STRATEGY OVERVIEW

Introduction

Welcome to the ZYPREXA Hyperglycemia/Diabetes Data on Demand Resource Guide. This guide will function as your "go-to" resource when you are faced with an objection surrounding hyperglycemia or diabetes. Since the launch of ZYPREXA four years ago for schizophrenia and almost one year ago for bipolar disorder, we have been very successful in communicating the outstanding efficacy and safety of ZYPREXA to our customers. You have helped thousands of patients with schizophrenia or bipolar disorder achieve either reintegration or balance. Now, with the launch of the new schizophrenia message—including the maintenance of treatment response data—we're taking ZYPREXA to an even higher level.

Our primary focus, as always, is on the outstanding efficacy of ZYPREXA. Clearly, this is the most important facet of an antipsychotic and a mood stabilizer to patients, family members, and the treatment team. Nevertheless, as you are well aware, over the last several years our competition has been relentless in trying to convince our customers that ZYPREXA is not appropriate for many patients because of weight gain. And, more recently, they have focused on a very logical argument: ZYPREXA causes more weight gain; significant weight gain is a risk factor for diabetes, and therefore (they want MDs to think) ZYPREXA causes more hyperglycemia and diabetes.

It is very important to have a good understanding of hyperglycemia and diabetes. This will allow you to be able to properly handle any possible objections you may get, and in the end, spend more time sharing the outstanding efficacy story with your customers. You will learn more about hyperglycemia and diabetes in the Scientific Background found on page 10 of this guide.

ZY 9370 312

Market overview

Not every physician has bought into the weight gain/diabetes argument, but there are a growing number of psychiatrists who have. For the most part, their perceptions of ZYPREXA and diabetes have been based on an intuitive argument, but many have either read about case reports in the literature, heard about a patient on ZYPREXA who has developed diabetes, or in some cases, have had a patient on ZYPREXA develop diabetes. In essence, most physicians' perceptions have been based on an argument put forth by our competition buttressed by some anecdotal evidence.

Market research has shown there are two groups of physicians with whom we must be prepared to deal. First, there is a group representing about 60% of psychiatrists who do not view diabetes as a particular concern with antipsychotics. However, this does not mean they have not heard the argument put forth by our competition. In fact, while these physicians may not be concerned enough to let this issue affect their prescribing of ZYPREXA, most of them have heard the argument. If you can get into a deep enough dialogue with them, we've found that many of them do wonder if it might be true. The other 40% of our psychiatrists have specific concerns about

3

ZYPREXA and diabetes, and perhaps half of this group has begun to shy away from ZYPREXA because of their concerns.

Diabetes, after all, is a pretty scary thought for most psychiatrists. First, most are not comfortable with the science around the disease. Though many remember some of their medical school training on the subject, most do not deal with diabetes on a day-to-day basis, so they may not be well versed in the basics, such as risk factors for the disease, diagnostic criteria, or treatments. Second, they are fearful of "causing" a disease that can lead to permanent complications. Even though they may be comfortable assessing the risks of using antipsychotics that may lead to tardive dyskinesia—they've had about 50 years to get used to thinking about that potential side effect. As one psychiatrist said, "We've had to be neurologists, and I don't want to have to become an endocrinologist."

Situation overview

We all have been aware of the competitive activity and changing physician perception for some time, and we've been fairly proactive in the marketplace. Along with proactively changing the PI in the second quarter of 2000, we launched a number of efforts to address physician concerns. It is clear that many of you have made some progress utilizing the first hyperglycemia sell sheet with some of your physicians. And there has been a steady DTP effort (CME, Strategy and Consultant Conferences, etc) on the topic. Also, last year, the neuropharm division of the FDA requested all preclinical, clinical, and post-marketing surveillance data from each of the manufacturers of newer antipsychotics. And, in late 2000, the FDA asked Lilly to remove the paragraph in the ZYPREXA PI relating to the relative incidence of treatment-emergent hyperglycemia pending its review of all manufacturers' data.

We anticipate that the FDA will make additional changes to the PIs of many or even all antipsychotics in the next six months to a year. We believe the most likely scenario is that there will be some sort of "class labeling" around hyperglycemia/diabetes.

So, how do we address this issue?

There are a number of "lessons learned" from our experiences selling [ ] and ZYPREXA that we need to remember as we address this issue. We've done some good things, and have also made some mistakes as we've dealt with competitive issues such as [Redacted] and weight gain with ZYPREXA.

- We must be fully aware that "brush fires can turn into forest fires." In essence, although we've handled the competitive attacks on diabetes fairly well to date, we must not be overly confident. We must work to make sure that the 60% of psychiatrists who don't have specific concerns about ZYPREXA remain confident in both the efficacy and safety of our agent.

ZY 9370 313

4

Zyprexa MDL Plaintiffs' Exhibit No.04202   Page 2

- We've learned that it's important to be forthcoming—we must not be perceived as "merely denying" a potentially serious side effect, and therefore must address the issue constructively, confidently, and empathetically.

- We must not fight a battle around just one side effect. We must make our first priority discussing the benefits of ZYPREXA with our physicians.

- We must continue to give appropriate tools to the neuroscience sales force, and help provide "air cover" in terms of physician-to-physician communications.

- We must be relentlessly consistent in our alignment and execution across the marketing mix—in the sales force and in our other marketing efforts.

- We must recognize and understand the nature of each customer's concern and tailor our objection handling based on our knowledge of that customer's concern.

Strategy overview

Our strategy for how to deal with this issue is based on a number of things:

- a firm understanding of our customers' perceptions of ZYPREXA and of Lilly;
- an understanding of the past, current, and likely future regulatory events;
- an ever-evolving understanding of the truth about ZYPREXA and other psychotropics with respect to hyperglycemia and diabetes; and
- an understanding of the patients our physicians are treating.

So what is the story behind hyperglycemia and ZYPREXA? Our US and Product Team physicians have been working diligently to learn more about the potential for treatment-emergent hyperglycemia and/or diabetes in patients who are treated with ZYPREXA and other agents.

Briefly, **diabetes may occur in patients taking antipsychotics and/or mood stabilizers, including ZYPREXA, at rates that are comparable to each other**. This is the key message that we will focus on, and the one that is most relevant to clinicians. After looking at data from pooled clinical trials, we have found that the incidence of treatment-emergent, diagnosed diabetes is comparable between ZYPREXA, haloperidol, and risperidone. We also looked at rates of abnormally elevated blood glucose across these three agents using four different cutoff points, and again found that the likelihood of patients experiencing elevations was not different between these agents *at any threshold examined*. We will go into more detail in the Scientific Background, page 20.

Of note, you will notice that the thrust of our new data on demand for diabetes/hyperglycemia focuses on comparable rates with relevant treatment alternatives in patients with schizophrenia, rather than placebo. One limitation of our placebo data in patients with schizophrenia is that the time of exposure to placebo in our trials is relatively short—on the order of a few weeks—making comparisons of rates challenging. On the other hand, our database comparing ZYPREXA to haloperidol, risperidone, and clozapine is quite robust, having a large number of

5

ZY 9370 314

randomized, prospectively assigned patients followed over a relatively long duration. And perhaps most importantly, these agents (particularly risperidone and haloperidol) are two very relevant alternatives in today's treatment paradigm for patients with schizophrenia and, perhaps to a lesser extent, bipolar mania. You'll note that we do not include data in this sheet on Depakote. This is simply because the data that we have are limited to the three-week HGHQ study, where we did not see differences in glucose levels, but would not have expected to, given the relatively short duration of the trial. In Abbott's 12-week comparative study of ZYPREXA and Depakote, no significant differences in glucose levels were found.

We have also analyzed the large head-to-head database looking at average blood glucose levels for patients taking ZYPREXA and the other comparator agents. Here, we did see some small elevations in patients taking ZYPREXA, but as Dr. Breier discussed in his video shown in the January meetings, these small increases were not clinically relevant. Nevertheless, it is important that we share this information with our customers because it helps build credibility. **We are NOT saying that there are no changes in blood glucose on ZYPREXA, nor are we saying that there are no differences in blood glucose for patients on ZYPREXA as compared with patients on the other agents. The key point is that we do not see differences in rates of diabetes or hyperglycemia across these agents.**

There are, of course, a number of other key messages that are essential to communicate.

