January 25-27, 2001
San Diego, California

Zyprexa Physician Strategy and Consulting Conference

Lilly
Answers That Matter.
Robert W. Baker, MD
Clinical Research Physician
Eli Lilly and Company

Safety Update

Lilly
Answers That Matter.
Effectiveness and Treatment Selection of Olanzapine

- Positive Sx Efficacy
- Negative Sx Efficacy
- Improvement of Core Depressive Sx
- Relapse Prevention
- Improved Quality of Life
- Prolactin Sparing
- Low Risk Of Acute EPS and TD
- Benign Cardiac Profile
- Weight Gain
- ? Hyperglycemia
Weight Gain/Plateau During Long-Term Olanzapine Treatment

Mean Weight Change Up to 3 Years: No Formalized Weight-Moderating Interventions Included in Study

Gain

Plateau

n=573

n=147

Note: Double-blind and open-label olanzapine. Patients who completed at least 39 weeks of therapy.

Intra-individual Variability in Weight Gain

Mean Change in Body Weight of Patients Treated With Olanzapine Up to 3 Years: No Formalized Weight-Moderating Interventions

Olanzapine n=573 at baseline, LOCF.
Weight Gain Variability in Haloperidol - Olanzapine Trials

Olanzapine vs Haloperidol - Weight Change at 1 Year

- Olanzapine (n=386)
- Haloperidol (n=85)

Weight Gain Variability in Risperidone - Olanzapine Trials

Olanzapine vs Risperidone - Weight Change at Endpoint (28 weeks)

Lost Weight
0 5 10 15 20 25 30 35 40 45 50

Gained Weight
0-5 kg 5-10 kg 10-15 kg 15-20 kg >20 kg

Olanzapine (n=102)
Risperidone (n=79)

% of Patients

Divalproex-Associated Weight Gain

Double-Blind, 8-Month Monotherapy Trial of Divalproex vs Lamotrigine for Epilepsy

![Graph showing weight increase over weeks for Divalproex and Lamotrigine.]

- Divalproex
- Lamotrigine

Mean dose- divalproex =1822 mg. LTG=254 mg. Initial n- divalproex =68. LTG=65.
Note - for now, no long-term head-to-head comparison of divalproex and olanzapine is available.
Predictors of Weight Gain

- Important predictive factors
  - Assignment to olanzapine or haloperidol
  - Positive therapeutic response
  - Low body mass index at baseline
  - Increased appetite during treatment

- Not important predictive factors
  - Assignment to olanzapine or risperidone
  - Olanzapine dose

Based on long-term comparative trials with risperidone and haloperidol (overall n=652).
Baseline BMI and Subsequent Weight Gain

Subjects with lowest baseline BMI had the greatest mean weight gain; subjects with highest baseline BMI had the smallest mean weight gain.

Mean Weight Gain (k)

- BMI<23.6
- 23.6<BMI<27.6
- BMI>27.6

*p<.001 compared to <23.6 or 23.6-27.6 groups

Weight Gain Was Not Dose Dependent

Potential Interventions for Weight

♦ Mechanisms
  • Being studied clinically and preclinically
  • 5HT2c and H1 receptor antagonism are possible candidates
  • Macronutrient partitioning shift?

♦ Nonpharmacological interventions
  • Diet and exercise
Behavioral Interventions:
Led to Weight Loss in Those Who Had Put on the Most

Weight Gain by Antipsychotic

- Maximum weight gain
- Final weight gain

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Maximum weight gain</th>
<th>Final weight gain</th>
</tr>
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<tbody>
<tr>
<td>Clozapine</td>
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<tr>
<td>Olanzapine</td>
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<tr>
<td>Risperidone</td>
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<tr>
<td>Haloperidol</td>
<td>43</td>
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</tbody>
</table>

Potential Interventions for Weight

♦ Mechanisms
  • Being studied clinically and preclinically
  • 5HT2c and H1 receptor antagonism are possible candidates
  • Macronutrient partitioning shift?

♦ Nonpharmacological interventions
  • Diet and exercise

♦ Pharmacological interventions
Medications that Potentially Counteract Weight Gain

- Topiramate
- Sibutramine
- Amantadine
- Nizatidine
- Others

None has been studied adequately to date.
Adjunctive Amantadine Attenuates Olanzapine-Associated Weight Gain

Mean amantadine dose=175 mg. Amantadine added after 13±13 weeks on olanzapine.
Overall olanzapine treatment equals 34±7 weeks.

