June 2001

ZYPREXA® (olanzapine)

Primary Care

Q3 Implementation Guide

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Strategy Overview

Overview

12 months ago, Lilly had not yet made the decision to launch ZYPREXA in primary care.

8 months ago, we met in Orlando for a very successful—and memorable—launch meeting.

Just over 3 months ago in Dallas, we reviewed the positive impact we've had on patients, families, doctors, and Lilly's bottom line.

"Viva ZYPREXA!" is more than a signature; it's a battle cry to make sure that every day we bring energy and passion to our customers, who are still getting acquainted with this incredible molecule. At the June 2001 district meetings, you will have the opportunity to take that energy to the next level. We have evolved the sales aid and message flow to better meet the needs of customers—identifying the right patient and linking that patient with the right safety and efficacy data. We are launching a powerful new reprint that highlights the efficacy of ZYPREXA in the treatment of mood and depressive symptoms. And we've just completed a 3-part "Lunch & Learn" CD that offers a new and effective way to tell a patient-focused ZYPREXA story.

New Sales Aid Message

The new sales aid message flow is an evolution, not a radical redesign. We've listened to our customers in market research, and we've listened to those in the field via the new Message Management process. The result is a tight, powerful sales aid that is effective in an in-depth 30-minute visit or a stand-up 30-second summary.

The primary difference in this piece is that we structure each major spread around a **patient**, not around data. In other words, when you paint a picture of a specific patient type, you need not jump around the piece to show supporting evidence. It's all right there, in one place, enabling you to create action on the spot.

You'll see an old friend (Martha) and meet two new ones: Michael and Kelly. Michael exhibits clear signs and symptoms of bipolar disorder, without appearing to be as threatening as his predecessor

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(David). Kelly struggles with mild to moderate psychosis, with visible elements of a mood component. Again, the intent was to make Kelly more "treatable" by a PCP (versus the defiant Christine).

In each spread, safety information and efficacy data have been tailored to the patient type. For example, a doctor may be more concerned about drug interactions in an older patient and pregnancy issues in a young female. Sounds obvious, but the goal is to open and close on a single patient type without turning a page. As with the previous piece, the more time you have, the richer the discussion; subsequent pages on safety and ease of use offer additional patient benefits.

You'll see more head-to-head data in the new sales aid, including the results from a recent trial of ZYPREXA versus Depakote. From listening to customers, it's clear that ZYPREXA doesn't get enough recognition as a mood stabilizer. The fact is, ZYPREXA is indicated for the treatment of acute bipolar mania, in the same league as lithium and Depakote but with big advantages. In addition to the data, you'll see more references in the script comparing ZYPREXA favorably with lithium and Depakote.

Under "Ease of Use," we've added ZYPREXA Zydis, the orally disintegrating tablet. While Zydis tablets cost about $1 more apiece than the original oral tablets, keep in mind that price comparisons in primary care favor ZYPREXA. At the most common doses in primary care, ZYPREXA is about equal to Risperdal and much less expensive (30% to 50%) than Geodon.

As we expand the ZYPREXA Brand in primary care, sales representatives can now order limited quantities of 10-mg samples. These are particularly appropriate for patients such as Michael, who will likely respond better to higher doses of ZYPREXA. Kelly and Martha are more appropriate for 5 mg and 2.5 mg, respectively. This segmentation by dose may help the PCP identify and differentiate ZYPREXA patients in his/her practice. As you educate your customers, encourage them to reach adequate doses of ZYPREXA. More severely ill patients—like Michael—require higher doses (eg, 10-15 mg).

Market Segmentation

Safety is the first and foremost consideration for PCPs when discussing ZYPREXA. Regardless of customer group, safety emerges as the most significant barrier to considering antipsychotics, and it is the first issue that must be addressed when speaking to PCPs about trying ZYPREXA.

But one size rarely fits all, and our marketing strategy is evolving to reflect just that. After 8 months of calling on customers, you know there are differences in how customers view the world. To help your precall planning, here's what we've learned in market research:

Family Practitioners

Family practitioners treat patients with a more holistic approach and are therefore more likely to treat their mentally ill patients rather than refer them. Mutual trust and established relationships, both with the patient and their family, are significantly important to how and when they prescribe. They are also more likely to have a working relationship with a psychiatrist.

When speaking with a family practitioner, focus on patient benefits. Be sure to include family involvement and support for the patient. Focus on themes such as rapport, trust, and help. Read through the family members' comments in the patient profile. Peer-to-peer contact with early adopter PCPs may be appropriate.

Internists

Internists are generally more "scientific" in their treatment approach and are more apt to refer patients, to call in specialists such as neurologists and psychiatrists, regardless of patient wait time. They are more likely to ask questions regarding diagnosis, mechanism of action, onset of action, and label indication.

When speaking with an internist, focus on data. Family comments should be de-emphasized when discussing patient profiles. Possible diagnosis and label indications should be discussed early in the conversation. Peer-to-peer contact with psychiatrists, as well as CME content, may be a good fit with this segment.

