

Bandick intro

Thanks for taking the time to strengthen your Zyprexa product knowledge, and in particular, how Zyprexa compares to another well-known antipsychotic: Risperdal. As you know, competitive differentiation is a key point of emphasis for us in 2001, and the Tran study is one of the most important and impactful pieces we have to demonstrate Zyprexa's superior profile for reducing symptoms associated with mood, thought and behavioral disturbances.

By all measures, we're off to a very good start with Zyprexa in primary care. The sales results have been terrific, and more importantly, we are helping to improve the lives of patients and their families by making this special drug available in primary care. Competitive noise will heat up in 2001, and we will meet that challenge by behaving like market leaders. We will offer our customers better data, more resources and unsurpassed customer service. In return, our customers will increasingly choose Zyprexa for their patients suffering from mood, thought and behavioral disturbances. A great molecule combined with a passionate, well-prepared sales organization is one heck of a competitive advantage.

Let's talk about the Tran study. Pierre Tran is the lead author of this ground-breaking study that was published in the *Journal of Clinical Psychopharmacology* in 1997. It represented the first-ever, head-to-head comparison between two atypical antipsychotics. It's a study of high quality, with 339 patients followed over 28 weeks, with the results published in a respected, peer-reviewed journal. And those results were dramatic.

Zyprexa scored four key victories over risperidone in this study: broader efficacy, more robust efficacy, significantly less incidence of relapse and a significantly better safety / side effect profile. Not surprisingly, Janssen has complained about many aspects of this study, including dosing, methodology, statistical analysis, you name it. But it's now 2001, and they still don't have a large, well-controlled, head-to-head study published in a peer reviewed journal to refute what Dr. Tran proved. And now you've got it in your hands.

Couple more comments, and then I'll hand things over to Art Snow and Jean Morrissey. First, this is a diamond reprint, which means this is not something you can or should share proactively with your customers. Nor can we negotiate for more business directly from a diamond reprint. However, it can and should be used to respond to the frequently asked question, "How does Zyprexa compare with Risperdal?" Second, and most important, this reprint is most effective when you focus on Zyprexa's great results, and what that means for patients. It's not about bashing Risperdal. It's about sharing good data that gives customers new reasons to choose Zyprexa instead of other agents whose profile doesn't match Zyprexa's. In compliance with Lilly policy, we'll have this study available as a diamond reprint for six months; let's make the most of it.

Closing thought: You've heard me state that primary care would be the first segment in which Zyprexa passes Risperdal in market share. And we're gonna do it this year. Watch the rest of the video, read the study and then answer this question: If you had a loved one who required treatment for a mood, thought or behavioral disorder, which of these two agents would you want them to take? We deserve to win. Viva Zyprexa!

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JEAN(AS DOCTOR): Art, all of the information on Zyprexa sounds great, but how does it compare to other atypicals out there, specifically Risperdal?

ART: Doctor, thanks for asking that question about the difference between Zyprexa and Risperdal. In our continuing efforts to keep you abreast of new clinical data on Zyprexa, I'd like to share and leave you this study that was published in the *Journal of Clinical Psychopharmacology* in 1997. Off label uses of Zyprexa and Risperdal are discussed in this study.

This is a powerful study I'd like to share with you today. In fact, this was the FIRST and LARGEST head-to-head study ever done comparing two atypical agents. This study clearly demonstrates Zyprexa's efficacy, safety and side effect profile as compared to Risperdal.

Doctor, may I share this study with you at this time?

JEAN: I'm sure it makes Zyprexa look wonderful.

ART: Let me start with the parameters of this head-to-head comparison to provide you with some background.

- The study was an international, multicenter, double-blind, parallel-group, 28 week study conducted with 339 patients who met DSM-IV criteria for schizophrenia, schizophreniform or schizoaffective disorder.
- The study was conducted to compare the efficacy and safety of Zyprexa vs. Risperdal.
- This was a flexible dosing study where dosing adjustments could be made based on clinical response. The mean ending dose for Zyprexa was 17.2mg and Risperdal was 7.2 mg. It is important to note that greater than 50% of risperidone treated patients were on 6mgs or less.

Now, let's move to the exciting overall results. Results demonstrated that both Zyprexa and Risperdal were safe and effective in reducing the overall psychotic symptoms. However, at 28 weeks, differences were noted between Zyprexa and Risperdal with regards to SANS negative symptoms, PANSS depression score, response rates, and time maintaining response. (pgs. 411, 412, 413, 415).

With regards to safety, both drugs were found to be safe (p.415). However, at 28 weeks, significant differences between Zyprexa and Risperdal were noted with regard to side effects, including EPS, prolactin elevations, and sexual dysfunction (pgs. 412, 413, 414).

Doctor, at this juncture, does this information surprise you?

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JEAN: Well, Art, the first thing that surprises me is the efficacy difference between Zyprexa and Risperdal since I've always thought of them as two equally efficacious drugs. Can you tell me more?

ART: I'd be happy to share more with you. Let's get into some of those details, because I believe the more you see, the more you'll appreciate the magnitude of the differences.

First, let's look at **efficacy**. Both olanzapine and risperidone showed equal relief in positive symptoms, such as hallucinations and delusions. I think you would agree that this is consistent with what many psychiatrists would suggest.

Now, where olanzapine separates from risperidone in terms of efficacy was in negative symptom improvement and response with regards to depression. (p, 411, 412, 412 (table 3) What this means to your patient is that he or she will be more likely to take an interest in friends, family and activities – things that you and I take for granted.

