Diabetes Mellitus and Antipsychotics

Findings from A Retrospective Cohort Study
Introduction

● A common perception of psychiatrists in US
  ➤ that Zyprexa has a greater association with diabetes than most other antipsychotics

● FDA request
  ➤ Lilly to look into the possibility of conducting an epidemiology study to assess the diabetogenic potential of Zyprexa
Introduction (con’t)

Janssen Pharmaceutical Company claimed that in their epidemiology studies:

➢ Olanzapine had a greater association with diabetes than risperidone

➢ Olanzapine was the only antipsychotic to demonstrate dose-dependent changes in the incidence of diabetes

➢ Risperidone had no apparent diabetogenic effect
Diabetes Study in US

Objectives:

- To compare the diabetogenic potential of
  - Atypical vs conventional antipsychotics as a class
  - Olanzapine vs Risperidone

- To determine whether the incidence of DM increased with the dosage of
  - Olanzapine
  - Risperidone
  - Haloperidol
Method

● Study Design
  ➢ Retrospective cohort study

● Database
  ➢ AdvancePCS prescription claim database

● Onset of diabetes mellitus (DM) was identified by
  ➢ Prescription claims for diabetes drugs for the first time during exposure to antipsychotics

● Statistical method
  ➢ Logistic regression model to estimate the odds of diabetes
  ➢ Age and gender as covariates
Cohorts Compared

Monotherapy Cohorts

- All conventional antipsychotics (N=19,782)
- Haloperidol  (N= 8,476)
- All atypical antipsychotics (N= 38,735)
- Olanzapine (N= 13,863)
- Risperidone (N= 20,633)
- Seroquel     (N= 4,196)
- Clozapine    (N= 277)

General PCS patient cohort (N= 6 millions)

- Served as the reference group for comparison with antipsychotic cohorts in regression analysis
RESULTS
Odds of Developing Diabetes for the Conventional and Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Antipsychotic Cohort</th>
<th>Odds</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Conventional</td>
<td>1.5*</td>
<td>1.3</td>
</tr>
<tr>
<td>Atypical</td>
<td>1.8*</td>
<td>1.6</td>
</tr>
</tbody>
</table>

* Significantly different (p<0.05) from the general patient population (odds =1.0) after adjusting for age and gender difference.
### Odds of Diabetes for individual Antipsychotic Cohorts (relative to general patient population)

<table>
<thead>
<tr>
<th>COHORTS</th>
<th>Odds</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds</td>
<td>Lower</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1.3*</td>
<td>1.1</td>
</tr>
<tr>
<td>Seroquel</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1.7*</td>
<td>1.4</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1.9*</td>
<td>1.7</td>
</tr>
<tr>
<td>Clozapine</td>
<td>2.9*</td>
<td>1.2</td>
</tr>
</tbody>
</table>

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The Odds of Developing Diabetes while taking Antipsychotics

- Olanzapine
- Risperidone
- Haloperidol

Odd Ratio +/- 95% CI
DOSE-INCIDENCE RELATIONSHIP
(between antipsychotics and diabetes)
CONCLUSIONS

- Hyperglycemia appears to be a class effect of both conventional and atypical antipsychotics.

- Contrary to the claims of Janssens Pharmceutical:
  - The diabetogenic potential of risperidone was comparable to that of olanzapine.
  - A dose-incidence relationship was suggested not only for olanzapine, but also for risperidone.

Pharmacovigilance, LRL
NEXT STEPS

● To perform Cox regression analyses
  ➤ for direct comparisons between antipsychotic cohorts in their risk of diabetes development

● To share our findings to
  ➤ Key regulatory agencies
  ➤ Practitioners worldwide
    ∗ through publications, scientific conferences, and our marketing folks