Increase from Pre-Olanzapine

Baseline (kg)
Nizatidine for the Prevention of Olanzapine-Associated Weight Gain

Study Period I
- Screening
  - 2-9 days

Study Period II
- Treatment
  - 16 weeks
  - Olanzapine 5 to 20 mg/day plus Nizatidine 150 mg twice daily
- Olanzapine 5 to 20 mg/day plus Nizatidine 300 mg twice daily
- Olanzapine 5 to 20 mg/day plus Placebo

Visit 1
- Randomization
- 2-9 days

Visit 2
- 6 weeks weekly visits

Visit 8
- 2 weeks bi-weekly visits

Visit 9
- 8 weeks monthly visits

Visit 11

Data on file, Eli Lilly and Company. 2000
The combination use of olanzapine and nizatidine has not received FDA approval.
The Effects of Nizatidine on Olanzapine-related Weight Gain (N=74)

Data on file, Eli Lilly and Company. 2000
Nizatidine 300 mg vs placebo
The combination use of olanzapine and nizatidine has not received FDA approval.
The Effects of Nizatidine on Olanzapine-related Weight Gain (N=74)

*p<.04, vs placebo

The combination use of olanzapine and nizatidine has not received FDA approval.
**Recommendations: Weight Gain on Olanzapine**

- Do not rule out olanzapine trial solely because of baseline obesity.
- Reduce likelihood of weight gain through upfront counseling and education.
- Expect substantial intra-individual variation.
- Consider early intervention for patients developing ravenous appetite or rapid initial gain.
- Expect weight to plateau after 9 months.
- Dose to therapeutic effect as reducing dose is not likely to remEDIATE weight gain.
- Consider behavioral and/or pharmacological measures as they are likely to remEDIATE weight gain for some patients.
Glucose Elevation
Incidence of Treatment-Emergent Diagnosis of Diabetes: Longer Term Comparisons from Olanzapine Schizophrenia Registration Trials

Data on file, Eli Lilly and Company.
Glycemic Effects of Treatment With Olanzapine and Other Psychotropic Medications

Olanzapine Clinical Trial Database:

Advantages: Size
Parallel group controls
Random treatment assignment

Limitation: Not primarily glycemia studies:
random glucose

Analyses Included:
Mean glucose change from baseline in all patients
Rates of individuals with treatment-emergent elevation
## Change in Mean Random Glucose During Head-to-Head Schizophrenia Trials

<table>
<thead>
<tr>
<th>STUDY</th>
<th>TRT</th>
<th>Δ GLUCOSE</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>vs risperidone</td>
<td>OLZ</td>
<td>2.6 mg/dl</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>RIS</td>
<td>1.9 mg/dl</td>
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<tr>
<td>vs haloperidol</td>
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<tr>
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<td>HAL</td>
<td>-0.1 mg/dl</td>
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<tr>
<td>vs clozapine</td>
<td>OLZ</td>
<td>3.0 mg/dl</td>
<td>.0002</td>
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<tr>
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<tr>
<td>vs placebo</td>
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<tr>
<td></td>
<td>PBO</td>
<td>-1.6 mg/dl</td>
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</tbody>
</table>

Change from baseline in least square mean of random glucose across controlled trials.
<table>
<thead>
<tr>
<th>Glucose Thresholds</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>Random capillary glucose (fingerstick)</td>
<td>Suggests diabetes</td>
</tr>
<tr>
<td>Random plasma glucose</td>
<td>Suggests need for further evaluation</td>
</tr>
</tbody>
</table>

- **Glucose (mg/dL)**
  - 110
  - 126
  - 140
  - 160
  - 200

Analysis of Likelihood of Random Glucose Elevation Over Specific Thresholds

- Olanzapine-treated patients not significantly different than haloperidol or risperidone controls at any examined threshold (126, 140, 160, 200 mg/dL)

- Olanzapine-treated patients significantly less likely than clozapine controls to cross 126 mg/dL or 140 mg/dL threshold

Diabetes and Hyperglycemia

- Common in the general US population
- More common in psychiatric patients
Hyperglycemia Is Prevalent in the General US Population

- Normoglycemic
- Diagnosed
- Undiagnosed diabetes
- Borderline diabetes

Estimated prevalence rates for the period 1988-1994, US adults:
- Diagnosed diabetes = 5.1%
- Undiagnosed diabetes = 2.7%
- Abnormally high but sub-threshold fasting glucose = 6.9%

Prevalence of Diabetes and Impaired Glucose Tolerance Are Relatively High in Schizophrenia and Bipolar Disorder

- Rates of Type II diabetes mellitus in schizophrenia reportedly are 2-4 times the general population\(^1\)-\(^4\)

- Rate in hospitalized bipolar patients reported 2-3 times the general population\(^5\)

- Several psychotropics have been associated with high insulin levels and possible insulin resistance (e.g., chlorpromazine\(^6\), divalproex\(^7\)), yet diabetes may be just as common in untreated patients\(^4\)

- Elevated rates of glycemic abnormalities were described in psychiatric patients even before the introduction of antipsychotics or mood stabilizers\(^8\)-\(^11\)

Conclusions

- Likelihood of diabetes or elevation of random glucose above threshold was similar on olanzapine to risperidone and haloperidol controls

- Diabetes is common in the US generally, and probably much more so in the seriously mentally ill

- Further research is underway
Attached is the "pre-read" for the Zyprexa update scheduled for the Policy Committee on Wednesday, February 14. An executive summary for your convenience, has been provided; however, detailed information has also been included should you desire more extensive background.

Zyprexa Executive Summary 2-12-01 from Harper Ziprasidone Zyprexa 2-14-01.p

JAH