- **Diabetes is quite common in the general population, and is higher in patients with psychiatric illness.**

  The incidence of diabetes is on the rise in the United States. In the general population, the incidence of diabetes is 7.8%, with about one third being undiagnosed. In other words, there are people who have diabetes and don't even know it. On top of this, an additional 6.9% have abnormal hyperglycemia, with blood glucose levels falling short of the diagnostic threshold for diabetes. *The incidence of diabetes among patients with schizophrenia and bipolar disorder is 2-4 times higher than the general population.*

  We do not mean to minimize the problem of glucose elevation at all. In fact, to the contrary, it is important our physicians understand that if they were to look carefully at their patient population, they likely would find elevations in glucose. Clearly, hyperglycemia and diabetes are part of a much bigger picture than merely the effects of psychotropic medications. This leads us to the next part of our message.

- **There are a large number of factors that affect risk for diabetes, such as obesity or other potentially stronger risk factors.**

  There are some factors that cannot be changed, such as family history, age, ethnicity, etc. On the other hand, there are a number of factors that are variable. Variable factors include diet and exercise, which can play a role beyond mere weight gain. Although significant weight gain is indeed a risk factor for hyperglycemia and/or diabetes, there are many other factors involved. Even though a patient has some or even all of these risk factors, he/she may not

ZY 9370 315

6

develop diabetes. Conversely, some patients with diabetes have none of these risk factors. Clearly, diabetes is a complex disease with a large number of contributing factors.

So then, how can ZYPREXA be associated with more weight gain, but still have comparable rates of hyperglycemia? In fact, differences in patterns of weight gain on various agents that we've analyzed did NOT translate into differences in rates of diabetes or hyperglycemia. As Dr. Breier outlined in his video, weight gain is just one part of the picture. In fact, the majority of patients (79%) who did have an episode of hyperglycemia did NOT experience substantial weight gain (i.e., increase of 10% or more from baseline). And even among those patients with substantial weight gain, over 95% had no glycemic abnormalities. Further detail is provided in the Scientific Background, page 21.

In essence, our strategy is to set the record straight regarding the incidence of hyperglycemia associated with antipsychotic medications. Specifically:

- Rates of hyperglycemia/diabetes are comparable among patients taking antipsychotic medications
- Diabetes is common in the general adult population and is more common in patients with psychiatric illness
- There are many factors that influence hyperglycemia/diabetes
- Obesity is one risk factor among many that may contribute to hyperglycemia

Market research testing

We have had the opportunity to test the new sell sheet with a number of your key customers. First off, in our testing, physicians had a very consistent takeaway of key message points. And, the message appears to be generally believable. Now, this is not to say that in all cases physicians "changed their minds" on the spot. In almost all cases, however, the dialogue with the physician succeeded in making them think.

If we deliver the right message to the depth required, we can get physicians thinking. And with the "air cover" that is being provided in CME programming and other peer-to-peer programs, it is our intent to reframe this issue over time so that fear of diabetes does not become a reason to avoid starting a patient on ZYPREXA (or on any other psychotropic).

ZY 9370 316

Resources available

At upcoming coaching clinics, you will be working with a new sell sheet. This guide includes photos of the front and back of the sell sheet, as well as a sample script.

In addition, there are a number of other resources that you have at your disposal. Of course there is a medical letter available. And, there are several enduring materials from DTP programs that can also provide good information on this topic for physicians who request it. Specifically, you may want to provide the November 2000 PsychLink (as discussed in the January meetings) to

7

those physicians who request it. We also have updated speaker slides that can be used in peer-to-peer selling efforts.

Critical observations on this new information

First, these data are an enhancement to and consistent with our previous message. Clearly, the information in this sell sheet is more relevant to physicians because it directly discusses comparable rates across certain psychotropic agents. Please note you must discontinue use of the previous sell sheet (OL # 18524) after the upcoming district meeting/coaching clinic.

Second, you must utilize the new sell sheet appropriately with your physicians. Specifically, if you know a physician (or treatment team member) who (a) has a deep-seated and specific objection to using ZYPREXA due to fear of hyperglycemia, and/or (b) brings up a serious hyperglycemia objection at the beginning of your detail, you should address the objection up front in your detail, utilizing the new materials. For other physicians (which will probably be most physicians), you should proceed with the usual "efficacy" message, making sure that you probe carefully during the safety/tolerability section of the detail to uncover an objection. Of course, if you discover one, please handle it appropriately with the new materials.

Additionally, it is critical that you tailor the objection handling to the physician based on a clear understanding of the physician's perceptions. In most instances, you can limit your discussion to the "comparable rates" page. If necessary, though, the second page provides additional information.

Third, our success will be largely dependent on our tone with physicians: we must handle the objection in a confident, non-defensive, forthcoming manner. But we must also answer the objection to the depth required, based on a good understanding of that physician's thoughts and perceptions of the issue. So, of course, active listening is required. Also, the sell sheet is designed so that you can limit your discussion to the "comparable rates" if that will handle the objection. If more is required, you can use the back page as well. In fact, based on our testing with physicians, we've learned that it is **essential** to avoid a "data dump." Therefore, we will practice utilizing this information both in a brief way and a more complete way in the upcoming coaching clinic.

Critical success factors for appropriately dealing with the hyperglycemia/diabetes objection:

1. Focus your sales presentation on the outstanding efficacy of ZYPREXA
2. Have a good understanding of hyperglycemia/diabetes
3. Understand how and when to properly use the hyperglycemia Data on Demand sheet
4. Frame hyperglycemia in the context of the overall safety profile of antipsychotic medications

ZY 9370 317

8

Zyprexa MDL Plaintiffs' Exhibit No.04202

In closing...

We hope you find this Resource Guide helpful as you prepare yourself to handle any hyperglycemia and/or diabetes objections that your customers may raise. We appreciate your dedication and expertise and are counting on those attributes as we move forward.

We wish you great success in the field!

ZY 9370 318

9

ZY1 00625565

SCIENTIFIC BACKGROUND

This section is designed to give you a brief but fairly thorough understanding of what hyperglycemia is, what diabetes is, and how they differ. Each condition affects the body in different ways. Certain risk factors may predispose one person more than the next. Some of these factors are manageable, some are not. Diabetes has become more common in the general population, and it may be even more common in patients with serious and persistent mental illness.

Once you have an understanding of the disease state, you will then be able to better understand our data on ZYPREXA and diabetes, and how these data compare to other antipsychotics. Obviously, we do not expect you to become diabetes experts. You are sales representatives for ZYPREXA, and your primary mission is to sell ZYPREXA. But unfortunately, for some customers, that may mean you will have to address their concerns about hyperglycemia and diabetes. We hope that we have provided the information to allow you to do that, and then easily transition back to our efficacy message.

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 these sugars is glucose, the body's main fuel. After glucose is created, it needs to be transported to the cells in order for the body to function. Glucose is oxidized (burned) in the cells to supply their energy. (Most cells can also use alternate energy sources, such as lipids or proteins, but generally use glucose first.) The blood is responsible for carrying glucose to individual cells. As glucose enters the bloodstream, a person's glucose levels begin to rise, but gradually return to the normal range.

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 in blood sugar levels. For example, by one measure of blood sugars (obtained by assessing blood glucose levels 8-12 hours after the last food intake), "ideal" plasma levels may range from 70–100 mg/dl[1] and nondiabetic individuals usually have fasting glucose of below 125 mg/dl.[2]

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 since 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.

ZY 9370 319

10

When this 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. Consistent elevation over a long period of time makes one more likely to develop diabetes.

Conversely, if blood sugar levels fall below 60-70 mg/dl,[3] this may be an indication of low blood sugar (hypoglycemia). When this happens, people may experience unpleasant symptoms, such as lightheadedness, nausea, drowsiness, or confusion. These symptoms can develop quite suddenly. Although hypoglycemia is usually easy to treat, serious reactions may result if it is not dealt with quickly, including passing out or having convulsions.