Geodon

Geodon launched in March. Almost immediately, we began hearing reports of its presence in primary care. This is exactly what we expected. We've listened carefully to customers who have some clinical experience with it, especially psychiatrists, and their feedback has been consistent with what we expected.

Here's what customers hear Pfizer saying:

1. Pfizer is positioning cardiac safety/QTc as a class effect
2. Weight gain hurts compliance, and leads to hyperglycemia and diabetes
3. Geodon efficacy is equal to that of ZYPREXA (especially in treating mood symptoms)
4. Geodon is less expensive

Here's how customers describe Geodon:

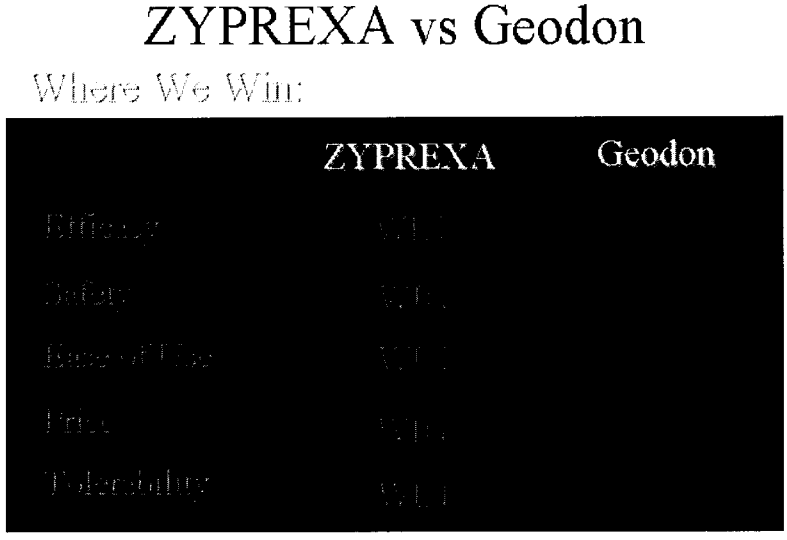
1. New treatment alternative is welcome
2. Cardiac risk relatively unconcerning
3. Efficacy is unimpressive—many of those who switched have been switched back
4. Target dose is unclear; physicians are not sure what dose to aim for
5. Geodon is not well tolerated and particularly seems to cause nausea
6. "Take with food" hard to enforce
7. EPS expected to be dose-dependent, like Risperdal

The key takeaway here is that Pfizer has overpromised. That doesn't mean they're going to go away quietly, however. It is absolutely critical that we continue to differentiate the efficacy, safety, tolerability, and ease of use of ZYPREXA.

Regarding QTc, the Brand team is working on an audioconference that frames the issue of cardiovascular risk, and we're preparing a one-page sell sheet with Pfizer's own data that proves that all atypicals are **not** created equal. In the March issue of the *Journal of Clinical Psychiatry*, a study of 2700 patients concluded that ZYPREXA has a **neutral** effect on key cardiovascular measures, including QTc prolongation. Cardiovascular risk is a choice, not a necessity; the data are clear that QTc prolongation is not a class effect. However, it's more important to note that in competing with Geodon, we have much more than just cardiac safety going for us. Listen to customers; they have concerns about Geodon's efficacy (no separation from Haldol), safety (EPS as well as QTc), tolerability (nausea), and ease of use

(BID, taken with food); the four cornerstones of the profile of ZYPREXA. Be confident in the superiority of ZYPREXA and don't give Geodon more airtime than it deserves. It's simply not a primary care drug.

Recall the following slide from the national meeting:



Which drug would you rather sell?

Weight Gain

You may have heard reports from the American Psychiatric Association meeting in which Lilly described encouraging results with concomitant use of Axid 300 mg BID. There was also a report demonstrating the benefit of counseling in the management of weight. These studies reinforce our message: not all patients on ZYPREXA gain weight, but for those who do, many will respond to ordinary diet and exercise interventions. Occasionally, the clinician will need to reevaluate the risk/benefit ratio and may elect a pharmacological intervention (such as Axid) or switch the patient to another agent. Because of its broad symptom efficacy, tolerability, safety, and ease of use, **ZYPREXA is the place to start**—and most patients will do very well.

Keep in mind that because ZYPREXA is an extremely successful and profitable brand, it carries a sort of bulls-eye on its back. This is a result of being a leader in a highly competitive environment. Because ZYPREXA has so few negatives, competitors load up on the issues where they think they can get traction: weight gain, hyperglycemia, diabetes, and cholesterol. The reality is that ZYPREXA has treated

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more than 6 million patients, so we know exactly what to expect. We know that weight gain can occur, but in the context of efficacy and other safety factors, psychiatrists, PCPs, and patients continue to choose ZYPREXA despite that possibility.

