

**HYPERGLYCEMIA/DIABETES
DATA ON DEMAND
RESOURCE GUIDE
September 2001**

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INTRODUCTION

Since the rollout of our Hyperglycemia/Diabetes Sell Sheet, we have heard from the field that you would like more data. We heard you loud and clear, and we are excited about the new and improved Hyperglycemia/Diabetes Sell Sheet! While the original sell sheet laid the groundwork to overcome these objections, you now have additional data from Janssen and Pfizer to support your message as well. Our primary focus, as always, is on the outstanding efficacy of ZYPREXA. To patients, family members, and the treatment team, this is the most important feature of an antipsychotic or mood stabilizer.

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. Our competitors have invested a lot of time and money preparing their representatives to speak intelligently about these disease states. Pfizer, for example, has trained its representatives on diabetes to the same extent that we have trained on bipolar mania or schizophrenia. Therefore, it is critical that we, too, have a thorough understanding of diabetes and hyperglycemia so that we can meet competitive challenges. By increasing your knowledge of these issues, you can more effectively and efficiently handle objections and get back to selling the outstanding efficacy story of ZYPREXA.

Market Overview

Market research has shown that ALL of our competitors are talking about a supposed link between hyperglycemia/diabetes and ZYPREXA. This is one of the biggest issues we face in the marketplace. The exciting thing is that we have more data than ever to back up our story of “comparable rates of hyperglycemia and diabetes across psychotropic agents.” It is critical to our success that we share this information with physicians. In October 2000, 60% of physicians 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 physicians surveyed. You can see that in a short period of time, perceptions can change dramatically. This tells us that although many customers do not voice a hyperglycemia or diabetes objection, the objection exists to some extent for virtually every one of them. It tells us also that although an objection may not exist today, it can arise tomorrow if we are not diligently probing to uncover customer needs.

The principle of active probing is important as you prepare to implement the new hyperglycemia/diabetes pieces. We’ve used the Hyperglycemia Sell Sheet for over six months, yet our customers have little recall of the data. Perhaps we were not delivering the material confidently enough in the past, didn’t have enough data, were being drowned out by the competition, or simply haven’t delivered the message enough times to enough key customers to make an impact in the market. We now have substantial new data that shows the same conclusion... comparable rates of hyperglycemia/diabetes among all agents. We must deliver this message with more confidence to more customers than ever before. We must also remember that repetition with each of those customers is key for message recall.

As stated earlier, 100% of physicians in our market research link hyperglycemia/diabetes to ZYPREXA. Therefore, you should feel a sense of urgency in sharing the "comparable rates" story with your customers. There is also an increase in physicians who link hyperglycemia and diabetes to Risperdal (26%) and Depakote (34%). However, by and large, the association is perceived to be stronger with ZYPREXA than with any of our competitors. Psychiatrists report that 25% of their patients are not given ZYPREXA due to the physician's concern over hyperglycemia and diabetes. Psychiatrists have also said that they discontinue ZYPREXA about 16% of the time due to existing hyperglycemia or diabetes, or fear of hyperglycemia or diabetes. Because of this objection, we are losing 25% of potential ZYPREXA patients up-front before a trial is even considered, and losing another 16% of refills. Taken together, this means that 40% of your business is being adversely affected! It is imperative that physicians feel that Lilly is adequately addressing their concerns and that they internalize the comparable rates message. This strategy presents a great opportunity for you in that neutralizing the hyperglycemia issue with just a few key customers could result in a dramatic growth in prescriptions, and ultimately big premier rewards for you!

Diabetes is scary for most psychiatrists, in part because they do not deal with it on a daily basis and therefore fear the unknown. Risk factors, diagnostic criteria and treatment standards are not fresh in psychiatrists' minds, and they are fearful of "causing" a disease that can lead to permanent complications. These doctors have dealt regularly with potentially severe side effects such as tardive dyskinesia for many years. However, diabetes and hyperglycemia as side-effect risks are relatively new on the horizon. Because of this, psychiatrists are generally less comfortable diagnosing and treating these conditions and are actively looking for more information. You are in a position to provide it to them! In recent market research, most physicians admitted that they have seen no really credible data on hyperglycemia or diabetes. The good news is that you DO have credible, large-scale studies to support the comparable rates message. You can be confident that you have the best set of data on hyperglycemia and diabetes over your competitors.

Situation Overview

Janssen, Abbot, and Pfizer have been hitting ZYPREXA hard on weight gain and hyperglycemia/diabetes. Now they are attacking on a myriad of additional concerns, such as cardiovascular disease and lipids. At the APA this 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. Nor do studies establish a 1:1 correlation between weight gain with ZYPREXA and hyperglycemia or diabetes. A patient taking ZYPREXA or any other psychotropic agent can experience any of these effects by itself or in combination—weight gain does not automatically lead to diabetes, and hyperglycemia can develop in the absence of weight gain.

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So that you and your customers can continue to have confidence in ZYPREXA's superiority over the competition, we continue to seek out information on the following topics:

- ZYPREXA's efficacy and dependability as an advantage over other agents.
- Data on weight gain and weight management, including valuable resources to help physicians and their patients effectively manage weight.
- Additional data that supports our position of comparable rates of diabetes and hyperglycemia across psychotropic agents.
- Data explaining why gaining weight does not necessarily lead to hyperglycemia or diabetes.
- More information on lipids, especially cholesterol, in order to counteract these objections as needed.

In this backgrounder, we will discuss diabetes/hyperglycemia and consider weight gain as it relates to the risk of these conditions. We now have more resources than ever for you to utilize in combating these objections, including the new Hyperglycemia Sell Sheet, Study Comparison Insert, and updated medical letters (available upon physician request). In addition, an unprecedented number of DTP activities are being conducted on this issue. Knowledge Management continues to be a good source of data for your review so that you remain current on recent developments, whether it's a new medical letter that has been posted or a rebuttal to a competitor study. As always, we welcome your comments and suggestions for additional materials and aids.

With all the competitive noise out there, how can we win in the marketplace? First, let us congratulate you for a job well done. Despite an increasing number of competitors, you ARE winning in the marketplace. As of July 2001, ZYPREXA sales are up 39% over the same period in 2000. Perhaps even more impressive is our performance above plan: almost 28 million dollars so far this year (also July data)! Remember—this plan was aggressive to begin with! Because of your efforts, customers do see an efficacy advantage with ZYPREXA that is leading them to write more ZYPREXA prescriptions than ever before, ultimately restoring hope to millions of patients.

Despite our success, what can we do differently to more effectively address the hyperglycemia/diabetes issue? First and foremost, in an increasingly competitive and noisy market, **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. It is important to admit that hyperglycemia and diabetes do happen in patients taking psychotropic drugs. Physicians are seeing patients who have hyperglycemia or diabetes, and they want credible data on the risks associated with psychotropic agents.

Because of these concerns, some physicians feel the risks of ZYPREXA are greater than the benefits. Our goal is to neutralize the hyperglycemia/diabetes issue, help physicians manage weight gain, and continue to sell ZYPREXA's unparalleled efficacy and

dependability. This message should allow us to tip the risk/benefits scale to the benefit side so that most physicians will agree that the many benefits of ZYPREXA are greater than any potential risks.

What do we mean by “neutralizing” physicians’ concerns about hyperglycemia and how do we go about this? By neutralizing we mean leveling the playing field, setting the record straight with the “comparable rates” message. In order to be successful we must do the following:

- Admit up front that ZYPREXA, **like all agents**, can cause weight gain and increases in blood glucose levels. Be forthcoming. If a physician has a concern, don’t hesitate to address it; then get back to selling.
- Admit that ZYPREXA can cause more weight gain than some other antipsychotics. Continue to provide resources for managing weight. To ease doctors’ concerns, show data that indicates there is not a 1:1 correlation between weight gain and diabetes.
- Always handle objections in the context of the efficacy message, or in terms of risks/benefits. You now have a new “risk/benefits” tool in your Hyperglycemia Sell Sheet to help you do this (see “What’s New”).
- Be patient focused. Doctors treat patients, not just diseases.
- Make sure you truly understand their concern. Be sure to probe on both hyperglycemia/diabetes and weight gain to understand how the customer perceives each issue as it relates or lacks relationship to the other.

Other points to consider when assessing your own tone with physicians on this issue:

- Are you setting the record straight on hyperglycemia and diabetes without sounding defensive or bashing the competition?
- Do you sound confident, calm and relaxed?
- Does your body language match your spoken words? Is your posture open and confident, or closed and defensive? Do you look attentive? Are you making eye contact?
- Are you dialoguing with the physician or simply data-dumping?
- Are you using active listening skills and the appropriate probes to really understand your customer so that he or she feels heard?