The next section of the Scientific Background will explain in a little more detail the difference between hyperglycemia and diabetes, as well as discuss how each condition can affect the body.

DISEASE STATE OVERVIEW
Hyperglycemia vs diabetes

Hyperglycemia and diabetes are conditions that center around abnormalities in the body's ability to use glucose. As mentioned, our bodies have a very elaborate mechanism to keep the amount of glucose in the blood within a range that is sufficient to keep body cells energized.

Hyperglycemia that persists for a short period of time usually does not have adverse effects on the body. Sometimes, hyperglycemia can cause symptoms such as excessive thirst and urination. If hyperglycemia persists for a long period of time (as occurs in untreated diabetes mellitus), 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 with the flu, usually the elevated glucose is transient and goes away without medical intervention.

> **An individual can have episodes of hyperglycemia and not have diabetes or any complications.**

Diabetes is a complex metabolic disorder predominantly characterized by blood glucose levels that are consistently higher than normal (hyper-glycemia). But diabetes is more than just hyperglycemia; frequently it also entails other metabolic problems, such as elevations in cholesterol and triglycerides, and symptoms or complications as discussed below. A diagnosis of diabetes is given when the patient meets a certain set of blood glucose criteria, measured by a

ZY 9370 320

11

couple different tests. Let's start by discussing the two types of diabetes, the measurement and evaluation of blood glucose level, and the role of insulin.

> **Diabetes is more than just hyperglycemia:**
> - **it is characterized by persistently elevated blood glucose levels above certain thresholds; and**
> - **it is also characterized by frequent lipid abnormalities and other complications.**

Types of diabetes

There are two major types of diabetes. Though both include blood sugar elevation, both types have very different causes and presentations, as described below.

Insulin-Dependent Diabetes Mellitus (Type 1 Diabetes) occurs when beta cells of the pancreas do not produce sufficient insulin, typically due to beta cell destruction. Circulating insulin levels are low or undetectable. As such, patients with Type 1 Diabetes require insulin administration for life. While Type 1 Diabetes can occur at any age, it usually presents in children or teens with symptoms such as extreme thirst, frequent urination, and weight loss. In most instances, insulin-dependent diabetes occurs with a background of genetic susceptibility to the disease but is precipitated by altered immune responses and/or environmental stressors. About 10 % of all patients with diabetes have insulin-dependent diabetes. As the name of the disorder suggests, most Type 1 Diabetes patients require daily insulin injections in order to live.

> **Type 1 Diabetes is characterized by very low or virtually absent insulin production.**

The other 90 % of diabetes patients have **non-insulin dependent diabetes mellitus (Type 2 Diabetes)**. Type 2 Diabetes usually occurs in individuals over the age of 40, is often without symptoms in its early stages, and may go undiagnosed for years (average is 7 years). In contrast to insulin-dependent diabetes, non-insulin dependent diabetes is a consequence of the body's cells using insulin inefficiently. Such individuals are not diabetic while blood glucose levels remain normal. The cells are said to be "resistant" to the effects of insulin. When this happens, the body compensates by producing a greater-than-normal amount of insulin. As a result of this compensation, the individual avoids having elevated blood glucose levels even though his or her body's cells have become "insulin resistant." However, the pancreas can only continue this increased insulin secretion for a limited number of years. Eventually the pancreatic beta cells (insulin-secreting cells) lose their ability to maintain adequately high levels of insulin. As the pancreas beta cells fail, insulin levels begin to fall below the supernormal values, and glucose levels begin to rise above normal. As the glucose levels rise above normal and the pancreas is no longer able to compensate by producing more insulin, persistent hyperglycemia develops, and Type 2 Diabetes can be diagnosed when glucose crosses diagnostic thresholds. This high

ZY 9370 321

12

glucose may occur even when measured insulin is in the normal range, because the cells are inefficient in their insulin use.

> **Type 2 Diabetes is characterized by the body's cells using insulin <u>inefficiently</u>.**

<u>Type 1 Diabetes vs Type 2 Diabetes</u>

	Type 1 Diabetes	**Type 2 Diabetes**
Onset	Sudden onset usually before age 30 but may occur at any age	Gradual onset usually after age 40 but increasing incidence in adolescents
Symptoms at onset	Excessive thirst, hunger, and urination; weight loss; fatigue; nausea/vomiting; sweet breath; frequent/recurring infections	Often mild or no symptoms early; blurred vision, frequent urination; cuts/bruises slow to heal; tingling/numbness in hands/feet.
Possible causes	Immune mediated, viral, or environmental causes	Not known, but family history and other risk factors are known
Level of insulin deficiency	Absolute insulin deficiency	Inefficient insulin use and insufficient compensatory rise in insulin level

Blood glucose levels

The diagnosis for hyperglycemia or diabetes centers on measurements of blood glucose. The measurements depend on the method of measurement, which can depend on the testing situation. It is extremely important that plasma glucose levels be interpreted within the context of the testing situation. The fasting plasma glucose (FPG) is the preferred method of measurement. The random plasma glucose is also a reliable method, but is not preferred over the fasting plasma glucose due to its limitations, which are described below. The other two tests mentioned below are not as commonly used.

- *Fasting plasma glucose (FPG)* – collected from a patient who has no caloric intake for at least 8 hours. This is the preferred method of evaluating blood glucose levels because it eliminates high measurements that may result from a patient's eating patterns, thereby allowing a more "standardized" comparison to published normal ranges. Once one abnormal result is obtained, this test is repeated before an actual diagnosis of diabetes is made.

- *Random plasma glucose* – collected any time of the day independent of when or what the individual last ate. Unfortunately, this measurement may not accurately reflect normal plasma glucose—if the patient recently ate a meal that he or she doesn't normally eat, such as a McDonald's Big Mac, this particular measurement may not be as reflective of the normal

ZY 9370 322

13

plasma glucose level as compared to a fasting plasma glucose measurement. Clearly, this test has some limitations. However, depending on the patient's situation, it may be the best alternative (patient is unable to fast for 8 hours, etc). This is the measurement that we have in our clinical database.

- **2-hour oral glucose tolerance test (OGTT)** – collected two hours after the patient consumes an oral drink "loaded" with glucose. The OGTT is inconvenient and uses more medical resources, so this method is not recommended for routine diagnosis of diabetes.

- **Hemoglobin A1$_c$ test** (sometimes called "glycosylated hemoglobin") – abnormally high amounts of hemoglobin A$_{1c}$ are produced when plasma glucose is high. As turnover of hemoglobin A1$_c$ is relatively slow, it is used to estimate severity of glucose elevation over several weeks. This measurement thereby gives a more longitudinal view than a single measurement of glucose itself. However, it is not currently recommended for the diagnosis of diabetes, and is more helpful in evaluating glucose control in patients with known diabetes.

Defining diabetes by blood glucose levels

The chart below lists the blood glucose levels that may suggest the presence of hyperglycemia or diabetes.[2]

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

It is important to understand that these numbers are arbitrary, as is blood pressure for example. It is not as though 127 mg/dl is significantly different from 125 mg/dl. However, if a patient has two different levels of blood sugars while fasting on two different occasions and both measurements are over 125 mg/dl, then that person would be diagnosed with diabetes. This is an important point, as the **diagnosis of diabetes requires several fasting measurements above 126 mg/dl**, as will be explained in greater detail later.

Impaired Glucose Tolerance (IGT): These criteria also recognize a group of patients who are hyperglycemic (have fasting glucose that is higher than the normal values of 110 mg/dl), but do not meet the criteria for a diagnosis of diabetes. Patients whose glucose values fall between "normal" and "diabetic" are said to have Impaired Glucose Tolerance (IGT) or Impaired Fasting Glucose (IFG). This is an important classification for several reasons. First, it is important to note that IGT and IFG are not clinical entities but rather risk factors for future diabetes and cardiovascular disease.[4] Patients with IGT do not necessarily progress to diabetes, and some patients with IGT revert to normal with appropriate diet and exercise. Whereas an estimated 16 million Americans have diabetes, an estimated 21 million Americans have IGT. And at least 35-40 % of these will go on to develop diabetes.[5] This means that 7 % of the population, or 1 out of 12 individuals, is at high risk for developing diabetes.[6]

ZY 9370 323

14

Zyprexa MDL Plaintiffs' Exhibit No.04202

Complications of diabetes and hyperglycemia

Remember, just because a person has hyperglycemia does not mean that he or she necessarily has diabetes. However, patients with diabetes do have hyperglycemia, but they also have other metabolic problems, such as elevated cholesterol and triglycerides. From a diagnostic perspective, though, it's really the severity of hyperglycemia that matters, not levels of fat or protein. Diabetes also begins to negatively affect many parts of the body.

