Canada 2000



# Weight Change Strategy and Tactics

January 2000

# Summary of Tactics and Implementation Summary

- 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)

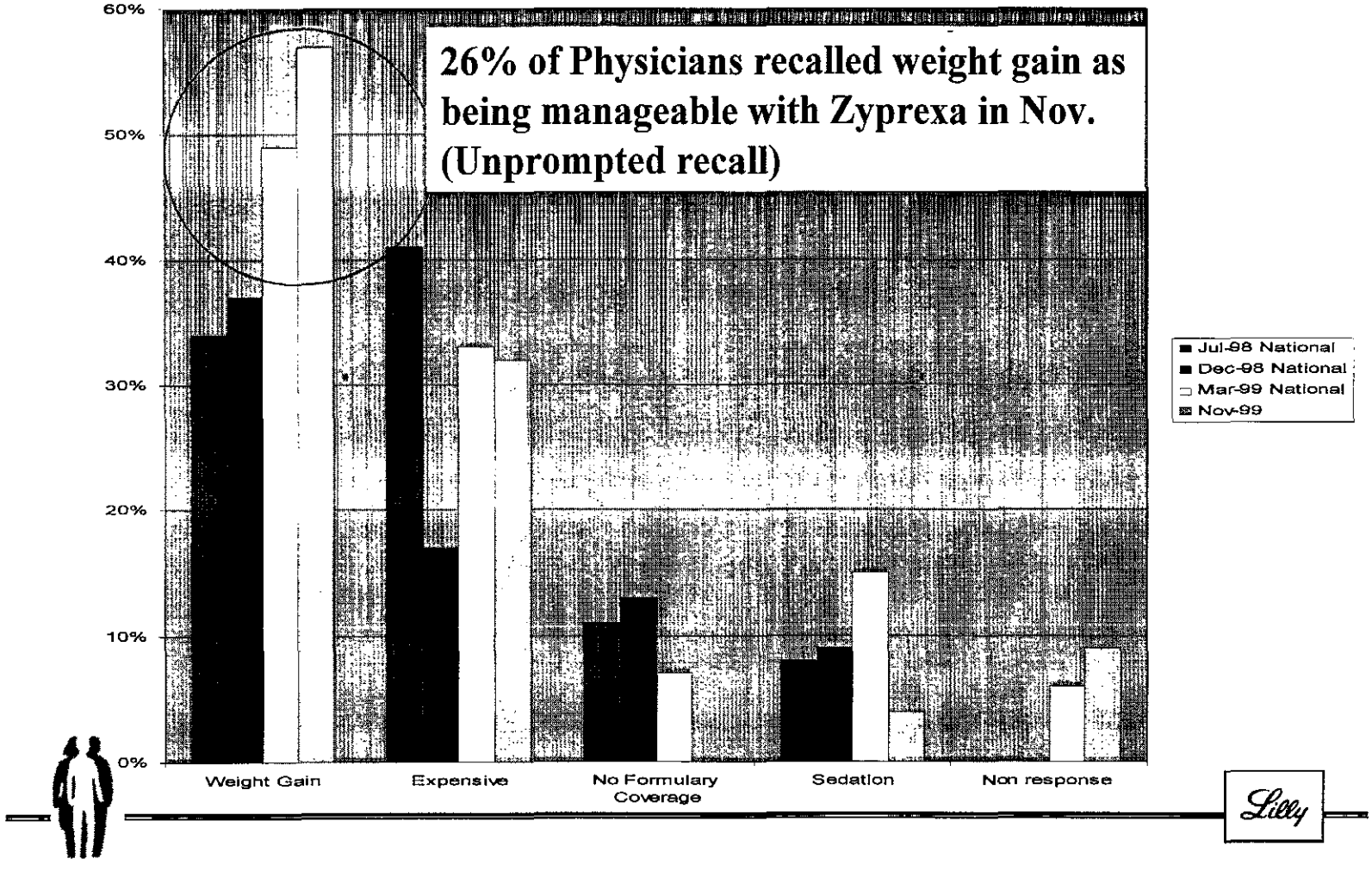
# Results Post Implementation

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 Message Recall - Limiting Factors

*What factors, if any, have limited you from prescribing Zyprexa (olanzapine)?*



"... the [illegible] – Canadian [illegible], CPA

# ZYPREXA: **FEWER SIGNIFICANT ADVERSE EVENTS** REPORTED

## Compared to risperidone*[7]

* Adverse events presented are those reported statistically significantly more often for the respective drug during 28 weeks, based on COSTART (Coding Symbol and Thesaurus for Adverse Reaction Terms) classification system.