Hyperglycemia and Diabetes

This new sell sheet can be summarized in 2 words: **comparable rates**.

Many variables can play a role in the development of diabetes, including age, family history, ethnicity, and excessive alcohol use. Obesity, defined as being more than 20% above ideal body weight, is also a risk factor. Janssen and Pfizer would have you believe that the weight gain associated with ZYPREXA causes diabetes in patients, accelerating its onset. The truth is, the incidence of diabetes in patients on atypical antipsychotics is comparable.

Obesity clearly increases the risk of becoming diabetic. But if the cause-and-effect relationship between ZYPREXA and diabetes were that simple, why don't we see drastically different rates of incidence? Primary care physicians may be more likely to appreciate the ZYPREXA data due to their comfort in the diagnosis and treatment of diabetes.

The front page of the sell sheet has 2 simple graphs: one is a head-to-head comparison with Haldol, the other is a head-to-head comparison with Risperdal. In both cases, the incidence of diabetes—in hundreds of patients over several months—was low (less than 1%) and comparable. The differences in random plasma glucose elevation were small and not clinically significant.

The back page contains helpful information regarding the prevalence of diabetes in the general population (approximately 7.8% of all adults) and the prevalence of type 2 diabetes among patients with schizophrenia and bipolar disorder (double to quadruple the rate found in the general population). There is also a listing of factors that affect risk for diabetes along with information about ZYPREXA and the relationship between weight gain and hyperglycemia.

The key takeaway is this: while diabetes is frequently seen in patients who take atypical antipsychotics, there are no data to support a claim that any one agent increases the risk of developing the disease.

Again, the bottom line when discussing diabetes and hypoglycemia is **comparable rates**.

ZYPREXA as an Atypical Antipsychotic

We are committed to positioning ZYPREXA as a broad-spectrum psychotropic to differentiate it from other antipsychotics, and to reflect its mood stabilizing properties. Our advisory board is passionate on this point. This type of branding takes time, repetition, and internal commitment.

The label of psychotropic is broader than antipsychotic, but it may confuse some customers who are trying to figure out what "box" ZYPREXA belongs in. As Geodon and Risperdal become more visible in primary care, they will try to commoditize efficacy. Our strategy is to prove that ZYPREXA, because of its unique pharmacology, deserves to be considered in a class by itself.

With regard to atypical antipsychotics, it is important that your customers understand what makes an antipsychotic "atypical." There are 3 attributes that separate the newer agents from drugs such as Haldol, Thorazine, and Mellaril:

1. Broader efficacy (in treating negative as well as positive symptoms)
2. Greatly reduced risk of EPS and TD
3. Neutral clinical impact on prolactin

As you can see, Risperdal doesn't exactly fit the criteria for atypicality. While this is an argument better reserved for academics and purists, it explains why we refer to Risperdal as an "older antipsychotic," rather than include it among the atypicals. Without question, Risperdal was an improvement over the agents that preceded it. But the broad symptom efficacy, safety, and ease of use offered by ZYPREXA have raised the bar much higher. We will be consistent and persistent in our customer communications—CME programs, symposia, publications, slide kits—to brand ZYPREXA as a broad spectrum psychotropic.

Message

Cover

Doctor, you see patients every day struggling with mental illness, presenting with symptoms like these: agitation, mood disturbance, emotional withdrawal. These are **your** patients. They **trust you** and **count on you** to help them. ZYPREXA can help.

Doctors like you are getting clinical experience—and good results—with ZYPREXA, which is a safe, proven atypical antipsychotic with broad symptom efficacy.

Until recently, antipsychotics didn't seem appropriate for primary care. But remember, the same could be said of antidepressants just 15 years ago. What changed? New drugs, like Prozac, were safer, better tolerated, and easy to use. In a similar way, ZYPREXA has a profile that is quite different from older antipsychotics and mood stabilizers. ZYPREXA is changing the way primary care physicians treat mental illness.

So who are the ZYPREXA patients in your practice?

High-Ground Opener

ZYPREXA was launched in 1996 and has since been used by more than **6 million patients** worldwide, so it has a **proven** track record.

ZYPREXA is indicated for the treatment of schizophrenia and acute mania. You may be thinking, "sounds like a drug for psychiatrists," and you're right. But ZYPREXA also has a place in primary care. The symptoms that make up common psychiatric scales are the **same symptoms** you see in your office—symptoms such as agitation and hostility, anxiety, emotional withdrawal, even suspiciousness. And many of your patients won't see a specialist. It's reported that only about **one third** of referrals to psychiatrists actually happen. So it's often **up to you** to deal with the problem. And ZYPREXA offers safety, broad symptom efficacy, and ease of use.

Let's meet one of your patients.

Martha Spread

This is Martha. Martha is a widow who lives independently and has been your patient for some time. She is becoming more complicated to manage, and you note increasing agitation. Her sleep is disturbed; she dozes during the day and is up most of the night. Her family has shared their concerns with you, saying, "She thinks we're trying to take advantage of her."