Diabetes can lead to a number of long-term complications. While precise mechanisms remain unknown, glucose elevation appears to play a key role. Controlling hyperglycemia, in other words, keeping the blood glucose as close to normal as possible, can prevent or delay many diabetes complications. The main types of complications brought about by diabetes are listed below.[7]

- Retinopathy causes the deterioration of the retina, which can lead to blindness; if detected and treated early, retinopathy can be prevented or delayed. Research indicates that the risk for retinopathy can be reduced through good glucose control.

- Nephropathy is a kidney disease that, left unchecked, can lead to kidney failure requiring renal dialysis or kidney transplant.

- Peripheral neuropathy, damage to sensory nerves in the extremities, may cause patients to be unaware that they've been cut or have an infection; hence, this kind of neuropathy increases the risk of more serious infections. Peripheral neuropathy often leads to amputations because infections of the feet or legs can become advanced before the patient realizes there's a problem (and because damage to blood vessels impairs healing). Diabetes is the leading cause of nontraumatic amputations in the US.

- Autonomic neuropathy, damage to nerves in autonomic systems, impairs the "automatic" functions of the internal organs. Difficulty in emptying the stomach, the bladder, or obtaining or maintaining an erection may result.

Microvascular complications include disease of the arteries/veins in the heart, extremities, and brain. A thickening of blood vessel walls and arteriosclerosis, a lipid buildup that clogs arteries, can lead to heart attack and stroke. Of patients with diabetes, 80% will die from a cardiac event.

While the above complications accrue due to long-term effects of hyperglycemia and are usually progressive, there are three other types of acute diabetic complications due to imbalance of glucose and insulin. These potentially severe "metabolic" complications are usually both treatable and preventable.

- Hyperosmolar coma is usually a complication of Type 2 Diabetes. Patients become abnormally drowsy and symptoms can progress to coma. Very high blood glucose and dehydration are responsible for the symptoms. Above a certain plasma glucose level

ZY 9370 324

15

(approximately 180 mg/dl), the kidneys cannot fully prevent glucose from "spilling" into the urine. This glucose pulls more water into the urine by osmotic force. Consequently, increased urination and compensatory increased thirst are common symptoms of hyperglycemia. These symptoms worsen as the blood sugar increases. Patients who are unable to drink enough to keep up with the urinary losses (eg, those who are bedridden) are particularly likely to progress to dehydration and hyperosmolar coma. Hyperosmolar coma is treatable with insulin, fluids, and other supportive measures.

- Diabetic ketoacidosis (DKA) is a potentially life-threatening situation. It usually reflects a very severe insulin deficit, so is more common in Type 1 Diabetes. DKA usually presents with gastrointestinal symptoms such as pain or nausea, but can progress to drowsiness and coma. In ketoacidosis, as in diabetic coma, blood sugar is elevated. However, unlike diabetic coma, DKA is characterized by greatly excessive blood levels of ketones. Ketones, derived from the body's fatty acids, are acidic and lower the blood's pH. This upsets electrolyte balance and leads to various potentially serious complications. DKA can be treated with appropriate insulin, fluid, and other supportive measures.

- Hypoglycemic (insulin) shock comes from abnormally low plasma glucose, resulting from excessive insulin dosing, or (to a lesser degree) from oral hypoglycemics. Nervous system functioning requires adequate availability of glucose. Patients with low blood sugar may experience headache, irritability, and confusion. In severe cases, this may lead to coma. It is treatable with glucose (for example, from orange juice).

It is becoming increasingly clear that the earlier diabetes is diagnosed and appropriately treated, the better chance the patient will have to delay or prevent its complications. Estimates reflect that the typical patient with Type 2 Diabetes has actually had hyperglycemia for at least 5 years before the diagnosis is made, so it is imperative that efforts to reduce and control glucose levels be made as quickly as possible.

Risk factors

There are several risk factors that either directly cause diabetes or are statistically associated with it. The correlation of a risk factor(s) with development of diabetes is never 100%; usually multiple factors are involved. The greater the number of risk factors present in an individual, the greater the chance the individual will develop diabetes. However, it is important to note that just because a person has some or all of these risk factors, it does NOT mean he/she will develop diabetes. And conversely, some patients with diabetes do not have ANY of these risk factors.

The major risk factors for Type 2 Diabetes include intrinsic factors (factors that a person cannot change) and variable factors (factors that can be managed).[2]

Intrinsic factors include:

- **Family history:** If a person has a parent or sibling in his or her family who has diabetes, that person's risk of developing Type 2 Diabetes is increased by 40%.

16

- **Race or ethnic background:** The risk of developing Type 2 Diabetes is 2 to 3 times greater for non-Caucasian Americans.
- **Impaired Glucose Tolerance (IGT) diagnosis:** Those patients with a prior diagnosis of IGT have a greater risk of developing diabetes.
- **≥ Age 45:** The risk of developing diabetes increases progressively as one ages.
- **Diabetes during pregnancy (gestational diabetes):** Women who become diabetic during pregnancy are 40% more likely later to develop persisting Type 2 Diabetes.

Variable factors include:

- **Dyslipidemia:** Those with abnormal blood cholesterol or trigylceride levels (HDL), or "good" cholesterol levels under 35 mg/dl, and/or a triglyceride level of over 250 mg/dl, have a greater risk of developing Type 2 Diabetes.
- **Hypertension:** Those with high blood pressure have a 20% greater risk of developing Type 2 Diabetes.
- **Obesity (> 20% over ideal body weight):** Almost 90% of all people with newly diagnosed Type 2 Diabetes are overweight.[8] In one 20-year study looking at the effects of weight gain over the first 10 years of the incidence of diabetes, the excess incidence of diabetes in those who gained the most weight (over 20 kg) was less than 1 % per year more than those who did not have significant weight change. [Ford et al, *Am J Epidemiology*, 146:214-22, 1997.] Obesity increases insulin resistance and contributes to many health problems. Sometimes, losing just 10 pounds can help the body to use insulin better and help bring diabetes under control.
- **Sedentary lifestyle:** Those who exercise or perform some form of increased physical activity 3-4 times per week may decrease their risk of developing Type 2 Diabetes by 40%.

There are a number of other factors that may affect glucose control. For example, excessive alcohol use over a period of many years has been associated with increased risk of Type 2 Diabetes. Also, diets high in fat have been implicated, since those who eat foods high in cholesterol may develop dyslipidemia and increase the risk of developing Type 2 Diabetes. Also, though not as robustly associated with hyperglycemia as the other factors listed above, there is some evidence to suggest that hyperprolactinemia may be associated with elevated glucose levels.

These risk factors are not necessarily causal links, but over time, correlations between one or more of them to diabetes have been observed. For example, weight gain by itself may not contribute to diabetes, but a person who gains weight in the presence of other risk factors may be more likely to get diabetes. In this sense, risk factors help describe the environmental factors that most often work together to produce diabetes. It is prudent that a patient whose history is positive for one or more of these factors be evaluated for the development of diabetes symptoms and/or tested for this condition.

ZY 9370 326

17

HYPERGLYCEMIA, DIABETES, AND MENTALLY ILL PATIENTS

Now that we have outlined hyperglycemia and diabetes, we need to know how this affects us, our customers, and their patients. Interestingly enough, diabetes is common in patients with serious and persistent mental illness. Below we present data on this subject.

