Weight Change Strategy and Tactics

January 2000
Summary of Tactics and Implementation

- Market Research Conducted - June 1999
- Recommendations
- Marketing Materials Development - August 1999
- Training/Implementation - September 1999
- What do the results say? - November 1999
Zyprexa Market Research - Weight Gain & Other side effects June 1999

Key Results:

- Weight gain important but less than EPS

- Lilly Perceived as minimizing weight gain problem.

- Need for more data on weight gain.

- EPS seen more frequently with Risperidone - an anti-parkinsonian agent is added instead of discontinuing the patient.
Marketing Materials

- New Visual Aid-Adherence section
  - Accomplished 3 things
    - Put weight change into perspective with EPS and Prolactin related side effects
    - Added additional “facts” to show that it is common with psychotropics, most patients gain little if any weight and few discontinue if they do gain and weight change plateaus over time without intervention
    - Bottom line weight change is manageable
Training/Implementation

- Message Flow Guide (see email word attachment and pictorial of visual aid section)
  - The purpose here was to guide reps on how to flow through the information and when to utilize it (i.e. answer the questions and handle the objections)
Results Post Implementation

- Message recall results (unprompted) indicate that although weight gain remains an important issue that a significant proportion (26%) do feel that it is manageable.
## ZYPREXA: FEWER SIGNIFICANT ADVERSE EVENTS REPORTED

Compared to risperidone*

*Some adverse events in this category require immediate medical attention and/or are often related to the potential long-term effects of the use of atypical antipsychotics as reviewed by the Canadian Antipsychotic Guidelines (CAG). This includes the direct proportion between dosing and side effect profile.

### Side-Effect Occurrence

<table>
<thead>
<tr>
<th></th>
<th>EPS</th>
<th>Weight Change</th>
<th>Prolatin Elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>risperidone (n=187) 4-12 mg/day</td>
<td>High 31.1%</td>
<td>2.3±4.9 Kg</td>
<td>Substantial 1.87 nmol/L</td>
</tr>
<tr>
<td>ZYPREXA (n=172) 10-20 mg/day</td>
<td>Low 18.6%</td>
<td>4.1±5.9 Kg</td>
<td>Minimal 0.02 nmol/L</td>
</tr>
</tbody>
</table>

1. Use atypical agent first-line

2. Add anticholinergic or antiparkinsonian co-medication

3. Lower the dose

4. Switch to atypical agent

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**Options**

**Potential Consequences**

*The advantages of using second-generation antipsychotics are many and fewer extrapyramidal side effects.*

- Canadian Antipsychotic Guidelines, CPA

*Long-term use of an antipsychotic agent may result in the development of tardive dyskinesia...*

- Canadian Antipsychotic Guidelines, CPA

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Expect More For Your Patients

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**EPS ↓**

**Efficacy ↓**

**Re-lapse**
ZYPREXA: LOWER INCIDENCE OF EPS

Compared to risperidone

With ZYPREXA, specific forms of EPS were not different from placebo

Expect More For Your Patients
PSYCHOTROPICS
AND WEIGHT CHANGE

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drugs causing weight gain</th>
<th>Drugs causing weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Fluoxetine, Citalopram</td>
<td>Amiptyline, Imipramine, other TCA's, Nortriptyline, Venlafaxine, Fluoxetine, Sertraline, Paroxetine, Trazadone, Haloperidol, Clozapine, Olanzapine, Quetiapine, Risperidone</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>None</td>
<td>Phenothiazines, Depot preparations, Haloperidol, Clozapine, Olanzapine, Quetiapine, Risperidone</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Amphetamines, Methylphenidate</td>
<td>None</td>
</tr>
</tbody>
</table>

Weight change is a common problem in patients on psychotropic medications.
- Approximately 60% of patients on lithium gain weight.
- Weight gain occurs in 25-50% of patients on valproate, antipsychotics and antidepressants.
- Weight gain of 4.5-6.8 kg is common during 1 or more years of neuroleptic treatment.

With ZYPREXA, weight change for most patients plateaus over time.

Weight change, a manageable side-effect:
- For most patients on ZYPREXA, an average weight gain of 2.8 kg was seen during acute therapy. Long-term, the average weight gain was 5.4 kg.

Expect More. For Your Patients.
PROLACTIN ELEVATION: SILENT, UNSPOKEN...