Martha's family doesn't want to send her to a nursing home, but her agitation and confusion must be addressed. Your goals of treatment for Martha may include reducing her behavioral disturbances without impairing her cognitive functioning.

PROBE: Do you see patients like Martha? What medication(s) do you prescribe in treating her behavioral disturbances?

ZYPREXA is a safe choice for Martha. It has a low potential for drug interactions and anticholinergic side effects. Unlike drugs such as Haldol or Risperdal, ZYPREXA has an **EPS profile that is comparable to placebo** across the full dosing range.

As I said before, ZYPREXA is quite different from older antipsychotics, so you can be confident treating Martha with a low dose. The most common side effect is somnolence, which is dose-dependent, so a starting dose of 5 mg—or even 2.5 mg—at bedtime is appropriate. In fact, this could help Martha's poor sleep.

Doctor, ZYPREXA works. It has proven effective in reducing hostility as early as the first week. Early improvement will give Martha—and her family—confidence in the treatment you've prescribed. And ZYPREXA won't impair Martha's cognition; in fact, it actually improved cognition in prelaunch trials. (If the physician asks, a medical letter on the use of ZYPREXA in older populations is available.) Would you agree that these are important benefits for this patient?

Doctor, will you give ZYPREXA a try in a patient like Martha? (Would you consider trying ZYPREXA in adults of all ages who present with secondary anger, agitation, and tension?)

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Michael Spread

This is Michael. Michael is a professional in his mid 30s. He's highly functional, but his wife says that he's always been prone to mood swings, and lately, things have gotten worse.

You rule out substance abuse and possible organic causes, and you're left with a complicated mood disturbance. The last time you saw Michael, he seemed down, unmotivated, detached. You prescribed an antidepressant. Now, 2 months later, he appears "wired," irritable, and anxious, and he hasn't been sleeping much.

His wife is very concerned, not only about Michael's health, but also his recent spending habits and erratic behavior.

Michael says he won't "see a psychiatrist." In fact, he denies that there's anything wrong with him. Simply switching antidepressants may not alleviate his symptoms. Your goals of therapy for Michael may include stabilizing his mood while reducing his agitation.

ZYPREXA, unlike mood stabilizers such as Depakote or lithium, does not carry any black-box or bolded warnings in its package insert. There is no routine blood monitoring required with ZYPREXA, and its cardiovascular safety is proven. ZYPREXA enables you to prescribe with confidence and without hassles. The most common side effect is somnolence, which is dose-dependent, and for a patient like Michael, a calming effect may be desirable.

Doctor, ZYPREXA works. In this head-to-head study versus Depakote, the most widely used mood stabilizer, ZYPREXA was **equivalent or superior in all symptoms** of bipolar disorder. Even if you don't use Depakote, notice how effective ZYPREXA was in treating elevated mood and irritability, and in improving sleep. Would you agree Michael could benefit from a trial of ZYPREXA? Dosing for a patient like Michael should be higher than in a patient like Martha; in fact, efficacy in bipolar mania was demonstrated at a dose range of 10 to 15 mg in clinical trials.

ZYPREXA has not been studied in bipolar depression, but it's worth noting that in bipolar mania trials, there was actually **improvement in depressive symptoms**. Does this give you enough information to try ZYPREXA in a patient like Michael?

Kelly Spread

This is Kelly. Kelly is in her early 20s and has gradually become socially isolated and fearful. Her personal hygiene is starting to decline and she is difficult to draw out. You rule out substance abuse and assess her to have a low risk of suicidal ideation. Still, the medications you've prescribed—including antidepressants—haven't helped much.

Kelly's family has shared their concerns with you, saying, "She thinks people are talking about her behind her back."

Your goals of therapy for Kelly may include improving her mood and ability to think clearly, while reducing her suspiciousness.

ZYPREXA is a safe choice for Kelly. Compared with Risperdal, an older antipsychotic, ZYPREXA has significantly fewer extrapyramidal side effects and a significantly lower elevation of prolactin levels. What this means for Kelly is that treatment-emergent side effects, such as movement disorders and sexual dysfunction, are much less likely with ZYPREXA.

Doctor, ZYPREXA works. In a head-to-head study with Risperdal, ZYPREXA patients were much more likely to achieve the highest levels of symptom improvement. At 20% or 30% improvement, Kelly might get out of her chair; ZYPREXA and Risperdal were roughly equivalent. However, at 40% and 50% improvement, the difference is dramatic: she may start to take pride in her appearance, be on the phone with friends, and may have a positive outlook on life. ZYPREXA patients were significantly more likely to reach this level of dramatic improvement.

In symptoms such as social withdrawal and blunted affect (which psychiatrists call "negative symptoms"), ZYPREXA was superior to Risperdal in resolving those symptoms. Have I convinced you to give ZYPREXA a try in patients like Kelly?

