HYPERGLYCEMIA/DIABETES DATA ON DEMAND RESOURCE GUIDE

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Situation Overview

The competition has been trying to convince our customers that ZYPREXA is not appropriate for many patients because of weight gain and the risk of hyperglycemia and diabetes. For our Lilly counterparts in the Retail Psych market, hyperglycemia/diabetes has become a major obstacle. In October 2000, 60% of psychiatrists surveyed in market research stated that they believed there was a link between ZYPREXA and hyperglycemia/diabetes. In April 2001, that number increased to 100% of psychiatrists surveyed. You can see that in a short period of time, perceptions can change dramatically.

With the launch of Risperdal into primary care, it is expected that these issues will be a key focus in their message. In addition, at the APA this past April, Pfizer and Janssen both sponsored programs to promote the idea that ZYPREXA causes diabetes and weight gain—despite the fact that there is no credible body of data that establishes causality between ZYPREXA and hyperglycemia or diabetes.

By knowing the facts, you can more effectively and efficiently handle any objections raised by physicians BEFORE it becomes an issue. **Four Key Message points in bold:**

- Patients treated with ZYPREXA, risperidone, haloperidol, divalproex, and ziprasidone in clinical trails had **comparable rates** of diabetes and hyperglycemia, even when the data was analyzed in 3 different ways.

- Although weight gain is one of the risk factors associated with diabetes, it is **there is no direct 1:1 correlation**. Weight gain can happen independently of diabetes, and diabetes can happen independently of weight gain.

- Pfizer's own study demonstrated comparable rates of hyperglycemia with ZYPREXA and ziprasidone (a supposedly "weight neutral" product).

- **Diabetes is common in the general adult population and is even more common in** psychiatric patients. Individuals with schizophrenia and bipolar disorder may have upward of a 2-to 4-fold increase in risk.

- **A number of factors affect a person's risk for diabetes**, including those that are intrinsic (such as family history/genetics) and those that are physical (such as weight gain).

- Psychotropic therapy in any individual patient should be evaluated in the context of that patient's overall response and toleration of therapy—the "risks/benefits" equation.

Strategy

First and foremost, striking the right tone with customers is essential. Many customers have stated they are tired of representatives who either "bash the competition" or who deny or minimize the doctors' concerns. We must be proactive with the weight gain issue and only use the diabetes sell sheet when responding to a concern from a physician.

Our goal is to continue to drive new patient starts on ZYPREXA, keep patients on therapy longer, and ensure the appropriate dose is utilized. In order to maximize this effort, we must neutralize the hyperglycemia/diabetes issue, help physicians manage weight gain, and continue to sell the unparalleled efficacy and dependability of Zyprexa.

By neutralizing we mean leveling the playing field, setting the record straight with a "comparable rates" message, and convincing physicians that ZYPREXA has the best safety and efficacy profile of any atypical antipsychotic. In order to do so, we must:

- Explain to doctors that **diabetes is a disease which Lilly takes very seriously. We have been a pioneer in this field for the last 50+ years and have studied the issue of hyperglycemia/diabetes extensively.**

- Admit up front that all antipsychotic medications can increase blood glucose levels.

- Admit that ZYPREXA can cause weight gain, but that does NOT mean it will cause diabetes. There is no 1:1 relationship between weight gain and diabetes.

- Explain that patients with severe mental illness are at higher risk for developing diabetes than the general population.

- Be patient focused.

