Diabetes Message - 2003

Table of Contents:

Diabetes Message: What’s New p. 1
Scientific Background p. 2-11
Diabetes Message Elements p. 11-12
Diabetes Message Script p. 12-13
Objection-Handling Algorithm p. 14

What’s New

Revised Diabetes Sell - OL 26260

· Diabetes Sell Sheet & Epidemiology Insert combined.
  (Destroy all old copies of Diabetes sell sheet & insert).

  Addition of an Independent Study (Sernyak).

  Elimination of weight gain pie charts - confusing to customers.

  Comparable rates changed to "no consistent differences" to increase message credibility. Some studies do show differences - not clinically significant.

  Risk/benefit tool up front to discuss the AOC in context of overall risks and benefits to patients.

  Up-front emphasis that patients with SPMI are at increased risk. We have made significant headway in this area!

  Summary page to either reiterate message or give quickly if necessary.

Scientific Background
- Diabetes Disease State

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. However, many of our customers do have concerns about Diabetes and being able to handle diabetes as well as weight gain areas of concern is an important part of the selling process. The information in this section should allow you to do that, and then easily transition back to ZYPREXA’S dependable control.

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 after a meal, a person’s blood glucose level begins to rise, then gradually returns to the normal range as glucose passes into the cells.

It is important to realize that there are daily fluctuations in blood glucose levels, as well as a great deal of inter- and intra-person variability. For example, a measurement of fasting blood sugars (obtained by assessing blood glucose levels 8-12 hours after the last food intake) results in “ideal” plasma levels that may range from 70-100 mg/dl. Non-diabetic individuals have fasting glucose levels below 126 mg/dl.

The body has a very complex system that makes glucose available to cells to produce energy, and generally this system keeps blood glucose levels within a normal range. When the body senses an increase in glucose, it sends a signal to the beta cells of the pancreas to make insulin. Insulin is a hormone that lowers the blood glucose by acting as a key to unlock the body’s cells, thus allowing glucose to pass from the bloodstream into the cells. Once the pancreas releases insulin into the blood, the blood glucose level begins to fall back to normal as the insulin allows glucose to pass from blood into the cell. The body’s cells either store the glucose or 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, 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. However, frequent and recurrent episodes of hyperglycemia may represent a pre-diabetic state of “impaired glucose tolerance” which is associated with end-organ damage and increased cardiovascular risk.

**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. 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 (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, the initial defect in type 2 diabetes is 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”

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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, or even high 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:

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

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 reflect 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 most studies in the Lilly clinical trial database.

- **2-hour oral glucose tolerance test (OGTT)** – collected 2 hours after the patient consumes a drink “loaded” with glucose. The OGTT is inconvenient and uses more medical resources.

- **Hemoglobin A1c test** (sometimes called “glycosylated hemoglobin”) – abnormally high amounts of hemoglobin A1c are produced when plasma glucose is high. As turnover of hemoglobin A1c 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.

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It is important to understand that these numbers, like blood pressure norms, are not absolute. 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 at or 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 less than 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. 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. This means that 7% of the population, or 1 out of 12 individuals, is at high risk for developing diabetes.

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.

- 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.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Diabetes</th>
<th>Impaired Glucose Tolerance (IGT)</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random glucose</td>
<td>≥200 mg/dl</td>
<td>140-200 mg/dl</td>
<td>&lt;140 mg/dl</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥126 mg/dl</td>
<td>110-&lt;126 mg/dl</td>
<td>&lt;110 mg/dl</td>
</tr>
</tbody>
</table>

- 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, may in some cases, lead to amputation 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 non-traumatic 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 or the bladder, or in obtaining or maintaining an erection may result.

- Macrovacular complications can 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 (e.g., those who are bedridden) are particularly likely to progress to dehydration and hyperosmolar coma. Inciting conditions

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such as infection often contribute to the development of this potentially life-threatening condition. Hyperosmolar coma is treatable with insulin, fluids, and other supportive measures.