Although you may have dealt with competitive attacks on diabetes and hyperglycemia, you must not be overly confident that you have “handled” the issue. You should consistently probe your physicians in every call, even those customers who have not voiced concerns in the past. Remember, many physicians do not proactively bring up the diabetes issue because of discomfort with the science around the disease state, fear of conflict with the rep, lack of time etc. Additionally, some doctors voice a weight gain concern that really encompasses a concern with hyperglycemia and diabetes as well...even if they haven’t spoken those words. As stated earlier, despite our efforts, physicians are more concerned about this issue than they were six months ago. Market research indicates that 100% of psychiatrists now link ZYPREXA either directly or indirectly with hyperglycemia/diabetes. With numbers like that, this issue will not go away overnight.

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However, we can neutralize the issue and sell more ZYPREXA in two ways:

- (1) by continuing to share that ZYPREXA offers patients a better chance to achieve reintegration and stay there, and that ZYPREXA is the most dependable mood stabilizer on the market, and
- (2) by proactively and effectively handling customers' concerns with confidence, a winning tone, and the most credible data available.

STRATEGY OVERVIEW

In essence, our strategy is to set the record straight regarding the incidence of hyperglycemia associated with antipsychotic medications. As stated earlier, we want to neutralize the hyperglycemia/diabetes issue so that more physicians see the benefits of ZYPREXA as outweighing the potential risks for most patients. If we can frame prescribing decisions in the context of risks/benefits, the physician is more likely to choose a medication based on the entire package rather than a single side effect. We know from market research that when physicians consider ZYPREXA in terms of risks/benefits, they do see an efficacy advantage for ZYPREXA! With this strategy in mind, our key message points are as follows:

- Patients treated with ZYPREXA, risperidone, haloperidol, divalproex and ziprasidone in clinical trials 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, there is not a 1:1 correlation associated with weight gain and diabetes. Obesity can happen independently of diabetes, and diabetes can happen independently of weight gain.
- Diabetes is common in the general adult population and is even more common in severe psychiatric patients.
- A number of factors affect risk for diabetes, including intrinsic factors such as family history and variables including 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.

This strategy is based on a number of points:

- An increasing understanding of our customers' perceptions of ZYPREXA and of Lilly.
- An understanding of past, current and probable future market issues, such as how the marketplace has perceived our handling of concerns like weight gain, hyperglycemia and diabetes.
- A wealth of data that can help us understand the truth about ZYPREXA and other psychotropics in regard to hyperglycemia and diabetes; and
- An understanding of the patients our physicians are treating.

Key Action Statement:

- **Fear of diabetes is not a reason to avoid starting a patient on ZYPREXA.**

What's New

What's new about the hyperglycemia message? Although we have new data points and additional tools to help you sell, the message itself isn't new. **This data enhances and remains consistent with our previous materials.** However, we are asking you to do some things differently, as follows:

- (1) Provide additional data to almost all physicians to reinforce the comparable rates message (even when they do not voice a concern),
- (2) Use the Hyperglycemia Sell Sheet up front for physicians who have voiced a hyperglycemia/diabetes objection. Use it from the side-effect page for those physicians who do not voice a concern.
- (3) Place more emphasis on handling the issue of weight gain and its association with hyperglycemia/diabetes (point #2), and
- (4) Consistently monitor your tone with physicians so that this new data comes across as credible, nondefensive, and adding value to their practice

Let's take a look at the new data sets and tools.

First, you may have noticed that the key message points have now been numbered. This is to help you deliver the key points quickly, increase your recall of the key points, and (most importantly) increase the physician's recall of the data.

On the first page, the top graph is essentially the same as before, with one exception: the Depakote data from the HQ extension has been added so that the physician now has comparative information with another mood stabilizer as well as antipsychotics. The second graph measuring baseline-to-endpoint changes in blood glucose presents information from a bulleted point in the previous detail aid, with the addition of the Pfizer study. We put this data in graph form to better highlight the information, especially the fact 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, "comparable rates" across the agents. By some standards, the Pfizer study even used a superior measure of elevated glucose elevations (fasting), and their results reinforced Lilly's findings.

The third graph measuring individual patients' likelihood of experiencing random glucose elevations was also derived from a bulleted point in the previous hyperglycemia piece. Putting this information in graph form illustrates for the physician the thresholds that were used to determine normal plasma glucose, elevated plasma glucose, and

diabetes. Again, the likelihood of a patient's exceeding any threshold (being an "outlier") was comparable with ZYPREXA, haloperidol and risperidone.

The weight gain information (point #2 on the new detail aid) is the same information as in the previous sell sheet. What's new is the placement of the material and illustration of the data in pie charts rather than bulleted form. You may recall that in the previous sales aid, the weight gain information was the last point on the back page. We have moved the data to point #2 to give it more airtime with physicians and to address the association between weight gain and hyperglycemia/diabetes earlier in the detail. Many physicians think there is a logical link between weight gain and diabetes. We see in market research 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. It is imperative that we ask the right questions of physicians to make sure we fully understand their issues. Do they link weight gain to diabetes? Does the issue affect which patients they will prescribe ZYPREXA for? (See "Open Probes" section for additional suggestions.)

Points #3 and #4 are exactly the same as in the previous piece. However, on the back page of the new piece we have developed a "risks/benefits" tool to use with customers. Physicians typically think in terms of benefits and risks to their patients when prescribing a medication. Therefore, when used correctly, this tool will assist you in helping the physician look at the entire package ZYPREXA offers, rather than making prescribing decisions based on side effects only. Additionally, it should help you transition back into the core Bipolar or Schizophrenia detail aid and get back to selling!

If time is an issue, the risks/benefits tool will allow you to summarize the benefits of ZYPREXA (chips gained from the physician), get commitment from the physician that in most cases the benefits outweigh the risks, and close on a positive point without having to return to the core detail aid. If you are able to successfully neutralize the hyperglycemia/diabetes issue with your customer, he or she is likely to agree that the benefits of ZYPREXA are greater than the potential risks. How and when should this new tool be used? We have found that when the risks/benefit construct is stated up front in the HGO and discussed throughout the message, there is greater likelihood of getting the physician to think in those terms.

Last, the Study Comparison Insert is a new tool for your toughest customers. It is a comparison chart that includes 2 Lilly-sponsored studies and 2 Janssen-sponsored studies comparing the incidence of diabetes and hazard ratios between ZYPREXA, quetiapine, risperidone, haloperidol and other typical antipsychotics. We will discuss the specifics of these studies in the "Scientific Background" portion of this resource guide. You should think of the Hyperglycemia Sell Sheet as a proactive message and the insert piece as additional data on demand for the tough customer. It should be used with the following customers:

- Those who are not sold on the "comparable rates" message after seeing the hyperglycemia sell sheet
- Those who need to see larger studies (the insert covers over 100,000 patients!)

- Those customers who are skeptical of company sponsored data (or Lilly specific data) and who would benefit from seeing data sponsored by the competition
- Those who just need more information

The back page is the actual selling surface, and can be used alone in most cases. Use the methodology section only to address specific questions about the data. After viewing the comparative chart on the back page, most physicians came to the “comparable rates” conclusion themselves. If a customer asks for additional information, request the medical letter on this issue (it covers all the data in the evolved hyperglycemia piece and the insert) and get back to selling. Remember, although the insert tested well in market research, physicians more often drew the conclusion of “comparable rates” from the core detail piece and the insert combined.

Targeting

It will be essential for you to find out where each customer stands on the hyperglycemia/diabetes issue. This will require creating a dialogue to get to the heart of the individual’s concerns. Once you have identified the customer’s specific concern and their level of concern, you will be able to craft the way you deliver this message. Remember, it is critical that we share this message with almost ALL of our physicians. However, its exact position in the detail will depend on what the physician currently believes about the issue. If you determine that a physician has serious concerns that are affecting his or her prescribing, lead with the hyperglycemia sell sheet (*not all physicians.*)

For physicians who have a general concern, or who do not verbalize a concern, **cover efficacy first**. Then, make sure you use the Hyperglycemia Sell Sheet during the side effect profile section (specifically weight gain) of the Melvin message and the Zy 3 section of the Bipolar message to handle any objections the physician may have either directly or indirectly linking hyperglycemia/diabetes to weight gain.

For physicians who offer objections after you have shown the main hyperglycemia piece, you will use the Study Comparison Insert. Again, these physicians will include those who have not bought in to the message of comparable rates, those who complain that the studies are small, and those who say, "These are all Lilly studies." (See “Message Algorithm.”)