| Side-Effect Occurrence[2] | EPS | Weight Change | Prolactin Elevation |
|---|---|---|---|
| risperidone (n=167) 4-12 mg/day | High 31.1% | 2.3±4.8 kg | Substantial 1.97 nmol/L |
| ZYPREXA (n=172) 10-20 mg/day | Low 18.6%[1] | 4.1±5.9 kg[3] | Minimal 0.02 nmol/L[4] |
| | Patients with any EPS event [1]p=0.003 | Mean change from baseline to week 28 [3]p=0.015 | Mean change from baseline to week 28 [4]p<0.001 |

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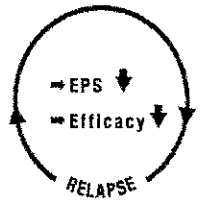
## CPA GUIDELINES FOR TREATMENT OF EPS

| OPTIONS | POTENTIAL CONSEQUENCES |
|---|---|
| **1.** Use atypical agent first-line | "The advantages of using second-generation [illegible] fewer extrapyramidal [illegible]." – Canadian [illegible] Practice Guidelines, CPA |
| **2.** Add anticholinergic or antiparkinsonian co-medication | "Long-term use of an anticholinergic or [illegible] may exacerbate [illegible] tardive dyskinesia..." Indications [illegible] review the dose and/or choice of antipsychotic in order to attain a minimum effective dose." – Canadian Clinical Practice Guidelines, CPA |
| **3.** Lower the dose |   |
| **4.** Switch to atypical agent | |

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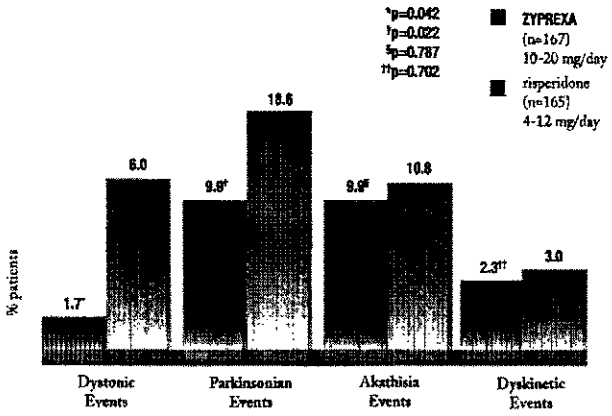
# ZYPREXA: **LOWER** INCIDENCE OF **EPS**

**Compared to risperidone[7]**




Adapted from Tran PV et al.[7]
Treatment-emergent EPS in 28 weeks, spontaneously reported.

**With ZYPREXA, specific forms of EPS were not different from placebo[2]**

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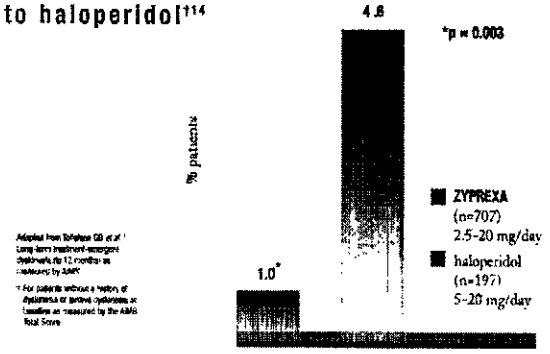
## ZYPREXA: SIGNIFICANTLY LESS TREATMENT-EMERGENT DYSKINESIA

**Compared to haloperidol[†14]**




Adapted from Tollefson GD et al.[14]
Long-term treatment-emergent dyskinesia (to 12 months) as measured by AIMS
* For patients without a history of dyskinesia or tardive dyskinesia at baseline as measured by the AIMS Total Score

**Compared to risperidone, the incidence of treatment-emergent dyskinesia was 2.3 times lower with ZYPREXA[‡7]**

‡ Treatment-emergent dyskinesia as measured by AIMS at week 28, n=338 ZYPREXA 10-20 mg/day, 4.8% risperidone 4-12 mg/day, 10.7%, p=0.046.

ZYPREXA should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. As with any antipsychotic drug, ZYPREXA should be reserved for patients who appear to be receiving substantial benefit from the drug. The lowest effective dose and the shortest duration of treatment should be sought and the need for continued treatment reexamined periodically.