- Diabetic ketoacidosis (DKA) is another potentially life-threatening situation. It usually reflects a very severe insulin deficit, and so is more common in Type 1 diabetes, but can occur in Type 2. 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 body'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.

DKA is often characterized as unpredictable and causing sudden, inexplicable death. However, when cases of DKA are explored, it has been found that pre-existing, undiagnosed or poorly controlled diabetes are often confounding factors.

Fortunately, this means DKA is potentially preventable if diabetes is identified and properly controlled. Because patients with schizophrenia or bipolar disorder are at increased risk for diabetes, it is essential that physicians identify, counsel and refer patients with diabetes, regardless of what agent they may be taking.

Cases of DKA have been reported in temporal association with Zyprexa treatment as well as with other atypicals. It is important to note that reports of DKA are very rare and a causal relationship has not been established. Most cases of DKA reported in patients taking antipsychotics are thought to be cases of type 2 diabetes.

- 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).

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.
- Polycystic ovary syndrome.
- History of gestational diabetes and delivery of a baby weighing greater than 9 pounds.

Variable factors include:
- Dyslipidemia: Those with “good” cholesterol levels (HDL) 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. 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

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have significant weight change. [Ford et al, Am J Epidemiology, 146:214-222, 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. According to 2003 ADA guidelines, being overweight, or BMI greater than 25 kg/m, is also a risk factor for diabetes.

- **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%.

  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 patients who are overweight and have one or more of the variable or intrinsic risk factors discussed above 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 our customers and their patients. Diabetes is common in the general population and even more common in patients with serious and persistent mental illness.

**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 (6.2%) have diabetes. As many as one third of the people with the disease, or about 5 million individuals, are undiagnosed. 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 higher in patients with major mood disorders, schizoaffective disorder and schizophrenia than in the general population, although reasons for this association remain unclear. Due to your efforts, there has been a dramatic increase in the percentage of our customers who are familiar with this data.

One 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 2 to 4 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:

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. Mukherjee and colleagues (1996) had found that approximately one third of young patients with schizophrenia had a positive family history of Type 2 diabetes.

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. Others have postulated that lifestyle issues, such as inactivity, poor diet and increase in cortisol levels due to chronic stress also contribute.

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:**

Cases of hyperglycemia have been found and noted in clinical trials with all atypicals. In fact, hyperglycemia and diabetes are included as adverse events in the package inserts of many typical antipsychotics and mood stabilizers and all currently approved atypical antipsychotics. Also, since BMI greater than 25 kg/m² is a risk factor for diabetes, clinicians may be anticipating more hyperglycemia risk among patients with substantial weight gain during treatment.

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

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 in ZYPREXA due to preconceptions about effects on glucose.

Additionally, because of ZYPREXA’s dependable control, one could hypothesize they may be putting sicker patients with more risk factors on ZYPREXA over other agents.

Beyond case reports in the literature, there have been a number of studies hypothesizing that ZYPREXA has higher rates of hyperglycemia or diabetes. Many of these studies have small sample sizes, flawed methodologies and treatment selection biases. Perhaps the best known is the 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.

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 blood glucose levels he used did not meet the criteria for diabetes.

Clearly, more robust methodology is essential 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 as well as many epidemiology studies.

### Scientific Background

**- Sell Sheet Data**

**Clinical trial data**

The main point of clinical trial graph is as follows:

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

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 patients treated with both agents had comparable rates.

The second graph depicts a 6-month study of ZYPREXA vs. risperidone in patients with schizophrenia (the Tran study). The incidence of treatment-emergent diabetes was 0.6% for patients treated with 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 patients treated with both agents had comparable rates.

The third graph (the HZ study) depicts an 11-month study of ZYPREXA vs. divalproex in patients with bipolar I disorder. The incidence of treatment-emergent diabetes for the ZYPREXA cohort was 0% and was 0.8% for the divalproex cohort. This means that none of the 125 ZYPREXA-treated patients and 1 of the 123 divalproex-treated patients developed treatment-emergent diabetes. The mean exposure time for both treatments was 4 months.