It is imperative that you have open and candid dialogue with your physicians on hyperglycemia and diabetes. Dialogue and the right questions are key to meeting their needs. However, you may be wondering *how* to uncover a physician’s concerns. What are the right words to wrap around a question? What is the right tone? How do you ask the physician about these issues without sounding defensive or aggressive? For some possible answers to these questions, we’ve included a “Suggested Open Probes” section. These probes are not required verbatims for every call, nor are they magic bullets. It’s up

to you to improvise and add your own words and style, while leveraging your relationship and knowledge of the customer.

Suggested Open Probes

You can use the following open-ended probes to help create a dialogue with your customers:

- Doctor, in the context of treating patients, what does the risk of hyperglycemia and diabetes mean to you?
- What does this concern over diabetes mean to your patients?
- How does this concern affect the ways you might use ZYPREXA?
- How important is the risk of hyperglycemia in selecting a medication?
- Doctor, what challenges do you face in managing side effects with your patients? Do these challenges affect the choices you make to treat these patients?
- What questions have other companies created regarding ZYPREXA that I need to address today?
- You have agreed that the efficacy of ZYPREXA is an advantage; what are the challenges you have in using ZYPREXA with your patients?
- Doctor, there has been a lot of noise around hyperglycemia and diabetes associated with psychotropic medications; what are your thoughts on the issue?
- Can you help me better understand your concern?
- How do you feel about the risk to your patients of developing diabetes on ZYPREXA compared to other agents?
- When choosing an agent you must look at risks/benefits. What benefits do you feel ZYPREXA brings to your patients?
- Now that I've shown you this data, how comfortable do you feel with a patient's risk of developing diabetes on ZYPREXA vs. other agents?
- Does this data change the way you view weight gain and hyperglycemia or diabetes?
- Are there any specific types of patients for whom your concerns about hyperglycemia or diabetes would make you reach for another product? What product would you reach for and why?

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Market Research

We have had the opportunity to test the new sell sheet with a number of our key customers. We learned that physicians had a very consistent takeaway of the key message points. Also, the message appears to be generally believable. This does not mean 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 and sometimes even in neutralizing the issue.

The key takeaways from market research are as follows:

- The Hyperglycemia Sell Sheet worked best when used after an efficacy discussion followed by the side effect page of the Bipolar or Schizophrenia detail piece. The side effect page was a good transition into the risks/benefit discussion and then to the Hyperglycemia Sell Sheet.
- **The right tone and implementation are critical to the overall impact of the new data on our customers.** When the proper tone was used, the message was credible, non-offensive, non-bashing, and perceived as providing important information. When the wrong tone was used, it was described as “defensive,” “overdoing it,” “salesy” and “denying” (that ZYPREXA causes weight gain or hyperglycemia/diabetes).
- For tough customers, the use of the Hyperglycemia Sell Sheet followed by the Study Comparison Insert increased the believability of the “comparable rates” message.
- Framing the discussion around risk/benefits is a concept that physicians understand and mirrors the way they make treatment decisions. After seeing the new pieces, most physicians agreed that the benefits of ZYPREXA were greater than the risks.
- Most customers said that Lilly is being proactive rather than reactive in addressing the issue with this new data.
- Although this new information is compelling, it is NOT a magic bullet. Customers require lots of repetition for message recall and true behavior change.

Remember, our success will depend largely on your tone and ability to dialogue with physicians: you must handle objections in a confident, non-defensive, forthcoming manner. You must also answer the objection to the depth required, based on a good understanding of that physician’s thoughts and perceptions of the issue. Remember that some psychiatrists say weight gain when they mean “weight gain, hyperglycemia and diabetes.” Most psychiatrists link weight gain to hyperglycemia and diabetes either directly or indirectly. Therefore, it is essential to probe for BOTH weight gain and hyperglycemia/diabetes issues to discover how these events are related in the physician’s mind. (See the “Objection Handling Algorithm” and the “Suggested Open Probes” sections).

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

- (1) Have a good understanding of hyperglycemia/diabetes.
- (2) Focus your sales presentation on the outstanding efficacy of ZYPREXA and frame hyperglycemia in the context of the overall safety profile and tie to risks/benefits.
- (3) Understand how and when to properly use the hyperglycemia Data on Demand sheet and the insert comparison chart. (See “Targeting” section and “Message Algorithm.”).
- (4) Be sure to use the appropriate tone with physicians—confident, positive and non-defensive.
- (5) Address the question: “How can you have comparable rates of hyperglycemia/diabetes if there is more weight gain with ZYPREXA in some patients?” (See Q & A section for answer).

We hope this Resource Guide and the new Hyperglycemia Sell Sheet give you what you need to knowledgeably and confidently handle these objections. Remember that effectively handling hyperglycemia and diabetes concerns is a win-win situation: Neutralizing these concerns with just a few key customers could provide the promise of ZYPREXA to more patients and at the same time put more money in your pocket! We appreciate your dedication and expertise. We are counting on those attributes as we move forward. Best of luck, and good selling.

SCIENTIFIC BACKGROUND

The first portion of this section is review. Please review it to the extent necessary to build your disease state knowledge and confidence level around hyperglycemia and diabetes. However, “Data from our clinical trial database” (p. 24) contains new information from there forward and will require a more thorough reading.

This section will 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—some that can be managed, some that cannot—may predispose one person more than the next to these conditions. Diabetes has become increasingly 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 that of other antipsychotics. Obviously, we do not expect you to become diabetes experts; your primary mission is to sell ZYPREXA. Unfortunately, to sell to some customers, you will first have to address their concerns about hyperglycemia and diabetes. The information in this section should 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 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 levels begin 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.¹ Nondiabetic individuals usually have fasting glucose levels 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 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 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 such as fainting or convulsions may result if it is not dealt with quickly.

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

Disease State Overview: Hyperglycemia vs Diabetes

Hyperglycemia and diabetes are conditions characterized by 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 (hyperglycemia). 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 criteria regarding blood glucose levels, measured by a couple of different tests. Let's start by discussing the two types of diabetes, the measurement and evaluation of blood glucose levels, 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 are characterized by 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. Thus, 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 in persons 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 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 inefficiently.

Differences between Type 1 and Type 2 diabetes:

	Type 1	Type 2
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. There are various methods of measurement, which can be affected by the testing situation. For example, 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 somewhat limited as 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 deluxe fast-food burger, this particular measurement

may not be as reflective of the normal 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 used in the Lilly clinical database.

- **2-hour oral glucose tolerance test (OGTT)** – collected two hours after the patient consumes a 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 A_{1c} test** (sometimes called “glycosylated hemoglobin”) – abnormally high amounts of hemoglobin A_{1c} are produced when plasma glucose is high. As turnover of hemoglobin A_{1c} 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	≥ 200 mg/dl	160-200 mg/dl	<160 mg/dl
Fasting glucose	≥ 126 mg/dl	110-126 mg/dl	<110 mg/dl

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

Impaired Glucose Tolerance (IGT): These criteria define 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; 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

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 (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. When a physician asks you about ZYPREXA and DKA, use the following **DKA Verbatim**:

As you know, Diabetic Ketoacidosis is a rare but serious complication of diabetes mellitus. It has been reported, rarely, on patients taking Zyprexa, as well as other psychotropics. These reports do not establish a causal relationship between DKA and olanzapine or other agents.

We are not certain what about these individuals makes them susceptible to this condition. However, in the case reports of psychiatric patients taking a variety of agents, DKA appears to be most likely a complication of uncontrolled or poorly controlled type 2 diabetes. This should not be a factor in choosing one agent over another, as patients appear to experience diabetes at comparable rates across various treatments.

Fortunately, DKA is potentially preventable if diabetes is identified and properly controlled. Therefore, it is essential that physicians diagnose and adequately treat patients with diabetes, regardless of what agent they may be taking.

- 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 a number of risk factors for diabetes. 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%.
- **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 triglyceride 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.

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.

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.

The role of psychotropics and hyperglycemia/diabetes:

Several psychotropics have been associated with high insulin levels and insulin resistance (eg, chlorpromazine,¹⁴ divalproex¹⁵). 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 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, and clozapine.