## ZYPREXA: SIGNIFICANTLY LESS ANTICHOLINERGIC THERAPY REQUIRED

**Compared to haloperidol or risperidone**

- ZYPREXA (n=1,796) 15.5%, haloperidol (n=810) 47.0%, p<0.001[15]
- ZYPREXA (n=172) 19.8%, risperidone (n=167) 32.9%, p=0.006[7]

(Based on proportion of patients requiring at least one week dose of an anticholinergic medication)

**In patients not taking an anticholinergic medication, the incidence of anti-muscarinic-like effects seen with ZYPREXA were no different to that of risperidone[§10]**

§ 28-week study, n=750, AIMS-6 combined adverse events of dry mouth, constipation, blurred vision, or micturition difficulties. ZYPREXA 10-20 mg/day, risperidone 4-12 mg/day.

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# PSYCHOTROPICS AND WEIGHT CHANGE

| Drug class | Drugs causing weight loss | Drugs causing weight gain |
|---|---|---|
| **Antidepressants** | Fluoxetine<br>?Bupropion | Amitriptyline<br>Imipramine, other TCAs<br>Isocarboxazid<br>Phenelzine<br>?Tranylcypromine |
| **Antipsychotics** | None | Phenothiazines<br>Depot preparations<br>Haloperidol<br>Clozapine<br>Olanzapine<br>Quetiapine<br>Risperidone |
| **Anxiolytics** | None | None |
| **Mood stabilisers/ antiepileptic drugs** | Topiramate<br>Felbamate | Lithium<br>Sodium valproate<br>Vigabatrin<br>?Carbamazepine |
| **Stimulants** | Amphetamines<br>Methylphenidate | None |

Adapted from The Bethlem & Maudsley NHS Trust Prescribing Guidelines (5th ed.) 1998.[14]

**Weight change is a common problem in patients on psychotropic medications[15]**

- Approximately 60% of patients on lithium gain weight[16]
- Weight gain occurs in 25-50% of patients on valproate, antipsychotics and antidepressants[15]
- Weight gain of 4.5-6.8 kg is common during 1 or more years of neuroleptic treatment[17]

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## WITH ZYPREXA, FEW PATIENTS DISCONTINUED THERAPY DUE TO WEIGHT CHANGE

- Only 0.4% of ZYPREXA patients (3 of 718) discontinued due to weight gain in long-term treatment[18]
- Weight gain was a significantly greater effect in patients with low body mass index (BMI)*[2]

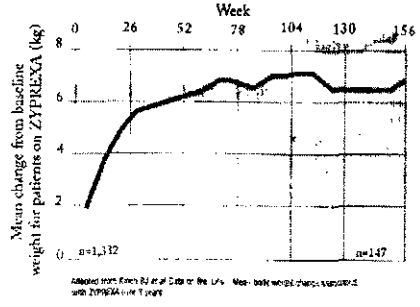
* Patients treated at higher doses (10±2.5 mg/day) had the greatest mean weight gain.

**ZYPREXA mean weight change distribution[18]**

| | 6 Weeks (n=2,976) (%) | 12 Months (n=778) (%) | 24 Months (n=472) (%) | |
|---|---|---|---|---|
| | 27 | 20 | 22 | 44% |
| | 57 | 25 | 22 | |
| | 15 | 25 | 22 | |
| 10-15 | 2 | 16 | 18 | |
| >15 | 0 | 14 | 16 | |

Adapted from Kinon BJ, et al. Data on file, Lilly. "ZYPREXA 6-week placebo-weight-weight change.

**With ZYPREXA, weight change for most patients plateaus over time[19]**




Adapted from Kinon BJ, et al. Data on file, Lilly. Mean body weight change in patients with ZYPREXA over 1 year.

- 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[2]

**Weight change, a manageable side-effect**

- Weight change needs to be discussed with patients in perspective with other more serious side-effects commonly associated with antipsychotics and overall clinical response to current therapy[18]

Control[illegible] and promot[illegible] help patient[illegible] change.[18]

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# PROLACTIN ELEVATION: SILENT, UNSPOKEN...