Explanation of Diabetes Sell Sheet (OL 21620)

<u>Message Point #1</u>

On the first page, the top graph is a comparison of the incidence of treatment-emergent diabetes in longer head-to-head trials. The physician will have data that compares ZYPREXA with other antipsychotics as well as a mood stabilizer. **Summary: All agents had <u>comparable rates</u> in treatment emergent diabetes and hyperglycemia.**

The second graph measuring baseline-to-endpoint changes in blood glucose presents information from a bulleted point in a previous sales aid, with the addition of the Pfizer study. This data

demonstrates that all agents except clozapine had mean blood glucose values within the normal range. The Pfizer study was added for 2 reasons: (1) to show a comparison vs ziprasidone (a supposedly "weight neutral" product, yet comparable rates of hyperglycemia were still found), and (2) to show that whether fasting (Pfizer) or random (Lilly) blood sugars were taken, the results were the same. **Summary: All agents (except clozapine) showed similar changes in <u>Random</u> Glucose Levels, and ZYPREXA vs. ziprasidone showed similar changes in <u>Fasting</u> Glucose Levels.**

The third graph measuring an individual patient's likelihood of experiencing random glucose elevations was also derived from a bulleted point in the previous diabetes piece. This information graphically illustrates the thresholds that were used to determine normal plasma glucose, elevated plasma glucose, and diabetes. **Summary: Individuals taking ZYPREXA were no more likely to experience glucose elevations than patients on haloperidol or risperidone, despite their initial glucose level. Therefore, a patient with a high blood glucose level at baseline was no more likely to show an increase than a patient who had a low glucose level at baseline.**

<u>Message Point #2</u>

Many physicians think there is a logical link between weight gain and diabetes. In market research we see that many of them even use these two words interchangeably. We believe it is essential to weaken this link in order to neutralize the diabetes/hyperglycemia issue.

The pie chart on the left demonstrates that patients who had an episode of hyperglycemia did not experience substantial weight gain. The right side looks at the patients who did see substantial weight gain and skows that an overwhelming number experienced no glycemic abnormalities. **Summary: Weight gain and hyperglycemia does not exhibit a 1:1 correlation. In the rare case that patients experienced hyperglycemia, the majority (79%) did not experience weight gain. Additionally, 96% percent of patients who had substantial weight gain did not experience any glycemic abnormalities.**

<u>Message Point #3 and #4</u>

These points are the same as in the previous diabetes sell sheet. Diabetes is a common illness in the general adult population, and is more common in patients with psychiatric illness. It also examines various intrinsic and variable risk factors for diabetes.

<u>Summary</u>

Eli Lilly and Company has a proud history in innovative diabetes research. The relationship between ZYPREXA and diabetes/hyperglycemia is a top priority for the company and has been studied extensively. The facts illustrate no difference in the incidence of treatment-emergent hyperglycemia and diabetes for patients ZYPREXA, haloperidol, risperidone, ziprasidone, or divalproex. Neutralizing any concern from our customers will be essential to the future growth of ZYPREXA in this marketplace.

Question/Answer

How can ZYPREXA show comparable rates of hyperglycemia to other agents when it causes more weight gain, and significant weight gain is a risk factor for diabetes?

Obesity is one of many risk factors for diabetes. Clearly, there is not a 1:1 correlation between weight gain and diabetes. In other words, weight gain can happen independent of diabetes and diabetes can happen independent of weight gain. The single most important risk factor in clinical trials may be persistent and severe mental illness. Additionally, other factors like lifestyle and family history all play an important role.

Your data looks good, but it is not what I am seeing in my daily practice. I have seen a higher incidence of hyperglycemia/diabetes in my ZYPREXA-treated patients. How do you explain this difference?

Doctor, your clinical experience is extremely important. However, your experience seems to be different from large-scale clinical studies.

There may be a couple of reasons why this may be the case. First, some physicians were more selectively assessing ZYPREXA patients for hyperglycemia or diabetes. When they began to assess patients on other medications as well, they began to uncover additional cases.

Secondly, other physicians have realized their perceptions have been influenced by the fact that they have significantly more patients on ZYPREXA.

Another possibility may be that your patient population may be different. For example, you may be treating a more severely mentally ill population and using more ZYPREXA than other physicians.

Does ZYPREXA affect risk factors other than weight gain?