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

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, 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 these new sell sheets is this:

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

We can say confidently that we have analyzed various data in 3 ways and still have found comparable rates, as follows:

First, comparable rates of treatment-emergent diabetes were found among patients on ZYPREXA, risperidone, haloperidol and divalproex. To demonstrate this, we included 3 graphs in the sell sheet that illustrate the incidence of diagnosed treatment-emergent diabetes in longer head-to-head schizophrenia and bipolar mania trials. These are actual cases of diabetes detected in the trials. The first graph depicts 3 pooled 1-year studies of ZYPREXA vs haloperidol, including the largest head-to-head study conducted between these two agents. The incidence of treatment-emergent diabetes for patients treated with ZYPREXA was 0.5%. This amounts to 5 patients out of 927 (mean exposure to ZYPREXA, 8 months). The incidence of diabetes with haloperidol was 0.4% (1 of 261 patients, mean exposure to haloperidol 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 (the Tran study), which again is the largest head-to-head study between these two agents. The incidence of treatment-emergent diabetes was 0.6% for both drugs. This corresponds to 1 patient of 172 treated with ZYPREXA vs 1 risperidone patient out of 167 (mean exposure to ZYPREXA was 5 months, mean exposure to risperidone was 4 months). The important point again is that both agents had comparable (low) rates of diabetes.

The third graph depicts an 11-month study of ZYPREXA vs divalproex in patients with bipolar I disorder. This is the same study featured in the bipolar core detail piece. The incidence of treatment-emergent diabetes for ZYPREXA was 0% and 0.8% for divalproex. This means that none of the 125 ZYPREXA-treated patients and 1 of the 126 divalproex-treated patients developed treatment-emergent diabetes. The mean exposure time for both treatments was 4 months. Because the analysis has not been completed yet, the data from this study is not included in the second graph (“Baseline to endpoint increase in average glucose level across comparative studies”).

The second way we analyzed the data was to look at 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 mean random 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 variables 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.

We know that the average random blood glucose increase 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 1.9 mg/dl above risperidone but this was not statistically significant). The increase with Zyprexa was 4.4 mg/dl **above** that found with Haloperidol and 10.1 mg/dl **below** that found with clozapine.

In a 6 week study, baseline to endpoint glycemic changes were comparable between ZYPREXA and Ziprasidone.

Additionally, the separated graph depicts a 6 week Pfizer study of ZYPREXA vs. Ziprasidone in acute inpatients with schizophrenia or schizoaffective disorder. The average change from baseline to endpoint in median “fasting” glucose levels was 1 mg/dl for both medications. Baseline to endpoint changes between the two agents were comparable and final median fasting glucose levels also fell inside the “normal range” provided by the ADA.

The Pfizer data are added to the graph and emphasized because it is a study sponsored by a competitor that demonstrates our message, comparable rates of diabetes and hyperglycemia among psychotropics. Ziprasidone is highly touted as “weight neutral” whereas ZYPREXA is known to cause weight gain in some patients. This may help to make the point that there is not a 1:1 correlation between weight gain and diabetes; even a supposed “weight neutral” product has comparable glycemic changes as other agents studied. Additionally, some Lilly sponsored studies have been criticized for using random measurements of blood glucose elevation. This Pfizer study reportedly uses fasting measurements, a more scientific measurement, and still demonstrates comparable rates between ZYPREXA and Ziprasidone. One weakness of the Pfizer data is the relatively short exposure time of 6 weeks.

A third way we analyzed the data was to determine the likelihood of an individual 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. Also, percentages of patients considered outliers at each threshold were not different between olanzapine and haloperidol or olanzapine and risperidone.

These data were positively received by most of the physicians we spoke with during market research. However, most physicians also 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: Obesity is clearly a risk factor for diabetes. However, there is NOT a one-to-one correlation between weight gain and diabetes. In other words, weight gain can happen independently of diabetes and diabetes can happen independently of weight gain.

In fact, in the context of studies done to date with Zyprexa, the majority of patients (79%) who did have an episode of hyperglycemia (random glucose elevations above 150mg/dl), did NOT experience substantial weight gain. The implication of this is that there must be other factors, many known and probably some unknown, beside weight impacting glucose regulation. In other words:

Obesity is only one among many risk factors for diabetes.

Furthermore, of those patients who did experience substantial weight gain, over 95% had no glycemic abnormalities at all. The implication of this is that weight gain does NOT necessarily lead to diabetes. Most patients, even those with significant weight gain, do not experience glycemic dysregulation.

The single most important risk factor for diabetes in patients with bipolar disorder or schizophrenia may, in fact, have something to do with the illness itself. After all, these patients are two-to-four times more likely to have diabetes than the general population. Additionally, other factors, such as lifestyle and family history, play an important role. In other words:

Other factors, such as a patient's inherent predisposition, may be a stronger risk factor for diabetes.

The data set 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 data set, 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.

Hyperglycemia Sell Sheet Insert

“Incidence of Diabetes with Antipsychotic Agents: Findings from 4 Epidemiological Studies”

Sometimes physicians criticize our core hyperglycemia sell sheet because it contains Lilly sponsored data, has studies of short duration or has too few patients. When you hear objections like these, or the physician still has hyperglycemia or diabetes concerns that are affecting his or her prescribing, use the insert.

The hyperglycemia sell-sheet insert contains the results of four pharmacoepidemiological studies, two conducted by Janssen and two conducted by Lilly, with over 100,000 patients in total. Pharmacoepidemiology studies are reviews of the claims databases of large insurers and other third party payers. These studies provide a real world estimate of the incidence of diabetes in patients receiving antipsychotics.

Epidemiological studies can provide useful information about large unselected patient populations. The large sample population allows analysis with sufficient statistical power to examine relatively rare events. Also, factors such as age, race, and gender can be analyzed in sub-populations with sufficient power to detect statistically significant differences. In addition, these studies may also be designed with less rigorous exclusion criteria than clinical trials, therefore, the results may be more easily generalizable.

Pharmacoepidemiology offers a reliable context for anecdotal case reports. Despite the desire by some to count case reports to estimate the relative risk of various medications, they simply cannot answer this question. One key problem is that they are not randomized so they do not account for important patient-related risk factors. (For example, if treatment refractory patients have higher baseline risk, then treatment related risk may falsely appear elevated in medications preferentially prescribed to the treatment refractory.) Pharmacoepidemiological studies may not address this either, but it is well handled by randomized clinical trials.

In terms of rates, case reports provide neither an accurate numerator nor denominator. Pharmacovigilance professionals assure us that a minority of side effects are ever reported; generally, published cases are likely to be a very small minority. What factors determine which cases are written up and published? For one, the report's author needs to view the event as likely medication-related, and preconceptions may be the deciding factor (i.e., when diabetes emerges, a clinician is likely to ascribe it to a medicine that he/she has been informed "causes diabetes" but not to one that he or she believes does not cause it). Epidemiology addresses these problems by identifying all patients taking the medication of interest (the denominator) and uses a uniform approach to identifying all treatment emergent cases (the numerator).

A useful pharmacoepidemiology analysis would include patients on only one antipsychotic, who had not been diagnosed with diabetes prior to the analysis period, and who have a readily identifiable diagnosis of diabetes if it occurred.

An understanding of the following terms is useful in understanding the limitations of epidemiological studies.

Incidence is the number of new events occurring in some time interval.

Prevalence is the relative frequency of cases in the population.

Relative risk is the ratio of the probability of the event occurring in one group (treated) to the probability of the same event occurring in another group (control or competitor). This is most useful if the event rates are low.

The **odds** of an event occurring is the probability of the event divided by the probability that the event does not occur. So, 3 to 1 odds means that the event is 3 times more likely to occur than not occur (i.e. the probability that the event occurs is .75). If patients experience differing exposure times, the hazard rate and hazard ratio are often applied.

These arise from "survival analysis", typically the proportional hazards model (also called Cox regression).

Odds ratio – This number describes the odds of developing diabetes. The odds ratio for the control group will be one and the odds ratio for the study groups will be the risk of developing diabetes relative to the control group. Odds ratio often does not control for factors such as age, gender and concomitant medications. Relative risk and odds ratios are most often used when all patients have the same exposure times and only a minority of the patients experience the event of interest.

The **hazard rate** is the probability of an event occurring at a given time among individuals who have not experienced it. For example, if you have diabetes now, what is the probability you'll have it 1 year later.

Hazard ratio – The hazard ratio is the odds ratio adjusted for other variables that may affect the outcome. The hazard ratio for our purpose controls for age, gender and concomitant medications. The hazard ratio is then the ratio of the hazard rate in one group to the hazard rate in another group.

Each study is described in the insert, but there are important details you should be aware of, as follows:

Lilly Advanced PCS Study

The Lilly Advanced PCS Study is a 3-year retrospective, pharmacoepidemiological study of an independent prescription claims database (Advance PCS) containing over 50 million members. The study estimated the incidence and risk of developing diabetes mellitus among patients in the United States who receive a single antipsychotic drug, irrespective of indication. Patients who had been prescribed a diabetes medication at any point during the 12 month period prior to enrollment or had been prescribed an antipsychotic during the 6 month period prior to enrollment were excluded. Diabetes Mellitus was identified by oral hypoglycemic or insulin prescription claims in both the study and control groups. Patients in the antipsychotic study group (n = 58,751) were prescribed a single typical or atypical antipsychotic during the 6 months of follow-up.