It is important to note that Lilly’s clinical trial data set is far larger 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

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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).

Epidemiology Data

Pharmacoepidemiology studies provide useful information about large unselected patient populations. A strength of these studies is the large sample sizes that allow sufficient statistical power to examine relatively rare events. Also, factors such as age, race, and gender can be analyzed in subpopulations with enough 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.

The primary limitation with pharmacoepidemiology is that treatment assignment is not randomized; therefore, limited information is available regarding individual patients (e.g., family history, weight, race etc). Because of this, it is difficult to ascertain causality.

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. Case reports provide neither an accurate numerator nor denominator to correctly assess rates of diabetes. Pharmacovigilance professionals assure us that a minority of side effects is 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).

So what is pharmacoepidemiology? Pharmacoepidemiology studies include reviews of 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. 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.

To better understand these studies, an understanding of the following terms is useful:

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 are 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 is the number describing the odds of developing diabetes. The odds ratio for the control group will be 1 and the odds ratio for the study groups will be the risk of developing diabetes relative to the control group. The odds ratio often does not control for factors such as age, gender, and concomitant medications. Relative risk and the 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 do not 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. For example, if ZYPREXA has a hazard ratio of 3.0, then you can expect 3 times as many patients on ZYPREXA to experience diabetes vs. the control group. Therefore, for every 5 patients in the control group that develops diabetes, you might expect 15 patients on ZYPREXA to develop diabetes.

The Epidemiology Graph in the Diabetes Sell Sheet contains the results of 5 epidemiology studies, 2 conducted by Janssen, 2 conducted by Lilly, and 1 independent study with over 100,000 patients in total. You may have noticed that we added a 5th independent, VA-sponsored study (Sernyak) because customers are
Diabetes Message - 2003

naturally more skeptical of pharmaceutical sponsored studies.

Let’s look at each study individually:

Lilly Advanced PCS Study (Buse)
The Lilly Advanced PCS Study is a 3-year retrospective, pharmacoepidemiology 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.

Results based on hazard ratio showed that there were no statistically significant differences in new antidiabetic prescriptions between patients treated with typicals or atypicals, or patients treated with ZYPREXA 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 ZYPREXA-treated patients.

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 of patients on ZYPREXA, risperidone, and typicals was in the same ballpark.

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.

Finally, a significantly increased risk of developing diabetes compared with the general population was observed in patients treated with typical or atypical antipsychotics.

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, average duration of treatment was not long, ranging from 68 days to 137 days, and the findings can only be generalized to patient populations similar to those represented in the PCS database.

Additionally, the PCS database did not contain information on well-known risk factors for diabetes, such as obesity, family history and non-caucasian ethnicity as well as the analysis also did not account for concomitant medications associated with glucose dysregulation.

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 carefully excluded patients recently taking antipsychotics and did not permit antipsychotic polypharmacy during the study, allowing a robust comparison among patients treated with conventional or atypical antipsychotics and a control group. 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. Additionally, the risk of developing diabetes was comparable between the ZYPREXA and risperidone cohorts.

Lilly IMS Study (Lage)
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 among patients treated with ZYPREXA, typical antipsychotics, and risperidone. The odds ratio for ZYPREXA- and risperidone-treated patients was not statistically significantly different from patients receiving typical medications.

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

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prescription claims and ICD-9 diagnosis information. Third, this was a yearlong 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 four 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. Third, the analysis does not control for patient ethnicity, a well-documented risk factor for diabetes. Last, the analysis does not control for family history of 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. Additionally, the actual incidence of treatment emergent diabetes was comparable among patients treated with ZYPREXA, typical antipsychotics and risperidone.