Next, let's take a look at response rates as noted in this particular table, which has profound take-aways in it. In all other antipsychotic studies, 20% improvement was seen as the response level and it was judged on a binary basis; either you were above it or not. This study went one step further. Instead of just looking at it on a binary basis, we stratified the improvement to gauge the robustness of response. The upper echelon of 40-50% improvement constitutes the "miracle" patient; the really special WOW stories. Our findings -- TWICE as many patients on Zyprexa achieved at least 50% response rate (p. 411, 412 table). So, bottom line, is Risperdal an effective agent? Absolutely. It was comparable at the minimum 20% improvement. But to get to the 40 or 50% improvements --the awakenings, the WOWs-- you will need Zyprexa.

Finally, let's look at maintenance of response. More patients in the olanzapine group maintained their clinical response than patients in the risperidone group. In fact, 9 out of 10 olanzapine-treated patients were still responding after six months compared to only 7 out of 10 risperidone-treated patients. (p. 411, 412) Viewed another way, Risperdal patients were 3 times as likely to relapse.

Doctor, let me stop at this point....do you have any questions with regards to the superior efficacy findings of Zyprexa vs. Risperdal?

JEAN: No, Art. This all sounds good to me. But I still am wary of the **safety and side effect** profile of Zyprexa as compared to Risperdal. Can you share with me your findings?

ART: Certainly.

Overall, patients on Zyprexa experienced significantly fewer adverse events than those on Risperdal (p.412, 413). In fact, there were nine events (nausea, amblyopia, EPS, increased salivation, suicide attempt, abnormal ejaculation, back pain, creatine phosphokinase increases and urinary tract infections) that occurred significantly more with Risperdal.

To summarize the most important factors:

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First, EPS rates with Risperdal were almost double the EPS rates of Zyprexa (p. 414). Since EPS with Risperdal may be dose related, this may preclude you from dosing to the therapeutic effect like you can with Zyprexa.

Second, Risperdal had sustained elevated prolactin levels. Now, you may not see elevated prolactin unless you test for it. As you know, many short-term consequences such as sexual dysfunction can occur with elevated prolactin and patients are not likely to readily share these concerns with you. In addition to short term problems, you will also need to keep in mind the potential long-term consequences of elevated prolactin, which include osteoporosis and breast cancer.

Lastly, both groups had weight change that was statistically significant- the olanzapine group averaged 9lb and the risperidone group averaged 5lb change at 28 weeks (p. 414). So, both are associated with weight gain, but Zyprexa is associated with it more than Risperdal due to a 4 pound difference.

So, Doctor, as a quick summary -- in a 28 week study, Zyprexa showed broader efficacy with statistically significant improvement in negative symptoms and depression; more robust response at high improvement levels of 40 or 50 % (those WOW patients); and better maintenance of response --- all at the same time having a better safety and side effect profile than Risperdal.

Doctor, we've covered a lot of information today. Do you have any questions for me?

JEAN: This sounds great, but I don't treat patients with schizophrenia. Why should I accept these data?

ART: Doctor, in a primary care setting, that question makes a lot of sense. However, there are some credible transferrable points in this study; certainly the safety and side effect profiles.

For example, at comparable high doses of each drug, the study points out a 4lb differential in weight gain, Zyprexa being higher, and nine more adverse events for Risperdal that are significantly significant occurring at the same time. That, I believe, transfers, whether the patient has schizophrenia, bipolar disorder, or agitation.

Another element that transfers is the maintenance of response data because that speaks to the extent the patient is improving over an extended period of time, avoiding relapse.

When we get into such items as positive and negative symptoms, even the depression piece, I would agree with you. We would need to study patients that you as a primary care doctor treat in order to make a claim that says Zyprexa is superior to Risperdal in the same ways that it is in schizophrenia. But I'd hope at the very least that you would accept these data as confirming that Zyprexa may in fact represent a safe, effective choice in the treatment of mood, thought and behavioral disturbances – clinical presentations you see everyday.

JEAN: I don't use antipsychotics in my practice.

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ART: May I ask you why you avoid these agents? I want to note that Zyprexa has actually been reclassified from an antipsychotic to a psychotropic because of its broad spectrum of use, including mood stabilizing properties.

JEAN: I don't use high doses of Risperdal, so is the EPS data relevant to me?

ART: You are right that in those patients at low doses of Risperdal, the incidence of EPS is somewhat diminished compared to those in this particular study who averaged 7mg/day. So, yes, you can avoid EPS by decreasing the dose; don't you also compromise efficacy?

JEAN: Didn't Janssen do its own head-to-head study that showed that Risperdal was superior to Zyprexa? How can I believe either manufacturer?

ART: Yes, I'm aware of Janssen's study. It's worth noting that their study was smaller, shorter in duration, poorly controlled and has not been published in a peer-review journal. As you can see, not all studies are created equal.

ART: So, Doctor, to summarize – This article which I will leave with you to read, points to some trends which we have been hearing from physicians with a lot of clinical experience with Zyprexa. Namely, Zyprexa has broad and robust efficacy, while being safe and well tolerated. So, as you're thinking of your patients with mood, thought and behavioral disturbances – the ones who haven't responded to earlier treatment or who could be doing better -- I want you to think of Zyprexa. Especially if that decision is between Zyprexa and Risperdal, I've hopefully given you some clear and powerful reasons why Zyprexa is the most appropriate choice.

Why don't you read the actual reprint and on my next visit, I can answer any additional questions that you may have and discuss your reaction and thoughts. As always, Doctor, thanks for your time.

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 - 2) BIP
 - 3) TRD
 - 4) B line person
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slide kit from just
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