Results based on hazard ratio showed that there were no statistically significant difference in new antidiabetic prescriptions between typicals or atypicals or Olanzapine and other typical or atypical agents except quetiapine, which was numerically (not statistically) lower. Risperidone treated patients actually had a significantly higher incidence of antidiabetic prescription compared to Olanzapine. However, we are not arguing from this that risperidone poses a greater risk for 2 reasons as follows: (1) there was not a statistical difference in calculated hazard ratios, and (2) magnitude of incidence on Olanzapine, Risperidone and typicals was in the same ball park. Although the risk of diabetes mellitus relative to the general PCS patient population was numerically lower in the quetiapine cohort, the risk of diabetes mellitus in the top quetiapine dose quartile was comparable to the risk observed in the other antipsychotic treatment cohorts. This finding may be related to the quetiapine cohort's smaller sample size, or it may reflect differences in diagnostic entities and illness severity across antipsychotic cohorts.

Like all studies, this study too has limitations as follows: disease diagnostic information was not available in the PCS database, the mean daily doses of antipsychotics were lower than average, time periods were studied and the findings can only be generalized to patient populations similar to those represented in the PCS database. On the other hand, the PCS study is one of the best sources of information to date on this question. It is the largest study to date; it is perhaps the most careful in isolating treatment effects (by excluding patients recently taking antipsychotics and not permitting antipsychotic polypharmacy during the study), and it allows the best range of comparison to active treatments and a control group.

Key takeaway: In the Lilly Advance PCS database, comparable incidence and risk of diabetes mellitus were observed in patients treated with both conventional and atypical antipsychotics.

Lilly IMS Study

The Lilly IMS study is a retrospective analysis of the IMS Lifelink claims database identified patients aged 18-65 (n=6,440) initiated on antipsychotic medicine between October 1996 and December 1998. The study included only patients with no antipsychotic use for 6 months prior and no diagnosis of diabetes or receipt of any diabetic medication for 1 year prior to antipsychotic initiation. The incidence of treatment-emergent diabetes was comparable between Olanzapine, typical antipsychotics and risperidone, although the incidence with risperidone was numerically (not statistically) higher. The odds ratio for Olanzapine and risperidone treated patients was not statistically significantly different from patients receiving typical medications. Finally, results indicate that use of olanzapine is associated with a numerically (not statistically) lower probability of being diagnosed with diabetes or receiving a diabetic medication compared to risperidone, though numerically higher compared to typicals. Neither finding was statistically significant.

There are a number of strengths for the study. First, the timeframe of the data for patients initiating on antipsychotics, 1996-1998, may be sufficiently early that there is a reduced likelihood of physician prescribing bias. Specifically, given that little information was presented in competitive activities suggesting a link between diabetes and atypical antipsychotic medications until relatively recently, physicians were less likely to be influenced by such considerations in choosing a medication. Second, this analysis incorporated a more comprehensive, inclusive definition of diabetes, including both prescription claims and ICD – 9 diagnosis information. Third, this was a year-long intent-to-treat study – i.e., recorded incidence of diabetes for a full year after prescription of the index antipsychotic. It likely is the major factor in the higher incidence rates observed in IMS compared to the other studies, where mean observation was shorter.

There are three notable limitations in this study. First, the analysis used prescription claims data from a large employer database. Patients in the system may not reflect patients utilizing services in other systems of care. Therefore, these results may not be generalizable to other care settings. Second, claims data may also introduce some

unobserved physician or prescribing bias. Last, the analysis does not control for patient ethnicity, a well-documented risk factor for diabetes. While recognizing these limitations, claims data have the advantage of allowing for the examination of a large population treated under routine clinical care.

Key takeaway: In the IMS study, the probability of developing diabetes was no more likely following treatment with atypicals than typicals. Within atypical use, the probability of developing diabetes was less during treatment with olanzapine than with risperidone, although the difference was not statistically significant. Additionally, the actual incidence of treatment-emergent diabetes was comparable between olanzapine, typical antipsychotics and risperidone.

Janssen Quebec Medicare Study

The Janssen Quebec Medicare study is similar in size to the Lilly PCS study and compares patients on risperidone and olanzapine, but there are no other comparison groups. The Janssen study included patients receiving antipsychotic polypharmacy. Patients included in the risperidone treatment group could not be on olanzapine or clozapine. To be included in the olanzapine group, patients could not be on clozapine. It can be reasoned that some of the olanzapine patients simultaneously were taking risperidone. Such patients likely had severe treatment refractory psychosis and some information suggest that these patients are at an especially high diabetes risk. The fact that these investigators assigned patients taking both drugs to the olanzapine group only reflects their pre-existing bias and may have inflated the risk for olanzapine. This study did not control for time on the medication. The actual incidence was not reported in the poster, but calculated based on information in the abstract.

One great strength of the PCS study is its consideration of all 4 atypical antipsychotic drugs as well as typical antipsychotics and a control group. The relative consistency across groups tends to validate the impression of comparable risk. The Quebec Medicare Study does not offer such reassurance, nor does it give it perspective on whether rates of risperidone are similar are much higher/lower than typical drugs.

The Cox proportional hazard ratio controlled for age and gender, but not for concomitant medications. In the poster they reported the relative risk adjusted for age and gender, and the relative risk adjusted for age in females.

Key Takeaway: Although numerically risperidone looks better than olanzapine, the incidence of diabetes and relative risk is clinically comparable and (depending on which analysis they use) of marginal statistical significance. This numerical difference may be due to methodological issues discussed. Overall, rates of diabetes were of clinically comparable magnitude on the two drugs.

Janssen Health Plans Study

This Janssen supported health plans database analysis generates messages that appear to be damaging to Zyprexa, but there are several flaws in the study, and the unmanipulated results actually suggest comparable rates. This study looks at two different managed care databases from different parts of the U.S. and combines them as one.

However, the authors do not provide much information based on patients, instead relying on “treatment episodes”. This means that individuals may be counted multiple times, e.g., if they came on and off drugs. This might be reasonable if we knew that medications posed a risk and if this risk were linear over time; in fact we wonder if either is true. This practice may have lowered apparent risk. If a subject did not develop diabetes (i.e. is not diabetes prone) he or she may be counted repeatedly, whereas if diabetes occurred, he or she could not be counted again. This may well have improved risperidone’s numbers. We expect that such patients were predominately in the risperidone group.

Second, the report is not clear regarding which cofactors are considered, but they are explicit that though a diagnosis was available, they did not control for it. If diabetes is more common in schizophrenia or in treatment refractory schizophrenia, this would disadvantage olanzapine, more so in that this study included only the first years of olanzapine availability, so that prescriptions would be more consistently “on label”.

Third, the control group is suspect; over 40% of “psychotic” patients were not prescribed any antipsychotic treatment. This does not match clinical practice and calls into question the quality of this dataset.

Fourth, this study is much smaller than PCS or Quebec Medicare and even compared to IMS. This negates some of the advantages of an epidemiology approach.

Fifth, the authors are not forthcoming regarding actual rates of treatment emergent diabetes. Instead, they report only the calculated odds ratio and report these only “per month”. That is, in some way they divided the incidence by time of exposure (a reasonable approach only if occurrence is linear with time); given that mean exposure was about a month longer on risperidone, this alone could more than account for the very small numerical risk advantage over olanzapine they report.

For their overall analysis, no statistical test is reported for olanzapine vs risperidone, but the difference is very likely not significant.

At least in scientific meetings, Janssen is emphasizing a complex sub-analysis that amplifies olanzapine’s risk. As you will see below, it is difficult to understand the analysis, but we are describing it in case you hear about it from doctors who have attended a Janssen event.

The primary analysis is in patients who had been followed in the database for at least four months prior to prescription of the antipsychotic of interest. For apparently arbitrary

reasons, they looked at subsets of this group who had been in the database for at least 6 or at least 8 months, and chose to report only the latter. Again, there is a small olanzapine – risperidone difference, albeit a bit under that in the overall group. Then, remarkably, they “estimate” annual risk by raising monthly risk to the power of 12. This exponential maneuver amplifies a small olanzapine – risperidone difference to an estimated four-fold difference in risk. This seems to be the finding that Janssen would like to emphasize, rather than the primary objective from this study or from the much larger Quebec study. We do not find this appropriate for one, given that this was a longitudinal study they could have used actual data to estimate risk, rather than this exponential approach. Secondly, this approach presupposes that risk is only drug related (although it is clear that patient predisposition is important) and is linear over time.