Safety Spread

Doctor, safety is a major factor for you in the selection of any drug, from any class. Clinical use of ZYPREXA now totals more than 6 million patients worldwide, so doctors know what to expect. And because of that clinical experience, **you can expect ZYPREXA to be a safe, dependable choice.**

ZYPREXA is proven safe in maintenance treatment. In this head-to-head study with Risperdal, 339 patients over 28 weeks, you can see that only about 1 in 10 patients experienced a relapse on ZYPREXA, while about 3 in 10 did on Risperdal.

Extrapyramidal symptoms have long been associated with the older antipsychotics, but ZYPREXA has a profile that is quite different. EPS is comparable to placebo in all doses, so you can prescribe ZYPREXA with confidence.

There is a low risk of certain serious medical complications associated with ZYPREXA, which makes it an appropriate choice for many patients. Think of the agents you currently use for patients who present with agitation, irritability, elevated mood, or emotional withdrawal, and compare those agents to ZYPREXA in these categories:

- Drug interactions

Patients are often on multiple meds; ZYPREXA doesn't inhibit P450 cytochromes.

- Cardiac safety

Patients at risk for cardiovascular disease need an agent that doesn't prolong QTc; ZYPREXA compares favorably here to agents such as Mellaril and Geodon, which carry a black-box and a bolded warning, respectively.

- Routine blood monitoring

Patients don't like needlesticks; ZYPREXA can save costs and improve compliance.

- Black-box or bolded warnings in the PI

Patients deserve safe agents; doctors appreciate avoiding liability.

- Anticholinergic side effects

Incidence of serious anticholinergic events with ZYPREXA was not statistically different from placebo.

- Elevated prolactin

Agents such as Risperdal and Haldol are more likely to cause hyperprolactinemia, which can lead to amenorrhea, galactorrhea, and sexual dysfunction.

- Teratogenicity

ZYPREXA is pregnancy category C, unlike older mood stabilizers such as lithium and Depakote, which are rated pregnancy category D.

The bottom line, doctor, is that ZYPREXA is a safe, proven solution for patients suffering from mood, thought, and behavioral disturbances.

Ease of Use Spread

Another reason ZYPREXA is so popular among your colleagues is its ease of use: once a day, with or without food, with no mandatory titration. It doesn't get much easier than that. And that's important for the patients we're talking about, who may be easily confused or overwhelmed. With some agents, like Seroquel or Geodon, the target dose is unclear. In contrast, the starting dose and therapeutic dose for ZYPREXA are often one and the same. Now that's simplicity.

The starting dosage for ZYPREXA depends on the patient. We recommend a lower dosage, such as 5 mg or 2.5 mg once a day, for a patient like Martha; a patient like Michael will respond better to a 10-mg QD dosage. Somnolence is the most common side effect, so we recommend bedtime dosing. For additional flexibility, consider our orally disintegrating tablets, which are called ZYPREXA Zydis. These are appropriate for patients who have difficulty swallowing or when you suspect a patient may "cheek" or spit their medication.

The best evidence I can show you that ZYPREXA is well tolerated is this graph. The **discontinuation rate due to adverse events is comparable to placebo**. Very few agents—in any class—can make that claim.

PROBE: Doctor, does this increase your comfort level with ZYPREXA?

All drugs have side effects, and ZYPREXA is no exception. We've discussed somnolence, which you'll recall is dose-dependent. You should also know that some of your ZYPREXA patients may gain weight due to an increased appetite. Not all ZYPREXA patients gain weight, and the majority of those who do will benefit from simple diet and exercise interventions. However, there may be situations in which weight gain causes you to reexamine the risk/benefit ratio of keeping a patient on ZYPREXA. Because of its profile of safety, broad symptom efficacy, and ease of use, many of your colleagues elect to manage the weight gain rather than switch agents.

Back Cover/Close

In summary, doctor, prescribing ZYPREXA is a **safe, proven solution** for patients like Martha/Michael/Kelly who suffer with **mood, thought, and behavioral disturbances**. It's easy to use, and it works.

What questions do you have about ZYPREXA? Are there patients in your practice like Martha/Michael/Kelly who could be doing better? How can I help you help these patients?

[*Gain agreement on 2 things: action to be taken to increase ZYPREXA use and involvement in peer-to-peer intervention, eg, program, audioconference, CME, etc.*]

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Objection Handling

I understand ZYPREXA works, but it causes so much weight gain.

Rep: Doctor, have your patients on ZYPREXA gained weight or have you heard ZYPREXA causes weight gain?

Dr: I've seen it in a few of my patients.

Rep: I can see how it could be a concern for you and your patients. Weight gain is associated with many antipsychotics, mood stabilizers, and antidepressants. Doctor, not all patients gain weight on ZYPREXA.