General population data

The number of patients with Type 2 Diabetes in the general population continues to increase at an alarming rate in the US and other developed countries. During the 1990s, the prevalence of Type 2 Diabetes increased by 33% overall, and by 70% among people in their 30s. Currently an estimated 16 million Americans (6 percent) have diabetes. As many as one third of the people with the disease, or about 5 million individuals, are undiagnosed.[9] Further, an additional 6.9% of the general population have fasting glucose levels that are above normal, but not high enough to be classified as diabetes.

Serious and Persistent Mental Illness (SPMI) patient data

The rates of Type 2 Diabetes have been reported to be more common in patients with major mood disorders and schizophrenia than the general population, although reasons for this phenomenon remain unclear.

> **Some studies even show that the rates of diabetes in patients with bipolar disorder or schizophrenia are 2-4 times greater than the general population.**[7,10-12]

Commonly, the onset of psychosis precedes the onset of diabetes, but usually the risk of diabetes is determined by factors other than those influencing age at onset and illness chronicity. Studies in the US found comparable rates of diabetes among patients with schizophrenia who were hospitalized or outpatients.[7] Mukherjee and colleagues (1996) had found that approximately one third of young patients with schizophrenia had a positive family history of Type 2 Diabetes.[7]

The relation between bipolar disorder and diabetes is less clear, but these patients seem to be affected in a similar way. As is the case for patients with schizophrenia, the cause of this relationship is unknown. However, Cassidy and colleagues suggest that possible reasons include: a genetic relationship between the disorders, an overlapping disturbance affecting similar regions of the brain, or the effect of psychotropic medications.[13]

Though increased risk is clear in this population, it is not yet clear whether this reflects a biological predisposition in schizophrenia or bipolar disorder or an individual or class effect of antipsychotic drugs. Quite possibly, it is due to a combination of factors.

ZY 9370 327

18

Ultimately, these analyses support the disproportionately high incidence and rate of hyperglycemia, IGT and diabetes in patients with schizophrenia, including those treated with placebo in clinical trials.

Antipsychotic-induced hyperglycemia/diabetes data

Several psychotropics have been associated with high insulin levels and insulin resistance (eg, chlorpromazine,[14] divalproex[15]). The National Diabetes Data Group listed chlorpromazine, haloperidol, and lithium under drugs that impair glucose tolerance.[7]

Your customers may already have heard the buzz surrounding recent reports suggesting a link between diabetes and clozapine treatment. These reports have stirred up a swarm of speculation suggesting that atypical antipsychotics as a class provoke increased glucose levels or incidence of diabetes at a greater rate than conventional antipsychotics.[16]

Today's clinicians may be unaware that speculation about a link to diabetes similarly implicated conventional antipsychotic drugs, especially phenothiazines, many years ago.

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.[16] Also, since obesity is a risk factor for diabetes; clinicians may be anticipating more hyperglycemia risk among patients with substantial weight gain during treatment.[17-19]

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.[16] In particular, of 15 case reports regarding treatment with ZYPREXA, 12 involved patients with a history of obesity.

One factor that may contribute to the higher number of case reports for patients on ZYPREXA as compared with risperidone or other agents could be that physicians may be more prone to monitor and/or report abnormalities on ZYPREXA due to preconceptions about effects on glucose.

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 unpublished (so far) work of Dr. Newcomer, who performed a retrospective study looking at hyperglycemia after an oral glucose load in patients on ZYPREXA, risperidone, haloperidol, and clozapine.

While provoking interesting medical research questions, the data has no practical application nor does it make concrete conclusions. Unfortunately, used and misrepresented by Janssen in a number of CME programs and physician programs, Newcomer's data is generating undue concerns and misinformation.

ZY 9370 328

19

The Newcomer study was restricted by a number of factors. First, the data are quite limited, 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, assignment to the different drugs was not randomized. Further, these data are not interpretable because of the methodology used to look at glucose levels: instead of a standard, 2-hour glucose test, Dr. Newcomer looked at values at 15, 45, and 75 minutes. Lastly, the glucose levels he used did not meet the criteria for diabetes.

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, which did not allow proper statistical evaluation (n=28). Like the Newcomer study, 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.

Clearly, more robust methodology must be employed to understand the relative incidence of hyperglycemia in patients treated with these various agents. For now, the best available data regarding ZYPREXA comes from Lilly's extensive clinical trial database.

Data from our clinical trial database

The main point of the new sell sheet is this:

> **Patients treated with ZYPREXA had rates of diabetes and hyperglycemia comparable to those in patients treated with risperidone and haloperidol in clinical trials.**

To demonstrate this, we included 2 graphs in the sell sheet that illustrate the incidence of diagnosed treatment-emergent diabetes in longer head-to-head schizophrenia trials. These are actual cases. The first graph depicts 3 pooled 1-year studies of ZYPREXA vs haloperidol, which includes the largest head-to-head study conducted between these two agents. The incidence of treatment-emergent diabetes for patients treated with ZYPREXA was less than 1%, 0.5% to be exact. This amounts to 5 patients out of 927 (mean ZYPREXA exposure = 8 months). The incidence for haloperidol was 0.4% (1 patient out of 261, with a mean haloperidol exposure of 7 months). These data demonstrate that both agents had comparable rates of diabetes.

The second graph depicts a 6-month study of ZYPREXA vs risperidone in patients with schizophrenia (ie, the Tran study), which again is the largest head-to-head study between these

ZY 9370 329

20

2 agents. The incidence of treatment-emergent diabetes was 0.6% for both. This corresponds to 1 patient treated with ZYPREXA out of 172 vs 1 risperidone patient out of 167 (mean exposure to ZYPREXA = 5 months and to risperidone = 4 months). Again, the important point here is that both agents had the same rate of diabetes.

Another way to help address physicians' concerns was to analyze what happened to the patients' random blood glucose levels on ZYPREXA and other agents. During the clinical trials, we saw a relatively small elevation in glucose, on the order of 3.2 mg/dl to 4.6 mg/dl for patients treated with ZYPREXA. [These elevations were examined using a "least squares mean" estimate, which corrects for baseline variable and dropouts.] To put this in perspective, the average random glucose level at baseline for patients treated with ZYPREXA in these trials was 95 mg/dl to 100 mg/dl. During market research, we found that most physicians were comfortable with this information, and recognized that these elevations in glucose levels were not clinically significant.

Now, we know that the average random blood glucose elevation with ZYPREXA was relatively small, but how did this compare to other agents? We found that there was a non-significant difference compared with risperidone (ZYPREXA was 1.5 mg/dl above haloperidol). The increase with ZYPREXA was 4.3 mg/dl **above** that on haloperidol and 10.1 mg/dl **below** that found with clozapine. Again, most physicians we spoke with during market research felt comfortable with the fact that indeed these agents are comparable. Some were even pleasantly surprised.

To determine the likelihood of a patient experiencing random blood glucose elevations, we looked at elevations above 4 different thresholds based on random blood glucose measurements—elevations above 126, 140, 160, and 200 mg/dl. The data show that there were comparable estimated rates of hyperglycemia across all treatments studied, with a total of 2850 patients included in the analysis. What this re-emphasized to physicians was that, regardless of the level of increase in blood glucose, all agents showed similar effects.

These data were positively received by most of the physicians we spoke with during market research. However, some brought up the fact that they associate weight gain with increased risk for hyperglycemia. Clearly, we must understand and be able to explain why ZYPREXA contributes to more weight gain than, for example, risperidone and haloperidol and yet rates of hyperglycemia are comparable.

What we are trying to communicate is this: in the context of these studies, substantial weight gain (>10% from baseline weight), was associated in most comparisons with some increase in risk of a glycemic event. However, the magnitude of this excess risk was consistently less than 1%, not enough to lead to clinically significant between-treatment differences in categorical risk. This likely reflects (a) weight gain did not occur exclusively within the ZYPREXA group; (b) even among those with substantial weight gain, the great majority did not have a glycemic event in the course of these observations; and (c) as there are many known (and probably unknown) factors beside weight impacting glucose regulation, glycemic events also occurred in the group without substantial weight increase.