It is worth pointing out that this finding is very out of line with the epidemiological studies; that they estimate that risk on risperidone is lower than on no antipsychotic treatment at all; and that even this tortured analysis places the risk on olanzapine squarely within the range of conventional antipsychotic drugs and about half that of clozapine.

Key takeaway: Competitors may use selected manipulation of this dataset to support their argument that olanzapine has greatly elevated diabetes risk compared to risperidone. This is the smallest and therefore the weakest of these four pharmacoepidemiological studies, but overall results suggest comparable risk in olanzapine vs risperidone and all of their analyses suggests comparable rates on olanzapine vs conventional antipsychotics. We find their conclusion of lower risk on risperidone to be unjustified because it reflects a smaller subgroup; tortured, inappropriate analysis; and biased study methodology. It conflicts with the overall results of this study and other available studies.

Other Studies:

We are aware of two other prevalence studies that are not in your hyperglycemia sales aids. These studies are cross-sectional assessments of a cohort of patients and they count how many have diabetes. These two studies also are consistent with our impression of comparable rates across treatments, but are not included in the insert because they are, frankly, weaker science than incidence studies. Prevalence studies do not consider whether diabetes develops before or after medication prescription. Both have been presented in 2001 scientific meetings. As far as we know, they were independent of pharmaceutical support.

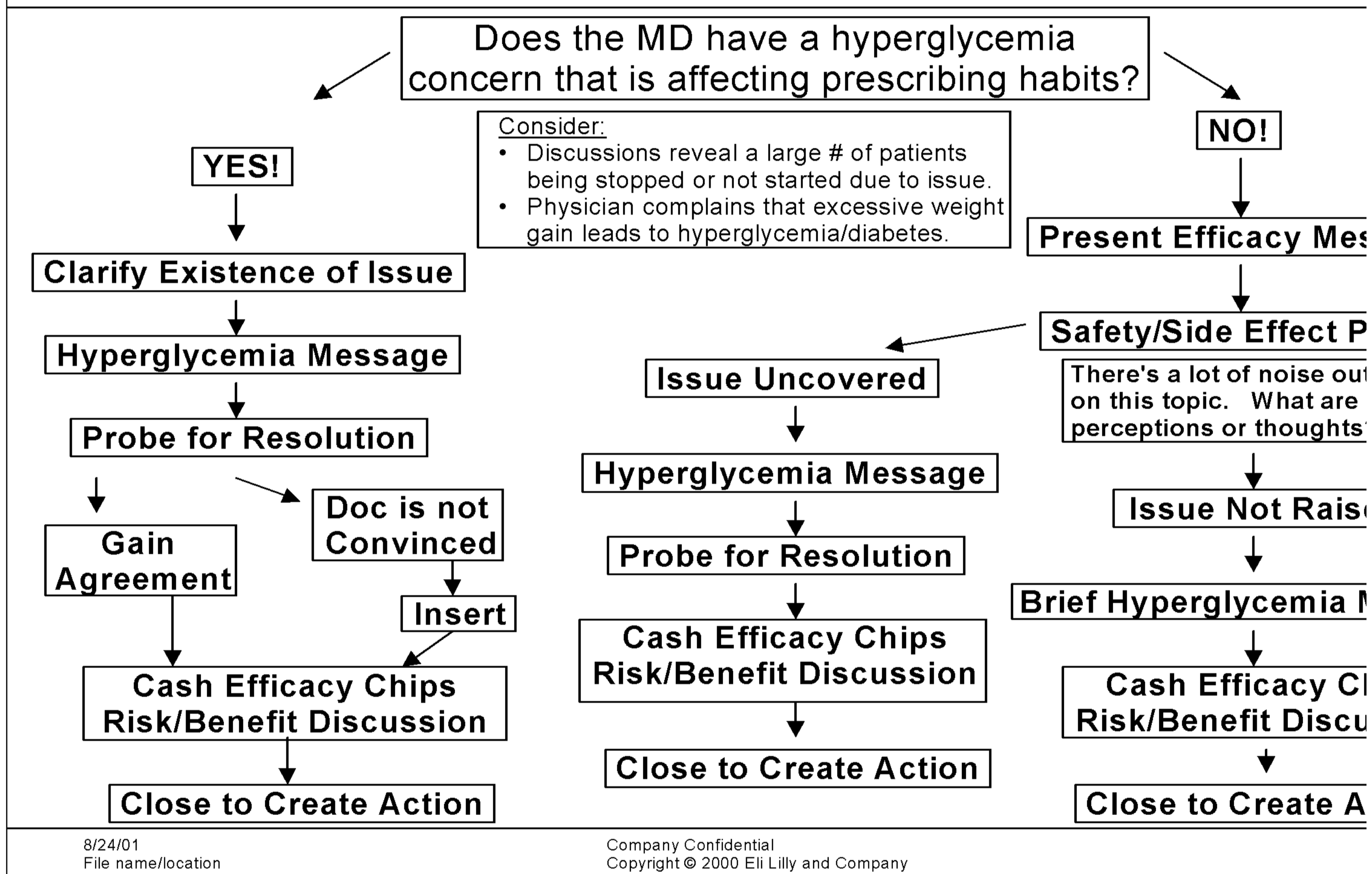
One, by a VA group, does not present actual prevalence, but a calculated risk ratio. On the surface, it is favorable to risperidone. This was the only atypical not statistically associated with a higher diabetes prevalence than typicals. Nevertheless, the study did not show large clinical differences in diabetes prevalence. They estimate that in equal samples, for every 100 individuals with diabetes on typicals, one might expect about 105 on risperidone, 111 on olanzapine, 125 on clozapine and 131 on quetiapine.

The second prevalence study was done in Texas. They report only unadjusted prevalence figures. Once again, rates were quite similar across agents and numerically lower on olanzapine than risperidone or quetiapine.

For your information only. Not for use in detailing.

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Hyperglycemia Objection Handling: "Message" Flow



MESSAGE SCRIPT

After getting the objection, first stop and take a breath. Second, clarify the objection using the objection-handling algorithm (is it something they have seen or heard, etc). Third, make sure you understand the objection in its entirety: “Are we talking about hyperglycemia and diabetes, or are we talking about weight gain; I want to make sure I understand your concern.” Fourth, is the objection affecting the physician’s prescribing of ZYPREXA? To get to the heart of the customer’s concern and learn if and how those concerns are affecting his or her prescribing, ask the following clarifying questions:

- (1) “What does your concern over diabetes mean to your patients?”
- (2) “How does this concern affect the ways you might use ZYPREXA?”
- (3) “For what specific patients (eg, obese patients, diabetic patients, etc) would you be so concerned about hyperglycemia or diabetes that you would reach for a product other than ZYPREXA? What product would you reach for?”

High Ground Opener

Doctor, there has been a lot of talk from various pharmaceutical companies on hyperglycemia and diabetes and the potential link to psychotropic medications. Due to the seriousness of this concern, we felt it was necessary to provide you relevant data from Lilly and other manufacturers. We’ve talked in the past about what you like (chip) about ZYPREXA. However, in the past you’ve mentioned concerns about hyperglycemia and diabetes. May I share with you some information that addresses your concerns and follows the approach you use when treating patients...evaluating all the risks and benefits to choose an agent?

Doctor, the takeaway point from this data is this: In several large-scale, double-blind studies, comparable rates of hyperglycemia and diabetes were seen among various agents including haloperidol, risperidone, divalproex, ziprasidone and ZYPREXA.

Core Message

We looked at the data in 3 different ways: 1) incidence of treatment-emergent diabetes, 2) risk of hyperglycemia and elevated blood sugars and (3) any individual patient’s likelihood of developing diabetes. No matter how we analyzed the data, each of these studies showed that the incidence of treatment-emergent diabetes was comparable between agents.

The first graph looks at three 1-year studies of ZYPREXA vs. active comparators. The study comparing ZYPREXA with haloperidol involved over 2,000 patients, and was the largest head-to-head study between two psychotropic agents. The second study is the largest head-to-head study ever done between ZYPREXA and risperidone. The third study, also one of the largest of its kind, compares ZYPREXA and divalproex. Each study showed the same results...that the incidence of treatment-emergent diabetes was comparable between agents and was relatively rare...less than 1%. What this means to your patients is that they can have the many benefits of ZYPREXA (use physician chips) without an increased risk of hyperglycemia or diabetes over other psychotropic agents.

PROBE: Does this surprise you?