**Janssen Quebec Medicare Study (Caro)**

The Janssen Quebec Medicare study is similar in size to the Lilly PCS study with respect to the number of patients on risperidone and ZYPREXA, but there are no other comparison groups. Patients included in the risperidone treatment group could not be on ZYPREXA or clozapine. To be included in the ZYPREXA group, patients could not be on clozapine. 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 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 a perspective on whether rates of diabetes differ significantly on patient treated with risperidone vs. other drugs.

**Key Takeaway:** In the Quebec Medicare study, the incidence of diabetes and relative risk in patients treated with ZYPREXA or risperidone were clinically comparable and (depending on the analysis) of marginal statistical significance.

**Janssen Health Plans Study (Gianfrancesco)**

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 2 different managed care databases from different parts of the US 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, i.e., 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 neither has been proven. 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.

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 ZYPREXA, more so in that this study included only the first years of ZYPREXA availability, so that prescriptions would be more consistently “on label.”

Third, 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.

Fourth, 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 count for the very small numerical risk advantage over ZYPREXA they report.

For their overall analysis, no statistical test is reported for the comparison of the ZYPREXA and risperidone treatment groups, but the difference is very likely not significant. At least in scientific meetings, Janssen is emphasizing a complex sub analysis that amplifies the alleged risk during ZYPREXA treatment. 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 4 months prior to prescription.
Diabetes Message - 2003

of the antipsychotic of interest. 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 difference between the ZYPREXA and risperidone treatment groups; then, remarkably, they “estimate” annual risk by raising monthly risk to the power of 12. This exponential maneuver amplifies a small difference between the ZYPREXA and risperidone treatment groups 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; 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 inconsistent with several other epidemiology studies; they estimate that risk on risperidone is lower than on no antipsychotic treatment at all. Taken to its logical conclusion and multiplied out - this would probably make risperidone an antidiabetic agent!

It is important to note that even this analysis identifies the risk of diabetes in patients treated with ZYPREXA as falling within the range of patients treated with typical antipsychotic and about half that of clozapine-treated patients.

Key Takeaway: Competitors may use selected aspects of this dataset to support their argument that ZYPREXA has greatly elevated diabetes risk compared to risperidone. This is the smallest and the weakest of these five pharmacoepidemiology studies. We find their conclusion of lower risk for risperidone-treated patients to be unjustified because it reflects a smaller subgroup; flawed; inappropriate analysis; and biased study methodology. It conflicts with the overall results of this study and other available studies.

Independent, VA-sponsored study (Sernyak)
The Sernyak study, published in the American Journal of Psychiatry, 2002, is a 4-month retrospective analysis of 38,000 Veterans with Schizophrenia in a VA Hospital. The study found an increased prevalence rate of diabetes mellitus for patients treated with atypicals vs. typicals. The overall odds ratios for developing diabetes vs. typicals were 1.05 for risperidone, 1.11 for Zyprexa, 1.25 for clozapine and 1.31 for quetiapine. These odds ratios achieved statistical significance for all of the atypical cohorts except patients treated with risperidone. However, the confidence intervals for risperidone and olanzapine overlapped and the differences in the odds ratios in these two cohorts are not considered clinically significant.

This is a useful study because it highlights diabetes as an important concern for patients with Schizophrenia and does so irrespective of which atypical antipsychotic is being used. The authors point out that diabetes risk may be linked to the severity of the underlying psychotic condition.

Additional key insights regarding the study are as follows: First, because this is a retrospective prevalence study, it does not establish a causal relationship between the medication being administered and the incidence of diabetes. No consideration was given to existing medical conditions such as obesity, family history, etc.

Second, the same authors, using the same VA sample, previously suggested that Veterans on risperidone were less severely ill than Zyprexa patients. Patients with a greater severity of illness often present with more risk factors for diabetes at baseline.

Third, in an issue of VFW magazine, the incidence rate of diabetes among veterans was cited as 1 in 5, which is substantially higher than the general population.