That's an excellent question, since there are many factors that impact a person's chance of developing diabetes. Some of these are intrinsic and can not be impacted by lifestyle or any agent (such as genetic risk, age, gender, etc.). In terms of variable risk factors like prolactin levels, ZYPREXA does not appear to have any effect that might raise glucose levels. Regarding various lifestyle factors (lack of exercise, excessive alcohol intake, etc.), these may improve to the degree that a patient experiences efficacy from ZYPREXA, potentially improving their risk profile.

Is there a direct effect of ZYPREXA on diabetes?

We've gone back and looked for evidence both preclincially and in our clinical comparison with other antipsychotics and mood stabilizers to determine whether or not ZYPREXA directly interferes with insulin release or insulin activity. We have not found a direct effect. Specifically:

- We have examined our longer-term preclinical animal studies and have not found any changes in insulin release or changes to the pancreas.

- We also looked to determine if there were higher rates of diabetes vs comparator drugs in clinical studies. If there was a ZYPREXA-specific effect, you would expect to find much higher rates of diabetes with ZYPREXA, probably in the first weeks or months of therapy. In fact, our head-to-head clinical trials show comparable rates of diabetes or hyperglycemia to haloperidol or risperidone. While this data can not rule out a class effect, it is evidence against a ZYPREXA-specific effect.

- We are continuing to investigate these questions quite carefully.

Does ZYPREXA cause Type I diabetes?

No. Most treatment-emergent diabetes reported with ZYPREXA and other psychotropics is Type II. We do know that there are patients, independent of the agent they are taking (and even some patients not taking any agent at all), who develop Type I diabetes. In our controlled clinical trials, rates of developing Type I diabetes are not higher with ZYPREXA than with haloperidol or risperidone. Even in pre-clinical animal data, there is no evidence to suggest that ZYPREXA causes Type I diabetes.

Scientific Background (review to extent necessary)

General Overview: Basic Biology

The human body needs fuel in order to function. As we eat, our body breaks down some of the food into sugars, one of which is glucose, the body's main fuel. After glucose is created, it must be transported to the cells, where it is oxidized (burned) to supply energy and allow the body to function. (Most cells can also use alternate energy sources, such as lipids or proteins, but generally use glucose first.) The blood carries glucose to individual cells. As glucose enters the bloodstream, a person's blood glucose level begins to rise, then gradually returns to the normal range as glucose passes into the cells.

It is important to realize that there are daily fluctuations in blood glucose levels, as well as a great deal of inter- and intra-person variability. For example, a measurement of fasting blood sugars (obtained by assessing blood glucose levels 8-12 hours after the last food intake) results in "ideal" plasma levels that may range from 70-100 mg/dl. Nondiabetic individuals usually have fasting glucose levels below 125mg/dl.

The body has a very complex system that makes glucose available to cells to produce energy, and generally this system keeps blood glucose levels within a normal range. When the body senses an increase in glucose, it sends a signal to the beta cells of the pancreas to make insulin. Insulin is a hormone that lowers the blood glucose by acting as a key to unlock the body's cells, thus allowing glucose to pass from the bloodstream into the cells. Once the pancreas releases insulin into the blood, the blood glucose level begins to fall back to normal as the insulin allows glucose to pass from blood into the cell. The body's cells then utilize the glucose for fuel, creating energy for the body.

When the system fails. . .

If the body doesn't make enough insulin or if the insulin doesn't function properly, the sugar cannot gain access to the cells. Instead, the glucose stays in the blood, causing the blood sugar level to be high, potentially signaling diabetes.

Just because a person's blood sugar levels may be elevated doesn't necessarily mean that person has diabetes. A person has "high blood sugar" or hyperglycemia when his or her blood sugar level has risen and stayed well above the ideal range. It requires consistent elevations over a long period of time to be considered diabetes.

Hyperglycemia vs Diabetes

Hyperglycemia and diabetes are conditions characterized by abnormalities in the body's ability to use glucose.