Another way to determine the risk for hyperglycemia or diabetes is to assess the potential of a patient to have elevated blood glucose levels with a particular psychotropic agent. Blood glucose levels can be classified into 3 ranges: normal, elevated (hyperglycemia) or high (diabetes). The chart compares ZYPREXA to haloperidol, risperidone, clozapine and ziprasidone. Across all four studies, average levels on ZYPREXA fall well within the normal range, even in the study conducted by Pfizer. Average levels with ZYPREXA were also below ADA guidelines for what is considered to be elevated blood glucose.

PROBE: Doctor, what is the clinical significance of this data to you and your patients?

You may be saying to yourself that you treat individual patients while these studies were based on averages. A third way to assess risk for hyperglycemia and diabetes is to look at an individual patient's likelihood of experiencing random glucose elevations. In trials of ZYPREXA vs. haloperidol and risperidone, individuals were assessed at 4 different thresholds: 126 mg/dl, 140 mg/dl, 160 mg/dl or 200 mg/dl. Again, the likelihood of any one patient's experiencing random plasma glucose elevation was not different between the drugs at any threshold. This means that the likelihood of being an outlier was not different for ZYPREXA, risperidone, and haloperidol at each threshold. I want to be clear: we are not saying that an individual patient may not develop diabetes, or that there isn't increased risk of hyperglycemia or diabetes for patients taking psychotropic agents. What we are saying is that it **can** happen, and happens at comparable rates between the agents.

TRIAL CLOSE

Doctor, now that I have shown you 3 different types of data that found comparable rates of diabetes and blood glucose elevations among psychotropic drugs, do you feel more comfortable regarding the risk of diabetes with ZYPREXA compared to other agents? Does this change the way you view weight gain and hyperglycemia or diabetes?

Doctor, you may be wondering how there can be comparable rates of diabetes across agents, given the reality that ZYPREXA may cause more weight gain in some patients. Even though weight gain can be a risk factor for diabetes, **there is not a 1:1 correlation** between weight gain and diabetes. In other words, patients can gain weight without developing hyperglycemia or diabetes, and a patient can develop hyperglycemia or diabetes without having gained weight.

As you know, patients taking psychotropic medications can experience weight gain as a side effect. When we looked at patients in our database treated with ZYPREXA, the majority (79%) of those who had an episode of hyperglycemia **DID NOT** experience substantial weight gain. In addition, of those patients with substantial weight gain, over 95% of them had **no glycemic abnormalities** at all. Clearly, research has shown that even if a patient gains weight, it is not likely he or she will develop diabetes as a result of this **one** factor.

PROBE: Doctor, today we have talked about psychotropics and diabetes or hyperglycemia. The various studies have shown the rates to be comparable among agents. When you decide which medication to prescribe, you must weigh benefits and risks. What benefits do you feel ZYPREXA brings to your patients?

*Wait for the answer and gain valuable chips. If the physician agrees with the comparable rates message and has no other concerns about weight gain as it relates to diabetes, **flip to the risks/benefit tool on the back page.** Remind the physician that they make prescribing decisions based on the total benefits and risks an agent has to offer. Summarize chips in the physician's own words, cash them in, and gain agreement that the benefits of ZYPREXA are greater than the potential risks. Negotiate for Melvin or a Bipolar patient using the CAPS process.*

If you can't gain agreement that ZYPREXA benefits are greater than potential risks, continue the detail:

If there isn't a 1:1 correlation between weight gain and diabetes, and if weight gain is only one factor to consider when assessing the risk of diabetes, what are the other risk factors? First, let's keep in mind that even in the general population, diabetes is a common health problem. In fact, according to one study the incidence of diabetes and hyperglycemia in the general population is 15%. That same study showed that almost 7% of non-diabetics had blood glucose levels above the normal range. Other studies have shown that the rate of diabetes is 2-4 times higher in the persistently mentally ill population. So in your practice, you should not be surprised to find patients who have elevated blood sugars regardless of the agent you choose.

Let's look at other more important factors to consider when assessing a patient's risk for diabetes. Family history, age, ethnicity and lifestyle including diet and exercise should be considered. Also, excessive alcohol use and high-fat diets can increase blood glucose. It's important to remember that just because a patient has risk factors, he or she will not necessarily develop diabetes. Conversely, some patients who develop diabetes may have very few or none of these risk factors.

PROBE: Doctor, based on what we've talked about today, how do you feel about the risk to your patients of developing diabetes with ZYPREXA compared to other agents? When considering overall efficacy and benefits to the patient, what do you feel that ZYPREXA offers your patients?

CLOSE

Doctor, you make prescribing decisions based on the total package offered by a product, including benefits and risks to the patient. In the past, you've said that ZYPREXA offers your patients (chips) over (name a competitor). Are there any additional benefits that you see with ZYPREXA for your patients? You've also mentioned that sometimes you worry about hyperglycemia. Today I've shown you data that shows patients taking any of these

agents are at comparable risk for hyperglycemia or diabetes. Would you agree that the benefits of ZYPREXA that you've described (chips) are greater than the potential risks?

If yes, negotiate for Melvin or for a Bipolar patient: "How can I help you help your patients like Melvin get started on ZYPREXA?" Offer proposals and continue on with CAPS process.

If still no agreement on comparable rates or ZYPREXA's benefits being greater than its risks, use the Study Comparison Insert. (For physicians who started with severe concerns, use the insert regardless of how they answer the probes).

(Flip to the BACK SIDE of the insert and show the comparison chart.)

Perhaps it would be helpful to see some additional studies, 2 of which were Lilly sponsored and 2 of which were sponsored by Janssen. Overall, this chart represents over 103 thousand patients treated with an antipsychotic. The first 3 are incidence studies where rates of diabetes are measured in patients who have developed diabetes while taking the antipsychotic medication studied. The last study looks at the odds ratio, which is the estimated likelihood of a patient's developing diabetes on the medications studied vs. the control group.

Take a look at this chart for a moment, and tell me your interpretation of the data.

If doc "gets it," ie, comparable rates, cash in chips, use the risks/benefits tool and repeat the previous close (above).

If the physician still objects, make sure he/she understands the following: "In 4 epidemiological studies, regardless of the sponsoring company...Lilly, Janssen, or Pfizer, and with an N of over 100,000 patients, all studies showed the risk of hyperglycemia and diabetes to be comparable among these agents." Ask if knowing more about these studies is helpful. Trial close again. If the physician requests more information, offer to have a medical letter sent.

Q & A

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

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 one-to-one correlation between weight gain and diabetes. In other words, weight gain can happen independently of diabetes and diabetes can happen independently of weight gain. In fact, in clinical trials, the majority of patients (79%) did not have substantial weight gain. Conversely, of the patients that had substantial weight gain on Zyprexa, 95% had no glycemic abnormalities at all. The single most important risk factor may be persistent and severe mental illness. Additionally, other factors like lifestyle and family history all play an important role. So, the fact that obesity was a relatively weaker factor in our data set shows that other factors, such as a patient's inherent predisposition, are stronger risk factors.

Why did you include the Pfizer study information in a Lilly brochure?

Many physicians have talked about a link between elevated blood glucose and weight gain. Pfizer has been promoting ziprasidone as a "weight neutral" product, yet in their study, the effect on blood glucose with ziprasidone looks similar to that with ZYPREXA. Therefore, the study's inclusion serves several points. First, it shows that not only Lilly's studies, but other drug companies' studies also, consistently show comparable findings among agents. Second, it promotes the conclusion that rates are comparable because there is NOT a 1:1 correlation between weight gain and hyperglycemia or diabetes. Third, the Pfizer study takes fasting blood glucose levels, a measure thought to be more accurate than random levels by most physicians. Even when fasting levels were taken, baseline to endpoint blood glucose changes were comparable between ZYPREXA and ziprasidone.

I don't believe studies from drug companies because they can make the numbers show whatever they want them to show.

Doctor, I understand your concern. That is part of the reason we have included data not only from our own trials but from other companies as well. If you will notice, there is a Pfizer study included as well as two Janssen studies. Obviously other companies would not have a vested interest in showing ZYPREXA in a favorable light. Even in these studies not sponsored by Lilly, the data shows comparable rates.

If it's true that you all have comparable rates, why do I keep seeing studies and information from other companies saying that ZYPREXA causes diabetes and hyperglycemia more often?

I would encourage you to ask the reps that have been sharing this data to show you the studies and information they have been referencing. What you will find are anecdotes, case reports and non-randomized, non-blinded retrospective reviews. The information

I've shared here analyzes the incidence of treatment-emergent diabetes, random and fasting blood glucose elevations, elevated blood sugars in individual patients, and pharmacoepidemiological studies. The large number of patients and multiple studies referenced in this information show Lilly's commitment to providing you answers that matter, with real data to back them up.

