, and tremor.

A small number of patients in premarketing trials experienced asymptomatic elevations of hepatic transaminase; none of these patients developed jaundice. Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

Prescribing should be consistent with the need to minimize the risk of neuroleptic malignant syndrome, tardive dyskinesia, seizures, and orthostatic hypotension.

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Date: 08/17/2001 01:07:04 PM
From: CN=Cassandra Mehlman/OU=AM/O=LLY
Subject: Diabetes Conference Call Opportunity

Hi everyone,

Per a voice mail I sent you today, I'd like to make you aware of an opportunity for your respective teams. On Wednesday the 15th, the Zyprexa Marketplace Management team piloted a live conference call with Dr. Robert Baker and 2 institutional districts in order to answer their questions regarding hyperglycemia and diabetes. The goal of the conference call was to enhance the representatives disease state knowledge and raise their confidence level regarding these issues. We'd like to offer your districts the same opportunity via a recording of the conference call with a 30 day playback feature. This featured will be offered 24 hours a day, 7 days a week, through Sept. 15th at noon. Some of the questions answered are as follows:

"How can there be comparable rates of diabetes among agents if Zyprexa causes more weight gain in some patients?"

"Does Zyprexa CAUSE diabetes?"

"What are the best ways to treat diabetes?"

"What is the best measure of elevated blood glucose levels?"

"Why are customers telling me that when patients with hyperglycemia are discontinued and put on Risperidal, their blood sugars return to normal."

"Should Zyprexa patients be excluded from a trial of Zyprexa."

"What are the most important risk factors to consider."

The 24/7 playback info is as follows:

Start date and time: August 15, 11:30 a.m. CDT
Stop date and time: Sept 15, 12:00 noon CDT
Phone number: 1.877.471.6581
Call in code: 577972

This will be available 24 hours a day/7 days a week until noon on September 15.

Please contact me if you have any questions or comments. Thanks! Cassie Mehlman, Zyprexa Brand Team, Marketplace Management, (317)-277-5847

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