ZY 9370 330

21

So, the majority of patients (79%) who did have an episode of hyperglycemia (random glucose elevations above 150mg/dl), did NOT experience substantial weight gain. Furthermore, of those patients who did experience substantial weight gain, over 95% had no glycemic abnormalities at all. So, while obesity is a risk factor for diabetes, differences in weight across the various treatment groups did not result in different rates of diabetes or hyperglycemia across these agents.

The dataset and analysis that we are presenting are far bigger than any other clinical trial on the topic. However, like all analyses, there are some limitations. Keep in mind that the clinical trial database was designed to study the efficacy of ZYPREXA for psychiatric disorders and NOT to look specifically at glycemic effects. Therefore, these studies did not require fasting blood samples (which probably would have been hard to obtain in long-term schizophrenia trials, even if we had so intended).

As discussed above, random plasma glucose is not the usual tool for diagnosing diabetes, and some elevations may be "false positives." The Lilly investigators dealt with this by defining cases by any of 3 criteria: elevation of 2 consecutive levels above the threshold; elevation of the last level above the threshold; or prescription of an antidiabetic medication. They also sought to characterize effects at a variety of thresholds. Of course, the higher the threshold the fewer the number of cases, and the lower the power to detect differences. For example, in the ZYPREXA-risperidone trial at the 200 threshold, there were just 2 cases on ZYPREXA and one on risperidone. There may or may not prove to be significant differences in risk of crossing glucose in extremely large databases. However, it is reassuring that there were not significant differences in this very large dataset, suggesting that it is unlikely an individual physician would observe a statistically or clinically significant difference in practice.

Finally, despite the fact that we cannot completely answer what happens to patients' glycemic levels over the long term (the maximum duration of these trials was 1 year), this analysis is based on a randomized data set that is bigger and longer than any other results available to date.

But what about Depakote and lithium?

We do not have longer term head-to-head data comparing hyperglycemia rates of ZYPREXA vs Depakote or lithium. However, there have been case reports of patients treated with Depakote who have experienced changes in glucose control, mainly as a factor of weight gain.[15] Likewise, lithium also has been associated with changes in glucose regulation, again, mainly as a factor of weight gain.[20] Lithium's effects on glucose metabolism have been reported as early as the late 1960s, with some studies finding increases in fasting glucose shortly after administration of lithium.[21]

In the three-week HGHQ study comparing ZYPREXA with Depakote, we did not see significant differences in glucose levels. Of course, one would not expect to see differences given the relatively short duration of the trial. Nevertheless, in Abbott's 12-week comparative study of ZYPREXA and Depakote, no significant difference in glucose levels was reported.
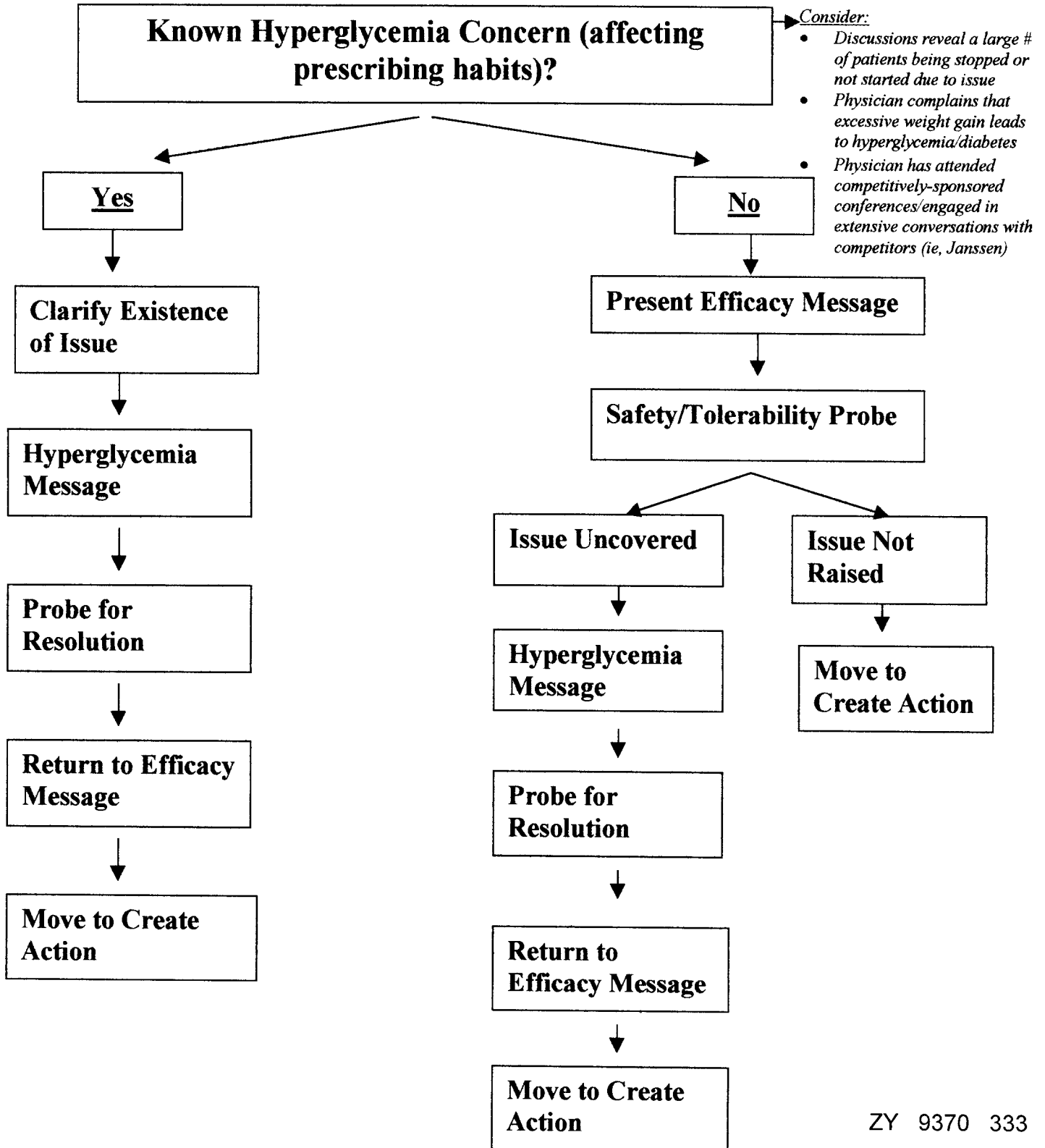
ZY 9370 331

We have given you a tremendous amount of information on diabetes and hyperglycemia, and the incidence of these two conditions with ZYPREXA and our major competitors. We hope that you will be able to take this information and use it in the manner that we will outline in the next sections of this Resource Guide.

ZY 9370 332

23

# MESSAGE ALGORITHM

When and High-level Implementation Hows

Known Hyperglycemia Concern (affecting prescribing habits)?

Consider:
- *Discussions reveal a large # of patients being stopped or not started due to issue*
- *Physician complains that excessive weight gain leads to hyperglycemia/diabetes*
- *Physician has attended competitively-sponsored conferences/engaged in extensive conversations with competitors (ie, Janssen)*

Yes

→ Clarify Existence of Issue

→ Hyperglycemia Message

→ Probe for Resolution

→ Return to Efficacy Message

→ Move to Create Action

No

→ Present Efficacy Message

→ Safety/Tolerability Probe

→ **Issue Uncovered**

→ Hyperglycemia Message

→ Probe for Resolution

→ Return to Efficacy Message

→ Move to Create Action

→ **Issue Not Raised**

→ Move to Create Action

ZY 9370 333

24

Zyprexa MDL Plaintiffs' Exhibit No.04202

MESSAGE SCRIPT

First, clarify the objection:

Doctor, help me understand your concern. Also, please help me understand the basis for your concern. If we can effectively address this concern, can I share some new information with you on the largest head-to-head study ever done between two mood stabilizers? ... or some new information about how ZYPREXA offers patients a better chance to achieve REINTEGRATION and stay there?

High Ground Opener

I understand that this is a potentially concerning issue, and there is certainly a lot of noise from pharmaceutical firms on this issue. This question deserves some dialog and to have large/controlled data to be brought to bear. Lilly wants to continue to be forthcoming in addressing this topic. This new information I have today is important in that it comes from the large, randomized, double-blind, controlled data within Lilly's clinical database.