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 clinical experience seems to be different from large-scale clinical studies. Do you mind if we explore what potential reasons there may be for this difference?

I've had this question from other physicians as well. And, when we dug deeper into the issue we found a couple 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 you may be using more Zyprexa than other physicians.

There are many reasons why your experience to date may differ from larger clinical and epidemiological studies. However, as we move forward, I would ask that you assess all of your patients on psychotropic medications. I think what you may find is that across the board, diabetes can and will happen at comparable rates in your patients.

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 levels, ZYPREXA does not appear to have an 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.

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

- The one other large, head-to-head, long-term database we have beyond risperidone and haloperidol is versus clozapine. This data shows that ZYPREXA-treated patients

had significantly less increase in mean random glucose levels than those on clozapine.

- In terms of other mood stabilizers, although our 3-week 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 in this study, and none of the 251 patients on either drug developed treatment-emergent hyperglycemia or diabetes. In the 47-week extension phase of this study, rates of treatment-emergent diabetes were comparable between ZYPREXA and Depakote (ZYPREXA=0 cases, Depakote=1 case).
- In addition, we know from case reports that hyperglycemia and/or diabetes has been reported with most psychotropics (including lithium, quetiapine, risperidone, and clozapine).
- It is too early to tell what the true efficacy or side-effect profile of Geodon may be. However, a Pfizer sponsored study presented in our detail aid shows comparable baseline to endpoint blood glucose changes between ZYPREXA and ziprasidone.

Is there a direct effect of ZYPREXA on diabetes?

We've gone back 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. 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 versus comparator drugs in clinical studies. If there were 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 and risperidone. While this data cannot 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 1 diabetes?

No. Most treatment-emergent diabetes reported with ZYPREXA and other psychotropics is Type 2. 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 1 diabetes. Since diabetes does develop in the general population, the specific question relates to whether ZYPREXA patients develop insulin-dependent diabetes at a rate higher than that in the general population. In our controlled comparative clinical trials, rates of developing Type 1 diabetes are not higher with ZYPREXA than with haloperidol or risperidone. We have reviewed our longer-term preclinical animal studies and have not found any changes to insulin release or to the pancreas. Acute reductions in insulin release could produce Type 1 diabetes. Lilly is conducting further extensive trials examining any direct reduction in insulin release related to ZYPREXA or other psychotropics.

I hear that ZYPREXA can cause diabetic ketoacidosis (DKA). Please tell me what you know about this.

As you know, diabetic ketoacidosis is a rare but serious complication of diabetes mellitus. It has been reported, rarely, in patients taking ZYPREXA, as well as other psychotropics.

We are not certain what about these individuals makes them susceptible to this condition. However, in the case reports of psychiatric patients taking a variety of agents, DKA appears to be most likely a complication of uncontrolled or poorly controlled Type 2 diabetes. This should not be a factor in choosing one agent over another, as patients appear to experience diabetes at comparable rates across various treatments.

Fortunately, DKA is potentially preventable if diabetes is identified and properly controlled. Therefore, it is essential that physicians diagnose and adequately treat patients with diabetes, regardless of what agent they may be taking.

Additionally, as you review these new materials you may have the following questions (these answers can also be provided to physicians but they are not meant to be verbatims).

Does the Study Comparison Insert also show comparable rates of diabetes among agents? What is the statistical significance of the data?

Our competitors are asserting that there are substantially different rates of diabetes with ZYPREXA versus other agents. This argument is based on a weak foundation, mainly from a compilation of case reports, theoretical arguments, and flat-out unsubstantiated claims. This backgrounder goes into detail regarding each relevant piece of evidence. However, it is very instructive to pull up from the details of each study and consider what they are telling us in the aggregate. And what we find in the aggregate is that, while an individual study may show a particular drug with a higher or lower risk (perhaps even marginally statistically significant), the actual risk for and rates of diabetes are in the same ballpark across these drugs.

It is important to note that although the odds ratios look numerically similar in the Health Plans study, the p-value has not been provided to us, so statistical significance is unclear. In the Quebec Medicare Database, the incidence of diabetes was not statistically different between ZYPREXA and risperidone, but the odds ratio (shown only in the methodology section) shows borderline statistical significance (slightly higher rates) for ZYPREXA. In the PCS study, risperidone showed a statistically significantly higher incidence of diabetes than ZYPREXA but the hazard ratios were not statistically different. The IMS study showed no statistical difference between agents. In sum, although statistical significance is not reported in some studies and some studies show small statistical differences, taking a broad view, these studies taken together point to an incidence of diabetes of clinically similar magnitude across treatments.

Why does the Study Comparison Insert show the incidence of diabetes in three studies and the odds ratio of developing diabetes in a fourth study?

The comparison chart reflects the way data were reported in each study. For the fourth study, only the odds ratio was reported. When incidence rates are available, we prefer to

show the incidence of treatment-emergent diabetes because this information is generally more easily understood than odds or hazard ratio data.

Why do you compare ZYPREXA to Haldol (as well as other agents) for risk of diabetes when most physicians do not use Haldol first-line anymore?

We use Haldol as a comparator because Haldol has been available since the 1950s, and patients also have comparable rates of diabetes with Haldol. This shows our customers that diabetes in patients taking antipsychotic agents is not new; what's new is the emphasis placed on it by some.

RESOURCES

The following resources are nonpromotional and are not for use in detailing.

CME Events and Enduring Materials:

- Optima: “Diabetes and Antipsychotics 2001”
Moderators: Fawver and Buse
Format: CME video direct shipped to physicians and reps in October, 2001
- Psychlink: Oct. 17, 2001 (not titled yet). Will address weight gain, hyperglycemia and diabetes with atypical antipsychotics.
Moderators: Baker and Breier
Format: Will be available on 24-hour-a-day Internet playback immediately after the program. Will also be available on video by the end of November.
- Psychlink: April 25, 2001, “Exploring the Spectrum of Recovery”
Moderators: Glazer, Fawver and Maguire.
- Provision: Jan. 11, 2001, “A Wellness Approach in Contemporary Psychiatry: From Efficacy to Quality-of-Life”
Moderators: Aquila, Goff, Maguire and Reid (cardiologist).
- Psychlink: Nov. 15, 2000, “Medical Controversies in Psychiatry: Solutions for Wellness”
Moderators: Glazer, Aquila and Dagogo-Jack
Format: Will be available on-line with 24-hour playback
- Psychlink: February 16, 2000, “The Drivers for Clinical Decisions Making: Optimizing Outcomes”
Moderators: Glazer, Aquila, Dickson, Petty and Littrell
Format: Will be available on-line with 24-hour playback

Medical Letters (available upon physician request):

- ZYPREXA – Effect on Cardiovascular Function.
- ZYPREXA – Weight Reduction and Management.
- ZYPREXA – Effect of Long-Term Treatment on Weight Change and Association With Changes in Glucose, Cholesterol and Diastolic Blood Pressure.

Knowledge Management (for your information only):

- “Diabetes Mailer to Physicians,” 7/31/01. Look in ZYPREXA – Schizophrenia, Brand Communications, Marketing Communications.

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- Meltzer et al. “Supplemental Rebuttal, Journal of Clinical Psychiatry”, 7/9/01. Look in ZYPREXA – Schizophrenia/Objection-handling, or Brand Communication, Marketing Communication.
- “Melkerson Reprint Rebuttal, Journal of Clinical Psychiatry”, 3/13/2001. Look in ZYPREXA – Bipolar/Brand Communications/Other.
- “Newcomer Data”, 11/01/00. Look in ZYPREXA –Schizophrenia/Brand Communications/Other.
- “Response to Journal of Clinical Psychiatry Oct. 2000”, 11/15/00. Look in ZYPREXA – Bipolar/ Brand Communications/Other.

Medical Speakers (nonpromotional programs available upon customer request:

Ralph Aquila, MD (psychiatry)
 John Buse, MD (endocrinology)
 Howard Brand, MD (endocrinology)
 Samuel Dagogo-Jack, MD (psychiatry)
 Jay Fawver, MD (psychiatry)
 William Glazer, MD (psychiatry)
 John Justice, MD (psychiatry)
 Ronald Koshes, MD (psychiatry)
 David Levine, MD (psychiatry)
 Thomas Liffick, MD (psychiatry)
 Kimberly Littrell, ARNP
 Gerald Maguire, MD (psychiatry)
 Richard Petty, MD (psychiatry/endocrinology)

Promotional and Educational Resources Available to Customers:

- NTTP “Solutions for Wellness”
- Local partners trained in delivering the message of NTTP
- Lilly “Healthy Lifestyles” materials

Websites:

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

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