When you have 500 patients on ZYPREXA (and I hope someday you will), this is what the weight-change curve will look like [*show weight-change sell sheet*]. 25% of your patients will have lost weight. 50% of your patients will either have lost weight or will have gained no more than 11 pounds. Of those patients who do gain weight, it will plateau at around 39 weeks. You'll also be glad to know that behavioral modifications such as diet and exercise can really help.

I'm sure you want your patients to experience the full symptom efficacy of ZYPREXA, so keep in mind that weight gain is usually seen in patients with lower BMIs and is not dose-dependent. So you wouldn't want to dose down if a patient experienced some weight gain.

Doctor, consider the efficacy of ZYPREXA for behavior, mood, and thought disturbances coupled with its safety and ease of use. Also take into account that weight change is manageable. Does this make you more comfortable with the overall profile of ZYPREXA? Are you willing to prescribe ZYPREXA for a patient like Martha/Michael/Kelly?

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I don't treat patients with schizophrenia or bipolar disorder, I refer them to psychiatric treatment.

Rep: Doctor, that makes sense. Patients with moderate to severe symptoms of schizophrenia and bipolar disorder should be treated by a psychiatrist. However, in your own practice there are probably patients who may experience symptoms such as elevated mood, emotional withdrawal, and agitation who may benefit from ZYPREXA. Keep in mind that referrals can be expensive, time-consuming, or logistically difficult. Also, it is reported that about two thirds of patients who are scheduled for a referral never make it. What will you do with them?

ZYPREXA is an excellent option. It improves the quality of the patient's life and therefore the lives of family members.

Let's spend some time reviewing who in your own practice might benefit from ZYPREXA. Let me introduce you to Martha.

Your Michael patient looks scary. I would not even want to be in the same room with him.

Rep: Michael is in the postmanic crash phrase. He is spending money he and his wife do not have, and the bills, lack of sleep, and manic behavior are catching up with him. You see him in your office when a family member has forced him to see an MD, and he is resisting your efforts to refer him to a psychiatrist.

Michael needs your help and he needs ZYPREXA. ZYPREXA will calm his elevated mood and help him get some sleep.

With Martha I would just prescribe a cholinesterase inhibitor, such as Aricept. They are supposed to be pretty good with agitation.

Rep: Have you tried to use Aricept with Martha for her behavior? Doctor, the cholinesterase inhibitors are indicated for dementia and do show some limited improvement in cognition. The Aricept

representatives are trying to expand their target patient population by reaching into behavior-type symptoms. But the data are limited at best. Why not prescribe ZYPREXA, which has proven efficacy for agitation and related behavioral disturbances, has been on the market for more than 4 years, and has helped over 6 million patients with symptoms just like Martha's?

I am concerned about the higher doses that you are recommending for Michael. I have never prescribed over 5 mg.

Rep: What concerns you about a higher dose? The incidence of EPS associated with ZYPREXA is equal to placebo across the entire dosage range. With ZYPREXA, you therefore have the flexibility to dose for desired therapeutic effect without worrying about unwanted side effects. If sedation concerns you, it may actually be a benefit in a patient like Michael.

The Pfizer rep was just here and told me about Geodon. I understand that it has the efficacy of ZYPREXA without the weight gain.

Rep: What efficacy data did the Pfizer rep share with you? Did he or she mention the QTc bolded warnings in the Geodon PI? Did he or she explain the complicated dosing?

If you look at the Geodon PI closely, a number of issues come to light, such as:

- Geodon's inconsistent efficacy data showed little—if any—improvement over Haldol.
- Ten bolded paragraphs highlight the warnings for prolonged QTc and unpredictable related risk of sudden death.
- Geodon was shown to have clinical efficacy only at higher doses (80-160 mg/day), which may lead to dose-dependent side effects.
- It must be taken with food and is BID.

Doctor, with ZYPREXA your patients will benefit from more than 4 years of market experience in 6 million patients, as opposed to trying an unproven product with a questionable safety profile. ZYPREXA is safe, effective, and easy to use. Let's explore some of the patients in your practice who would benefit from ZYPREXA.

Commonly Asked Questions

How should I transfer patients from a typical agent, such as Haldol, to ZYPREXA?

There are limited data to suggest a definitive method for transferring a patient from one antipsychotic to ZYPREXA. Although each patient will require a tailored approach using your best clinical judgment, we suggest adding ZYPREXA at a full target dose to the patient's current regimen and gradually tapering the other agent to reduce the risk of rebound symptoms. In an older or more sensitive patient, such as Martha, you may consider using a lower starting dose of ZYPREXA, such as 2.5 mg [offer medical letter].

What is the recommended starting dose of ZYPREXA?

The recommended starting dose depends on the patient and the severity of symptoms that are present. A patient like Martha, who may be fragile and especially vulnerable to side effects, may require a lower starting dose (2.5-5 mg). In addition, you might consider this low starting dose for patients with multiple medical conditions.