Fourth, while the authors state that risperidone-treated patients, overall, did not have an increased prevalence of diabetes relative to patients treated with atypical antipsychotics, the confidence intervals overlapped with those of the ZYPREXA cohort. Moreover, in patients less than 40 years old, a significantly increased prevalence of diabetes was observed in all atypical cohorts.

Key takeaway: An increased prevalence of diabetes was observed in patients treated with clozapine, quetiapine and ZYPREXA, but not risperidone, compared to patients treated with typical antipsychotics. However, the confidence intervals of the ZYPREXA and risperidone cohorts overlapped and the differences in prevalence rates are not considered clinically significant. Some may misconstrue this study as showing that risperidone is safer than other atypicals. It would be detrimental to patients if clinicians lowered vigilance for diabetes when prescribing risperidone, given risperidone showed only numerically, not statistically lower risk than other atypicals. Clinicians should assess patients for risk factors of diabetes irrespective of psychotropic prescribed.

Now that we have reviewed the disease state of diabetes as well as scientific data in the Diabetes Sell Sheet, let’s look at the message itself.

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Diabetes Message - 2003

Diabetes Sell Sheet – Overview of Message Elements

1. Diabetes is **common** in the general population, and **even more common in patients with mental illness**. Patients with severe mental illness are 2-4 times as likely to develop diabetes than the general population.

2. Clinical trial and epidemiology studies show **no consistent differences** in rates of diabetes across frequently prescribed psychotropic.

3. Given this, it is important to **assess patients for risk factors of diabetes – irrespective of psychotropic prescribed**. Risk factors include: family history, non-Caucasian ethnicity, age over 45 etc.

4. Treatment selection should be based on the patient’s **underlying psychiatric condition** and the overall **risk/benefit profile** of the product.

**Message Element #1**

**Transition Statement** *(Use Risk/Benefit visual)*

“Doctor, you’ve told me today that Zyprexa helps you help your patients by __________. (use chips collected). But, you also have some concerns about diabetes. Let me share some information with you so that you can make your prescribing decisions based on the entire risk/benefit profile of Zyprexa.”

“**First, keep in mind that** ……..

· Diabetes is **common** in the general population, and **even more common in patients with mental illness**. Patients with severe mental illness are 2-4 times as likely to develop diabetes than the general population.”

**Message Element #2**

New language – “**No Consistent Differences** in rates of diabetes across frequently prescribed psychotropics.”

**Transition Statement**

“Although data shows that there is an increased prevalence of diabetes in patients with mental illness…..”

· “Clinical trial and epidemiology studies show **no consistent differences** in rates of diabetes across frequently prescribed psychotropics.”

(Show Clinical Trial and Epidemiology graphs).

**Message Element #3**

**Transition Statement**

“Given that patients with severe mental illness are at greater risk for diabetes than the general population and the lack of consistent differences in rates of diabetes among frequently prescribed psychotropics…”

· “It is important to **assess patients for risk factors of diabetes – irrespective of psychotropic prescribed**. Risk factors include: family history, non-caucasian ethnicity, age over 45, etc.”

(Reason for review – don’t assume they know them!)

**Message Element #4**

**Transition Statement**

“Doctor, like always, wouldn’t you agree that….”

· “Treatment selection should be based on the patient’s **underlying psychiatric condition** and the overall **risk/benefit profile** of the product.”

**Check for agreement:**

“Given ZYPREXA’S dependable control that helps you help your patients, wouldn’t you agree that the benefits of Zyprexa exceed the risks?”