There are two main points that I want you to walk away with. The first is that in this head-to-head data, incidence of diagnosed treatment-emergent diabetes was comparable between ZYPREXA and risperidone and also between ZYPREXA and haloperidol. The second point I want you to walk away with is that incidence of increased random blood glucose is also comparable across these 3 treatment groups. Let's take a closer look at this information.
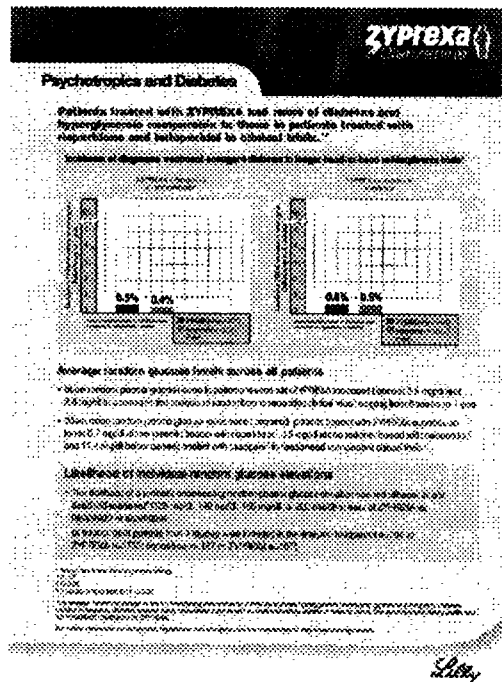
Core Message

The first graph is from 3 year-long studies of ZYPREXA vs haloperidol with over 2,000 patients, which includes, in fact, the largest head-to-head study ever done between these two agents. The incidence of treatment-emergent diabetes, that is, diabetes diagnosed during the clinical trial, was less than 1% for each agent. Notice that the same holds true in a six-month study comparing ZYPREXA to risperidone, which, again, was the largest head-to-head study between these two agents. In this case, the incidence of treatment-emergent diabetes was 0.6% for both ZYPREXA and risperidone.

PROBE: *Are you surprised by this? Any comments or questions?* (wait for the answer)

Another way to look at this is to compare what happened to the patients' random blood glucose levels on ZYPREXA with these other treatments. On ZYPREXA, across all patients, we see a relatively small elevation in glucose, on the order of 3.2 mg/dl to 4.6 mg/dl. To put this in perspective, the average random glucose level at baseline for patients treated with ZYPREXA in these trials was 95 mg/dl to 100 mg/dl.

PROBE: *Do you consider this to be clinically significant?*

*When looking at how this small increase might compare with changes seen on other agents, we found that changes on ZYPREXA were very similar to changes on risperidone (a difference of >2mg/dl). Also, the small increase of ZYPREXA was 4.3 mg/dl **above** that on haloperidol, and it was 10.1 mg/dl **below** that on clozapine.*

We found comparable rates of diabetes, and saw some small increases in average random glucose levels. We delved deeper into the relative rates of hyperglycemia between these agents. To do this, we looked at the likelihood of blood glucose elevations above four different thresholds based on random blood glucose measurements—elevations above 126, 140, 160, and 200 mg/dl. What the data shows is that across treatment groups, there were again comparable rates of hyperglycemia at each of these thresholds.

PROBE: *Do you find this surprising? Or comforting? How does this data effect the way you think about this issue?* (wait for answer)

IF THIS ADDRESSES THE MD's QUESTIONS, collect the chip for a concern answered and get back to a sense of joint discovery with the efficacy-oriented discussion.

If physician still has concerns based on weight gain, (ie, "but ZYPREXA has more weight gain, and I know weight gain can cause diabetes") then continue on.

ZY 9370 335

26

Considering the contributing factors to incidence of diabetes, we ought to look at the general population as a baseline. In the general population, the incidence of diabetes or abnormally elevated blood glucose is about 15%. Now, other studies show that with the persistently mentally ill population that you deal with, that rate may be anywhere from 2 to 4 times higher. So, in your practice, you should not be surprised to find patients who are having elevations in blood glucose regardless of choice of agent. Clearly, while there are comparable rates of diabetes and hyperglycemia in patients taking these various medications, Lilly does not want to minimize the extent or seriousness of this common illness.

Now, there are a lot of factors, independent of treatment choice, that affect risk of diabetes. There are a number of intrinsic factors such as family history, age, and ethnic background. Other factors that may be more controllable by a patient include exercise, diet, and obesity. Also, excessive alcohol use, hyperprolactinemia, and diets high in lipids have been implicated in higher levels of blood glucose. Clearly, this is not as simple as saying the presence of one factor means a patient will get diabetes. In fact, you may have patients who have all of these risk factors and do not develop diabetes, and conversely you may have patients diagnosed with diabetes who have none of these risk factors.

PROBE: *Any questions? What are your thoughts? How does this information, in the context of the overall efficacy of ZYPREXA, impact your selection of a mood stabilizer?* (Wait for answer.)

(If needed—eg, the physician is looking for an explanation of how ZYPREXA can have more weight gain and yet have comparable rates of diabetes/hyperglycemia)

ZY 9370 336

27

Clearly, obesity is a risk factor for diabetes, but it is one of many that may increase a patient's risk for diabetes. The majority of patients—in fact about 79%—who did have an episode of hyperglycemia, did NOT experience substantial weight gain in our clinical studies. Furthermore, of those patients who did experience substantial weight gain, over 95% had no glycemic abnormalities at all.

So while obesity is a risk factor for diabetes, differences in weight gain across the various treatment groups did not result in different rates of diabetes or hyperglycemia across these agents. In fact, large controlled data demonstrate that rates of diabetes and hyperglycemia are comparable across these agents.

[handwritten: weight gain tie-in]

Frame in terms of efficacy, GET BACK TO JOINT DISCOVERY!

Does this information I have provided address your concern?

If "Yes"-- Doctor, we have just talked about how your choices are comparable in one respect. Now, let me show you how ZYPREXA stands alone in its broad-spectrum efficacy. (Get back to selling)

If "No"—Probe deeper to expose where concern still exists.

ZY 9370 337

28

Q & A

During your sales calls, you may encounter other kinds of questions surrounding hyperglycemia and/or diabetes. Use the verbatims below as answers, then, as always, refocus on your Selling Message.

How can you be comparable in rates of hyperglycemia to other agents when you cause more weight gain, and significant weight gain is a risk factor for diabetes?

In fact, we have examined Lilly's large database of prospectively, randomly assigned patients in longer-term trials. In these trials, weight gain was not found exclusively on ZYPREXA treated patients, although it is no doubt more common in ZYPREXA treated patients.

Clearly, obesity is a risk factor for diabetes, but it is one of many that may increase a patient's risk for diabetes. The majority of patients—in fact about 79%—who did have an episode of hyperglycemia, defined as random glucose levels above 160 mg/dl, did NOT experience substantial weight gain (defined as an increase of 10% or more from baseline).

Furthermore, of those patients who did experience substantial weight gain, over 95% had no glycemic abnormalities at all (again, defined as random glucose levels above 160 mg/dl).

So while obesity is a risk factor for diabetes, differences in weight gain across the various therapies in our head-to-head database did not result in different rates of diabetes or hyperglycemia.

How do you explain the Newcomer data?

The data from the Newcomer study raise a question pertaining to relative impact of the various agents on hyperglycemia. It is not consistent with other data presented in the work described here. When reviewing the study, several limitations became apparent:

- It was a retrospective study designed to look at cognition, not hyperglycemia.
- The study was grossly underpowered (about 8 patients in each group).
- The original study was not controlled—there was no distinction made due to intrinsic risk factors (family history, gender, etc.), nor was the patients' behavior monitored (diet, exercise, etc.). Most importantly, assignment to the different drugs was not random.
- These findings are not readily interpretable because standard 2-hour glucose levels were not taken. You cannot rely on glucose levels taken before 90 minutes (Dr. Newcomer took levels at 15, 45, and 75 minutes).
- The glucose levels in the study (even with all other limitations) do not meet the criteria for diabetes.