Hyperglycemia that persists for a short period of time usually does not have an adverse effect on the body. Sometimes, hyperglycemia can cause symptoms such as excessive thirst and urination. If hyperglycemia persists for a long period of time (as in diabetes), it can damage certain organs of the body such as the kidneys, eyes, and nerves. Although many individuals experience hyperglycemia, such as after quickly eating a high calorie meal or when they are ill, usually the elevated glucose is transient and goes away without medical intervention.

Diabetes is a complex metabolic disorder predominantly characterized by blood glucose levels that are consistently higher than normal (hyperglycemia). But diabetes is more than just hyperglycemia; frequently it also entails other metabolic problems, such as elevations in cholesterol and triglycerides.

Other definitions

Fasting plasma glucose (FPG)—collected from a patient who has no caloric intake for at least 8 hours. This is the preferred method for measurement because it eliminates high measurements that may result from a patient's eating pattern.

Random plasma glucose—collected any time of the day independent of when or what the individual last ate. This test has its limitations but depending on the patient's situation, it may be the best alternative.

Impaired glucose tolerance (IGT)—These criteria define a group of patients who are hyperglycemic but do not meet the criteria for a diagnosis of diabetes.

Defining diabetes by blood glucose levels

Measurement	Diabetes	Impaired Glucose Tolerance (IGT)	Normal
Random Glucose	≥200 mg/dl	160-200 mg/dl	<160 mg/dl
Fasting Glucose	≥126 mg/dl	110-126 mg/dl	<110 mg/dl

The role of psychotropics and hyperglycemia/diabetes:

Several psychotropics have been associated with high insulin levels and insulin resistance (eg, chlorpromazine, divalproex). The National Diabetes Data Group listed chlorpromazine, haloperidol, and lithium under drugs that impair glucose tolerance.

Cases of hyperglycemia have been found and noted in clinical trials with atypicals; in fact, hyperglycemia and diabetes are included as adverse events in the package inserts of most typical antipsychotics and mood stabilizers and all currently approved atypical antipsychotics. Also, since obesity is a risk factor for diabetes, clinicians may be anticipating more hyperglycemia risk among patients with substantial weight gain during treatment.

There have been a number of case reports describing new-onset diabetes during treatment with ZYPREXA. Of note, many of the reports of abnormal glucose levels involved patients with other risk factors for developing hyperglycemia including race, obesity before treatment, or personal/family history of diabetes. In particular, of 15 case reports regarding treatment with ZYPREXA, 12 involved patients with a history of obesity.

Beyond case reports in the literature, there have been a number of studies implicating ZYPREXA as having higher rates of hyperglycemia or diabetes. Perhaps the best known is the as-yet unpublished work of Dr. Newcomer, who performed a retrospective study looking at hyperglycemia after an oral glucose load in patients on ZYPREXA, risperidone, haloperidol, or clozapine.

While provoking interesting medical research questions, the data does not have practical application, nor does it draw concrete conclusions. The Newcomer study is limited by a number of factors. First, the database is quite small, including <10 patients per group. Second, the study was designed to focus on cognition and was NOT intended to examine hyperglycemia. As such, it did not control for variables such as patient diet or family history of diabetes. Most importantly, assignments to different drugs were not randomized.

To point out how potentially spurious Dr. Newcomer's findings are, it is instructive to look at a very similar study undertaken by Dr. Prior and colleagues from Alberta, Canada. Dr. Prior conducted a study to investigate whether patients taking clozapine, risperidone, and ZYPREXA have unusual responses to oral glucose challenges. Unfortunately, this study also had a small sample size (n=28) and the patients were not randomly assigned to treatment. However, the results indicated that none of the patients treated with ZYPREXA had abnormal glucose metabolism, 40% of patients treated with risperidone had abnormal results, and 67% of patients treated with clozapine had abnormal results.