**Diabetes Message Script**

– Putting It All Together

After getting an objection, first clarify the objection using the objection-handling algorithm. Make sure you understand the objection in its entirety. If a customer believes that weight gain leads to diabetes, then first handle the core concern of weight gain. However, given the level of noise in the marketplace on diabetes, customers often feel that there is something inherent to
Zyprexa that may be "causing diabetes" irrespective of weight gain concerns. At the conclusion of this backgrounder there is an AOC objection-handling algorithm to better help you get to the heart of your customers concern. Also remember that all physicians are not created equal. Knowing your customer will help you assess what is the right tool or resource to best handle the objection. Remember, the Diabetes Sell Sheet is one of many tools you have in your objection-handling arsenal. The NTTP program including Solutions for Wellness Personalized program, the "Ask the Experts: Addressing Treatment Issues: DVD", the Diabetes Education Program as well as weight management patient resources are all tools to assist you in helping customers help their patients. Additionally, the PCS Buse reprint and medical letters are available to answer unsolicited questions. Lastly, many of our customers like to hear from peers on these issues, making customer programming increasingly important.

Diabetes Message Script

Doctor, you’ve told me today that Zyprexa helps you help your patients by ______ (use chips collected). But, you also have some concerns about diabetes. Let me share some information with you so that you can make your prescribing decisions based on the entire risk/benefit profile of Zyprexa.

First, keep in mind that Diabetes is common in the general population at 6.2%, but it is even more common in patients with mental illness. Patients with severe mental illness are 2-4 times as likely to develop diabetes than the general population. An increased risk of diabetes for patients with mental illness has been reported since the 1950s even before the introduction of antipsychotic treatment.

Although data shows that there is an increased prevalence of diabetes in patients with mental illness, clinical trial and epidemiology studies show no consistent differences in rates of diabetes across frequently prescribed psychotropics. Doctor, I have 8 of these studies to show you today.

The first graph shows three 1-year studies of ZYPREXA vs. haloperidol, ZYPREXA vs. risperidone and ZYPREXA vs. divalproex. The study comparing ZYPREXA with haloperidol involved over 2000 patients and was the largest head-to-head study between 2 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.

The second graph contains five epidemiology studies, 2 by Lilly, 2 by Janssen and 1 independent, VA-sponsored study. These studies combined contain well over 100,000 patients and also show no consistent, clinically significant differences in rates of diabetes among patients treated with ZYPREXA and risperidone, quetiapine, clozapine as well as typical antipsychotics. As you can see, in some studies, the rate or risk of diabetes in patients treated with ZYPREXA was higher than in patients treated with other atypical antipsychotics and, in others, the rate or risk was lower.

Doctor, given that treatment selection of any one agent will not eliminate a patient’s risk for diabetes and these patients are at greater risk than the general population, it is important to assess your patients for risk factors of diabetes—irrespective of psychotropic prescribed. Risk factors include (but are not limited to): non-Caucasian ethnicity, age 45 years or older, being overweight (BMI greater than 25), dyslipidemia, lack of exercise, hypertension, polycystic ovary syndrome, history of glucose intolerance, family history, and a history of gestational diabetes or delivering a baby greater than 9 pounds.

Doctor, like always, wouldn’t you agree that treatment selection should be based on the patient’s underlying psychiatric condition and the overall risk/benefit profile of the product?

Check for agreement:
Given ZYPREXA’S dependable control that helps you help your patients, wouldn’t you agree that the benefits of Zyprexa exceed the risks?

If no, ask what other information or resources the customer needs.

If yes, “allow me to show you some more information on how ZYPREXA’S dependable control can help you help your patients.”
Revised AOC Algorithm - Retail

AOC- wt. gain

"I like Zyprexa but I am concerned about weight gain"

Review chips already gained from dialogue

Show customer how to predict pronounced weight gain early using rapid/non-rapid graph

Solutions for Wellness and CAPS

AOC- diabetes

"I am concerned that Zyprexa causes diabetes"

Clarity: Is the AOC actually weight gain?

YES

Diabetes Sell Sheet

NO

Uncorrelated question that PCS report can answer. Use to answer question only per OPP 01/2004

Proactive Use: PCS Repeat Verbatim and copy (could be used at beginning or end of week)

Back to core message

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That number seems high. I couldn’t find anything to confirm or refute.