## What is the 'cost' of this side-effect to the individual patient?

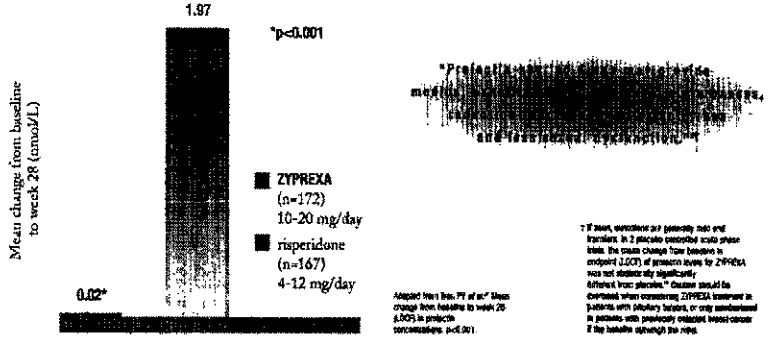
Hyperprolactinemia is associated with hypogonadism (i.e. estrogen deficiency in women and testosterone deficiency in men)[20,21]

| Clinical Signs & Symptoms[20,21] | |
|---|---|
| **IN WOMEN:** | **IN MEN:** |
| • Sexual dysfunction<br>– Anorgasmia, vaginismus, decreased libido<br>• Breast abnormalities<br>– Swelling, tenderness, galactorrhea<br>• Menstrual irregularities<br>– dysmenorrhea, amenorrhea, metrorrhagia<br>• Compliance | • Sexual dysfunction<br>– impotence, inhibition of ejaculation, decreased libido<br>• Gynecomastia<br>• Compliance |

- Data supporting the link between neuroleptic-induced hyperprolactinemia and increased risk of osteoporosis and cardiovascular disease is preliminary and inconclusive[20]

# ZYPREXA: **MINIMAL** EFFECT ON **PROLACTIN**†

## Compared to risperidone[22]




Adapted from Bos PT et al.* Mean change from baseline to week 28 (LOCF) in prolactin concentrations. p<0.001.

† If men, sometimes are generally male and transient. In 2 placebo controlled acute phase trials, the mean change from baseline to endpoint (LOCF) of prolactin levels for ZYPREXA was not statistically significantly different from placebo.* Caution should be exercised when considering ZYPREXA treatment in patients with pituitary tumors, in any combination in patients with previously detected breast cancer if the baseline value is high.

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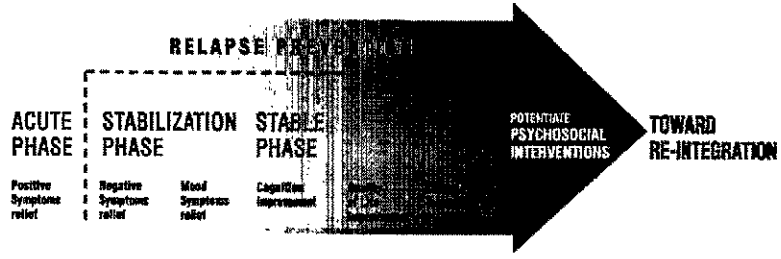
# ZYPREXA: **EXCELLENT** EFFICACY IN **SYMPTOMATIC CONTROL AND RESPONSE** TO TREATMENT...




**Superior efficacy in positive symptom control**, compared to haloperidol*

- Similar onset of action
- Superior reduction in agitation
- Therapeutic dosing from day 1

**Superior efficacy in negative symptom relief**, compared to risperidone†

**Superior efficacy in depressive symptom relief**, compared to risperidone‡

**Superior improvement in cognition**, compared to risperidone and haloperidol¶

**Superior relapse prevention**, compared to risperidone‡ and haloperidol‡

- Superior maintenance of response
- Greater reduction in hospitalization rate/patient

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

* 8-week, acute phase study, n=1,996, BPRS positive score. ZYPREXA 5-20 mg/day, haloperidol 5-20 mg/day, p=0.022.
† 28-week double-blind parallel study, n=326, SANS summary score. ZYPREXA 10-20 mg/day, risperidone 4-12 mg/day, p=0.009.
‡ Double-blind parallel study, 8-week acute phase, n=639, PANSS depressive cluster (27 points). ZYPREXA 10-20 mg/day, risperidone 4-12 mg/day, p<0.05.
¶ 54-week study, n=65, Neuropsychological Cognitive Score (composite of 6 domains). ZYPREXA 5-20 mg/day, risperidone 4-10 mg/day, haloperidol 5-20 mg/day, p<0.001.
§ Survival analysis of relapse over 6 months. ZYPREXA 10-20 mg/day, risperidone 4-12 mg/day, p=0.001.
‡ Survival analysis of relapse over 1 year. ZYPREXA 2.5-20 mg/day, haloperidol 5-20 mg/day, p=0.004.

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**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, lets talk about* Zyprexa benefits in terms of **adherence.**

So Doctor, let talks 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!*

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

**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)

**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.

Zyprexa is considered, a prolactin-sparing agent, which means you can offer you patient another adherence benefit.

**Rep Action:**
*Create a problem for risperidone!*

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