For a patient like Michael, who may be suffering from bipolar disorder, we would recommend a higher starting dose of 10-15 mg. Two placebo trials were completed for the indication of ZYPREXA in bipolar mania, and both proved ZYPREXA was effective. Patients responded quickly, as early as week one, and robustly, while experiencing few adverse events.

A patient like Kelly offers you the flexibility to "start low and go slow"—but to go as high as needed based on therapeutic effect. One advantage of ZYPREXA is that you generally do not have to worry about increasing side effects as you raise the dose. Please keep in mind that several dosage forms (ranging from 2.5 to 20 mg) are available for your convenience.

Can I break the tablets?

Since ZYPREXA tablets are not scored, we don't recommend breaking them. Split or broken tablets will oxidize, thereby potentially corrupting the integrity of the tablet. However, for your convenience, we offer several dosage forms (2.5, 5, 7.5, 10, 15, and 20 mg), as well as ZYPREXA Zydis, orally disintegrating

tablets in 5 and 10 mg for those who have difficulty swallowing pills or those who cheek or spit their medication.

Isn't there sedation with ZYPREXA?

In both of the placebo-controlled clinical trials mentioned here, somnolence was reported as the most common adverse event and occurred more often than with placebo. Some of your colleagues have mentioned that sedation can be transient, and, in fact, may be a benefit for those having trouble sleeping. Patients have described ZYPREXA as having a "calming" effect. One recommendation would be to dose ZYPREXA once daily at night to help with sleep and avoid possible drowsiness during the day.

Why are the EPS numbers you're showing me so high, especially in relation to placebo?

Doctor, I understand one of the biggest safety concerns you have is EPS/TD. You can be assured that whether your patient needs a low or high dose of ZYPREXA, the risk for EPS is low. Unlike other products, both conventional and atypicals agents, ZYPREXA does not have dose-dependent EPS.

The data on this particular table [page 8 of sales aid] were taken from a schizophrenia study in which patients were very sick and had been on several medications for years, including conventional antipsychotics. Therefore, the percentages shown for EPS are considerably higher than they would be for a less sick population or one that hadn't been on many older agents to control their schizophrenia in the past.

Therefore, to reiterate, since its EPS profile is comparable to placebo, you can prescribe ZYPREXA with confidence.

What does pregnancy category C mean—and is that good?

Pregnancy category C means that no teratogenic effects were observed in clinical trials. Compare this with a pregnancy category D medication, like Depakote or lithium, with which teratogenic effects have been observed. We are not recommending that ZYPREXA should be used in pregnant women. However, should a patient become pregnant (and 50% of all pregnancies are unplanned), isn't a category C drug less worrisome compared with a category D medication?

What can you tell me about blood glucose and ZYPREXA?

As you know, glucose elevation is an issue in the general US population and more common in those with psychiatric illness. Lilly, as a leader in diabetes care, will continue to offer solutions for managing glucose.

In a retrospective study of more than 5000 patients, the incidence of treatment-emergent glucose elevation with ZYPREXA was similar to that of placebo. If you do see a patient with elevated glucose, it is important to look for the root cause [offer medical letter].

Does ZYPREXA lead to an increased incidence of diabetes?

No. During 3 yearlong studies of ZYPREXA versus Haldol with over 2000 patients, the incidence of treatment-emergent diabetes, that is, diabetes diagnosed during the clinical trial, was less than 1% for each agent. Note that the same holds true in a 6-month study comparing ZYPREXA to Risperdal; in this study, the incidence of treatment-emergent diabetes was 0.6% for both ZYPREXA and Risperdal [offer medical letter].

How much does ZYPREXA cost?

I understand that price is a concern for your patients, or that some of my competitors may have talked to you about the cost of ZYPREXA. I recently visited our local pharmacy and found the average monthly cost for 5 mg QD of ZYPREXA was $____. I also reviewed the cost of other atypicals and found these costs at starting doses: Risperdal (0.5 mg BID) $____, Seroquel (200 mg BID) $____, and Geodon (20 mg BID) $____.

I hate to ask my patients to pay for a prescription when I'm not sure how they will respond to the drug.

I am more than willing to assist you with resources (samples, trial scripts) to provide an initial trial of ZYPREXA for your patients suffering from behavior, mood, or thought disturbances. In addition, for those of your patients who are indigent, Lilly has an excellent program called "Lilly Cares," which assists those in need with medication on a regular basis.

Helpful Hints

Cover

Michael may be perceived as a little threatening. During market research, doctors were much less hesitant to treat him if they knew he was a bipolar patient and we framed him as being in the postmanic "crash" phase. He has just spent months spending money he and his wife do not have, the bills are piling up, and he is feeling the pressure.

High-Ground Opener

In longer calls, it may help frame this page with the following statement: "Doctor, the goal of today is to get you to consider using ZYPREXA in patients whom you may not have considered before. I will present patients who are suffering from behavior, mood, or thought disturbances. I will frame our discussion of ZYPREXA around its safety, efficacy, and ease of use."