What is the 'cost' of this side-effect to the individual patient?
Hyperprolactinemia is associated with hypogonadism (i.e. estrogen deficiency in women and testosterone deficiency in men).**

<table>
<thead>
<tr>
<th>Clinical Signs &amp; Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IN WOMEN:</strong></td>
</tr>
<tr>
<td>- Sexual dysfunction</td>
</tr>
<tr>
<td>- Arthralgia, myalgia</td>
</tr>
<tr>
<td>- Decreased libido</td>
</tr>
<tr>
<td>- Breast asymmetry</td>
</tr>
<tr>
<td>- Vomiting, tenderness</td>
</tr>
<tr>
<td>- Galactorrhea</td>
</tr>
<tr>
<td>- Menstrual irregularities</td>
</tr>
<tr>
<td>- Exacerythemia, amenorrhea, metrorrhagia</td>
</tr>
<tr>
<td><strong>IN MEN:</strong></td>
</tr>
<tr>
<td>- Sexual dysfunction</td>
</tr>
<tr>
<td>- Impotence, inhibition of ejaculation, decreased libido</td>
</tr>
</tbody>
</table>

* Data supporting the link between neuroleptic-induced hyperprolactinemia and increased risk of osteoporosis and cardiovascular disease is preliminary and inconclusive.*

ZYPREXA: EXCELLENT EFFICACY IN SYMPTOMATIC CONTROL AND RESPONSE TO TREATMENT...

ZYPREXA: MINIMAL EFFECT ON PROLACTIN^1

Compared to risperidone^2

Superior efficacy in positive symptom control, compared to haloperidol^1
- Similar onset of action
- Superior reduction in agitation
- Therapeutic dosing from day 1

Superior efficacy in negative symptom relief, compared to risperidone^1

Superior efficacy in depressive symptom relief, compared to risperidone^1

Superior improvement in cognition, compared to risperidone and haloperidol^1

Superior relapse prevention, compared to risperidone^1 and haloperidol^1
- Superior maintenance of response
- Greater reduction in hospitalization rate/patient

...TO HELP YOUR PATIENTS REACH A HIGH LEVEL OF IMPROVEMENT.

ZYPREXA Olanzapine Novel antipsychotic power for realistic use
Adherence – page 12

When we talk about the vicious circle, we talk about efficacy and adherence as being the two key factors that can in fact impact your goal of relapse prevention and ultimately the patient’s potential for reintegration.

Now that we’ve shown you the superior efficacy profile of Zyprexa, let’s talk about Zyprexa benefits in terms of adherence.

So Doctor, let’s talk about adherence in terms of side effects and how they can be managed.
When we look at the overall side effect profile of Zyprexa has fewer significant adverse events reported vs. risperidone.

Rep Action: IF weight gain is a TRUE objection (i.e. preventing the use of Zyprexa 1st choice) you can use this page to put the three side effects into perspective. If not, move on to EPS.

EPS & the CPA Guidelines – page 13

Starting with EPS, which is really one of the greatest concerns because of its long-term effect on the patient and it’s link with tardive dyskinesia, let look at what the CPA has come up with in terms of guidelines for minimizing EPS.
1. First, they suggest using an atypical agent first line
2. If you are not using an atypical agent, the CPA recommends adding an anticholinergic and antiparkinsonian co-medication. The precaution here is that long term use of these medications may exacerbate cognitive dysfunction.
3. Or you can lower the dose. The problem here Doctor, is the impact on efficacy and your patient’s potential to be caught in the vicious cycle of relapse again. Because lack of efficacy will lead to relapse.
4. So now is the time to re-evaluate. The CPA Guidelines recommend switching to an atypical agent.

EPS – pages 14 & 15

So when you look at the two atypical options, Zyprexa offers lower incidence of EPS, compared with risperidone.

In fact, with Zyprexa, you see a placebo-like EPS profile.

And because there is less incidence of EPS with Zyprexa, there is significantly less anticholinergic therapy required.
So for those patients on other antipsychotics who are taking antiparkinsonian medications such as Cogentin*, a switch to Zyprexa may improve their adherence.

**Rep Action:**
*This is an opportunity to create a problem with risperidone in EPS!*

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**Rep Action:**
*IF weight change is a TRUE objection use this section otherwise answer question and move on.

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**Weight Change – page 16 & 17**

Weight changes are a common side effect of all antipsychotics and are a manageable side effect.

With Zyprexa, only 0.4% of patients discontinued due to weight change in long term treatment.

As shown in this chart of patients without dietary management, weight change with Zyprexa patient's plateau's over time. What this means is that with some dietary and lifestyle guidance, your patients can benefit from Zyprexa while minimizing the impact of weight change. (Unlike EPS and Prolactin elevations, weight change is manageable for most patients)

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**Prolactin – page 18**

Prolactin is another adherence issue that until now, has been silent and unspoken, but must be considered a serious side effect with both short term and long term consequences. It is not perfectly clear yet what the long term consequences are but the literature suggests that they might be quite important. We are talking about osteoporosis and cardiovascular disease.

What is quite clear is the short-term consequences of hyperprolactinemia. Specifically, sexual dysfunction is a very important factor for non-compliance. It became quite obvious with the SSRI antidepressants that when a patient begins to feel well, but starts to feel that the medication is having a negative impact on his/her sexual life, he/she might be tempted to skip doses... and eventually abandon treatment altogether. Doctor we are talking about reintegration and giving patients a chance for a more "normal" life and that life includes sexual functioning.
Zyproxa is considered, a prolactin-sparing agent, which means you can offer you patient another adherence benefit.

Rep Action:
*Create a problem for risperidone!*