ZY 9370 338

29

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 cannot be impacted by lifestyle or any agent (such as genetic risk, age, gender, etc.). In terms of the variable factors like prolactin, ZYPREXA does not appear to have an effect that might increase the risk of diabetes. In addition, we have not seen any effects of ZYPREXA on other factors such as hypertension or dyslipidemia. Regarding various lifestyle factors (lack of exercise, excessive alcohol intake, etc.), these factors may improve to the degree that a patient experiences efficacy from ZYPREXA, potentially improving their risk profile.

What does Lilly's database say about the rates of diabetes with other agents (such as Seroquel, Depakote, Clozaril, or Zeldox)?

- The one other large head-to-head, long-term database we have beyond risperidone and haloperidol is versus clozapine. Those data demonstrate that ZYPREXA is much safer in this respect vs clozapine.
- In terms of other mood stabilizers, although the HGHQ head-to-head data vs Depakote has the limitation of being relatively short-term, there was no significant difference in changes in average random glucose levels and none of the 251 patients on either drug developed, treatment-emergent hyperglycemia or diabetes.
- In addition, we know from case reports that hyperglycemia and/or diabetes has been reported with virtually all psychotropics (including lithium, quetiapine, risperidone, and clozapine).
- Lastly, it is too early to tell what the true efficacy or side effect profile of ziprasidone may be.

I know that the structure of ZYPREXA is close to that of clozapine. How it is that clozapine has this problem and ZYPREXA does not?

- It is correct that the two compounds are structurally similar. ZYPREXA was derived from clozapine, but with changes in the molecule which were specifically designed to preserve efficacy and remove toxicity.
- In regards to hyperglycemia, as with agranulocytosis, it looks like the changes worked.

Is there a direct effect of ZYPREXA on diabetes?

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

ZY 9370 339

30

ZY1 00625586

- 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 versus comparator drugs in clinical studies. If there was a direct 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.

- We are continuing to investigate these questions quite carefully.

Does ZYPREXA cause Type 1 Diabetes?

We do know that there are patients, independent of the agent they are on (or they may not be on any agent at all) who develop insulin-dependent diabetes. Since diabetes will develop in the general population, the specific question relates to whether ZYPREXA patients develop insulin-dependent diabetes at a rate higher than the general population. In our controlled comparative clinical trials, rates of developing Type 1 Diabetes are not higher on ZYPREXA than on haloperidol or risperidone. We have gone back to our longer-term preclinical animal studies and have not found any changes to insulin release or changes to the pancreas.

How is this different from what you were telling me over the last few months?

It is consistent with what we've been saying. What we're telling you about rates on ZYPREXA has not changed at all. What we have done is expand our analyses comparing rates on ZYPREXA to other antipsychotics, which may be more clinically relevant to you. This new data presents the finding of these various analyses, which conclude that the rates of developing diabetes or hyperglycemia are comparable across agents.

Why do I need to monitor blood when you tell me that no blood monitoring is required with ZYPREXA?

The fact is, you do not have to conduct routine blood monitoring of patients on ZYPREXA. The data suggest that if the right factors are present, hyperglycemia can happen with a patient. Accordingly, just like any other concerns you may have relative to a specific patient, regardless of what agent they're taking, you may need to look further. Fortunately, that's likely to be only a relatively small fraction of patients who are taking ZYPREXA and a number comparable to that found with other agents as well.

ZY 9370 340

31

How does ZYPREXA affect a person who has diabetes? Glucose intolerance?

As with adding any new medication to the regimen of a patient who has hyperglycemia or diabetes, you may want to check to see what effects the medication may have.

The controlled comparisons that showed comparable rates for blood glucose elevations excluded patients with pre-existing diabetes. Lilly is currently conducting analyses of patients with diabetes in clinical trials.

Which patients should I be concerned about?

As you begin to treat any patient, the assessment of their general health is a standard and important step. The risk of hyperglycemia and diabetes are two factors within each patient's scope of overall health that should be considered (along with mental health, lifestyle, etc.). Specific to hyperglycemia and irrespective of disease state and agent used, there may be some people who are inherently at a higher risk relative to other people. They are as follows:

- Clearly, the group of Pima Indians within your practice deserve some special attention since we all know that their risk of developing hyperglycemia is far higher than that of the general (and mental health) population
- Patients who have a number of risk factors (intrinsic and variable)
- Patients who have poor glucose control to begin with
- Patients with extreme weight gain (regardless of source)

32

MATERIALS AVAILABLE

In addition to the Hyperglycemia Sell Sheet, you may find these other resources helpful when addressing this question with your physicians.

Enduring Materials:

November 2000 Psychlink
January 2001 Provision

Educational Resources:

NTTP educational resources related to healthy lifestyles
Local partners trained in delivering the message of NTTP

Websites:

www.diabetes.org (official website of the ADA)
www.lillydiabetes.com (Lilly-sponsored website on diabetes)

ZY 9370 342

33

REFERENCES FOR SCIENTIFIC BACKGROUND

1. Harrison's Principles of Internal Medicine. Vol 13; p 1988. To come.

2. American Diabetes Association. Screening for type 2 diabetes. *Diabetes Care*. 2000;23: (suppl 1).

3. National Institute of Diabetes and Digestive and Kidney Diseases. Hypoglycemia. http.www.niddk.nih.gov/health/diabetes/pubs/hypo/hypo.html. Accessed 1/17/01.

4. Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H: Coronary heart disease risk and impaired glucose tolerance: the Whitehall Study. *Lancet* 1980;1373-1376.

5. Diabetes care module. Instruction module. Eli Lilly and Company. March 1999.

6. Harris MI. Classification, diagnostic criteria, and screening for diabetes. IN: to come.

7. Mukherjee S, Decina P, Bocola V, Saraceni F, Scapicchio. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry*. 1996;37:68-72.

8. American Diabetes Association. Weight loss—think thin: how you may eat may be just as important as what you eat. http.www.diabetes.org/ada/c40g/asp. Accessed 1/16/01.

9. Harris MI, Hadden WC, Knowler WC, Bennett PH: Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in the U.S. population aged 20-74 yrs. *Diabetes*. 1987;36:523-534.

10. Keskiner A, Toumi AE, Bousquet T. Psychotropic drugs, diabetes, and chronic mental patients. *Psychosomatics*. 1973;16:176-181.

11. McKee HA, D'Arcy PFD, Wilson PJK. Diabetes and schizophrenia: a preliminary study. *J Clin Hosp Pharmacy*. 1986;11:297-299.

12. Mukherjee S. High prevalence of type II diabetes in schizophrenic patients. *Schizoph Res*. 1995;15:195 (abstr).

13. Cassidy F, Ahearn E, Carroll, BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. *Am J Psychiatry*. 1999;156:1417-1420.

14. Erle G, Basso M, Federspil G, et al. Effect of chlorpromazine on blood glucose and plasma insulin in man. Eur *J Clin Pharmacol*. 1977;11:15-18.

15. Isojarvi JI, Laatikainen TJ, Knip M et al. Obesity and endocrine disorders in women taking valproate for epilepsy. *Ann Neurol*. 1996; 39:579-584.

ZY 9370 343

16. Beasley CM, Kwong K, Berg PH, Taylor CC, Dananberg J, Brier A. Incidence and rate of treatment-emergent potential impaired glucose tolerance (IGT) and potential diabetes with olanzapine compared to other antipsychotic agents and placebo. ACNP Poster.

17. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. *Am J Epidemiology*. 1997;146:214-222.

18. Colditz GA, Willet WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Int Med*. 1995;122:481-486.

19. Chan JM, Rimm EB, Colditz FA, Stampfer MG, Willet WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care*. 1994;17:961-969.

20. Garland EJ, Remick RA, Zis AP. Weight gain with antidepressants and lithium. *J Clin Psychopharmacol*.1988; 8:323-330.

21. Mellerup ET, Dam H, Wildschiodtz G, Rafaelsen OJ. Diurnal variation of blood glucose during lithium treatment. *J Affective Dis*. 1983;5:341-347.

ZY 9370 344

35