Martha Spread

An important point here is the low potential for anticholinergic side effects such as dizziness, dehydration, and lack of steadiness. Martha cannot afford to fall and potentially break a hip due to her medication.

Secondly, older patients are frequently on several medications, such as cholesterol-lowering agents or anti-hypertensive medications. It is crucial to point out that with ZYPREXA, the potential for drug-drug interaction is minimal.

You will note that on the right-hand side of the spread under the cognition information is a space that has been intentionally left open. Upon launch of the IM formulation of ZYPREXA, we will be placing a sticker in this spot to announce the new formulation and new indication (agitation associated with dementia).

Michael Spread

When presenting the Michael profile, it is critical to understand that patients suffering from bipolar disorder will not want to see an MD during the manic phase. They like feeling manic and cannot

understand how their actions are hurting others. Typically, patients will be more willing to see an MD when they are depressed. The MD will more than likely diagnose depression and prescribe an antidepressant. Typically, this will induce mania, and the patient and family members are back in the MD's office wondering what went wrong. Therefore, the MD must do a more thorough examination of the patient's history. If the MD takes the time to ask, more details of manic phases in the patient's background may come to light. This will lead to a more accurate diagnosis and a more positive outcome.

As noted in the script, it is important to mention that the MD has ruled out drug abuse and organic causes, so that the focus is on his mood disturbance. A phrase that resonates with many MDs is talking about the patient with "mood instability."

It is tempting to skip over the somnolence bullet, because it appears to be a negative for ZYPREXA. However, this can be positioned as a calming effect for a patient like Michael and therefore become a positive.

Obviously, we have a tremendous amount of data here on the treatment of manic symptoms as compared to Depakote. In market research, elevated mood, irritability, speech, and disruptive/aggressive behavior were selected as the most important by MDs. It is important to ask your MD which of these symptoms are most important to his/her patient.

Physicians may ask, "Is ZYPREXA indicated in bipolar depression?" (NO) or, "Will ZYPREXA help with depressive symptoms?" (YES). In one study of manic and mixed patients with substantial depressive symptoms, ZYPREXA did show improvement in depressive symptoms.

As you can see on the bottom right of the spread, we are recommending a higher dose in patients suffering from bipolar mania. In monotherapy, titrating to a dose of 10 to 15 mg may be necessary. Your physicians may be initially uncomfortable with this high dose. Remind them that bipolar patients need a higher dose, a lower dose may not alleviate symptoms, and the incidence of EPS is equal to placebo across the entire dose range.

Kelly Spread

Primary care physicians who treat patients like Kelly will diagnose and prescribe either an antidepressant for her mood symptoms (emotionally withdrawn or guilt feelings, for example) or an antipsychotic for her thought disturbances (fear, isolation, poor hygiene, or delusions, for example). For that reason, the Tran

data is presented on the right-hand side of the spread. These are powerful data, but much time can be wasted trying to explain the 20, 30, 40, and 50% levels of symptom improvement. The best way to present this chart is to say, "At the 20 and 30% improvement of symptoms, ZYPREXA and Risperdal showed relatively equal efficacy. However, at the 40 and 50% levels, ZYPREXA was statistically superior. In other words, at 20% Kelly may be getting out of bed—at 50% she may get up and begin to reach out to friends again." As noted in the script, it is very important to mention that Kelly's risk of suicide is assessed to be minimal (otherwise, she would be referred or even hospitalized).

Safety Spread

The Tran data presented here are a great tool to affirm the safety of ZYPREXA. At 28 weeks, almost 90% of patients remained on therapy, as compared with Risperdal where only 70% of patients remained on therapy. Put in a different way, patients on Risperdal were 3 times more likely to stop taking their medication.

Ease of Use Spread

In market research, most physicians responded favorably to Zydis. One of the more common questions was, "Does it work faster than the oral formulation?" The answer is no; the tablet dissolves very quickly in the mouth, but the onset of action is the same as the tablet formulation.

Close

In addition to creating action and gaining commitment to initiate ZYPREXA in appropriate patients, augment your sales efforts with an invitation to one or more of the brand's marketing activities:

- Teleconference (live)
- Audioconference/enduring material (taped)
- Peer-to-peer programs
- Regional consultant meeting
- CME programs

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Resources

Item	OL#
Core Folder	20756
File Card	21186
Martha leave-behind	21152
Michael leave-behind	21153
Kelly leave-behind	21154
Lunch & Learn CD	20849
Shelton reprint	21059
Sample bins	18564
Pens	18639
Post-it notes	18640
Patient Education	17908
BPRS tear pads	18554
Display panels (1)	19845
Display panels (3)	18568
Magnets	18571
Performance scripts	16081-pc
Weight-change sell sheet	19616
EPS sell sheet	20093
Diabetes/Hyperglycemia sell sheet	20741
QTc sheet	19123
Stickers	20839
CD Visor	20845
Premium travel mugs	20283