DIABETES ASSOCIATED WITH ANTIPSYCHOTIC USE IN VETERANS WITH SCHIZOPHRENIA

Fran Cunningham, Pharm.D.
Department of Veterans Affairs*
University of Illinois at Chicago

Bruce Lambert, Ph.D.
University of Illinois at Chicago

Gregory Dalack, M.D.*
University of Michigan Ann Arbor

Donald Miller, ScD*
Boston University

Kwan Hur, Ph.D.*
University of Illinois at Chicago
This research project was supported in part by Bristol Myers Squibb
Several studies associate atypical and typical antipsychotics in schizophrenic patients with Type II diabetes mellitus (Koro et al, BMJ 2002; Serynak et al., Am J Psych 2002; Fuller et al, Pharmacotherapy 2003; Koller et al., Am J Med 2001)

Mechanism – Unknown

– Potential factors
  - Weight gain
  - Metabolic side effects
Previous Studies

- Study Design
- Study Validity
- Specific Agents

Some inconsistencies and uncertainty exist in regards to the association, the magnitude and variation with different agents.
BACKGROUND

Department of Veterans Affairs has a high prevalence of mental health disorders with schizophrenia approximately 5%

VA decision makers requested a detailed evaluation of antipsychotic agents be performed in reference to safety endpoints such as diabetes mellitus and weight gain
OBJECTIVE

To determine the relative risk of developing Type II diabetes in schizophrenic veterans on atypical antipsychotic monotherapy compared to those on typical antipsychotic monotherapy.
Linkages with PBM Pharmacy Data

- BIRLS Mortality data
- VA National Health Surveys
- VA National Patient Care Databases
- CMS Medicare data
- DEpiC Diabetes Epidemiology Cohort
- Other Potential Data:
  - VA Rehab
  - VA Dz Registries
DATA SOURCES

- **VA PBM v.3.0 Prescription Database**
  - Prescription data - FY 1999-2001
    - Antipsychotic, antidiabetic, diabetogenic agents
    - Facility, Rx date, days’ supply, quantity, SIG, drug name, dose
    - Outpatient and Inpatient Rx data

- **Austin Automation Center**
  - Inpatient, Outpatient Data FY 1997-2001
    - Patient characteristics
    - Eligibility
    - ICD-9-CM codes
    - CPT-4

- **BIRLS**
  - Mortality Data
STUDY DESIGN

- Retrospective Multiple Inception Cohorts
- Observation Period
- Population – Veterans with:
  - Schizophrenia
    - (ICD-9 CM-295.xx) on 2 separate days
  - No hx of Diabetes
    - FY 1997
    - (ICD-9 CM-250.xx) or Rx for antidiabetic medication
  - Medication Initiators
    - No Rx for antipsych previous 3 months-Index Jan 1999
  - Current System Users
    - VA system use at least 3 months prior to date of first antipsychotic Rx
Antipsychotic Medications

- **Atypicals** – olanzapine, risperidone, quetiapine
- **Typicals** – haloperidol, thioridazine, perphenazine, chlorpromazine, fluphenazine, thiothixene, trifluoperazine, loxapine, mesoridazine, molindone
- **Agents not included in primary analysis**
  - Clozapine – due to sample size
  - Ziprasidone – newly marketed
  - Aripiprazole – not available
STUDY DESIGN

Outcome - Diabetes

- Diabetes dx (ICD-9 CM-250.xx) on 2 separate days
  OR
- Prescription for at least one antidiabetic medication

  Insulins, Sulfonylureas, Biguanines, Thiazolidinediones, Meglitinides, Alpha-Glucosidase Inhibitors
DATA ANALYSIS

- SAS v 8.0
- Descriptive Statistics
- Cox Proportional Hazard Model
  - Hazard ratios for individual atypicals vs typicals
DATA ANALYSIS

- **Adjustment**
  - Gender
  - Race
  - Marital status
  - Diabetogenic agents (lithium, VPA, phenytoin, corticosteroids, beta blockers, thiazide diuretics)
  - Diabetes screening panels
  - Age

- **Effect Modification**
  - Interaction terms used to assess effect of age on risk of developing diabetes

- **Evaluated Use of Adherence Score**
DATA ANALYSIS

- Time to Event
  - Diabetes onset
  - Censoring

- Censored
  - Died
  - Last Prescription
  - Switched to another agent
  - End of study
# PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>OVERALL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE (mean ± SD)</strong></td>
<td>51.0 (11.6)</td>
</tr>
<tr>
<td><strong>GENDER (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>94.2 %</td>
</tr>
<tr>
<td>Female</td>
<td>5.8 %</td>
</tr>
<tr>
<td><strong>ETHNICITY (%)</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>47.7 %</td>
</tr>
<tr>
<td>African-American</td>
<td>31.1 %</td>
</tr>
<tr>
<td>Other</td>
<td>21.2 %</td>
</tr>
<tr>
<td><strong>DIABETOGENIC MEDS (%)</strong></td>
<td></td>
</tr>
<tr>
<td>B-Blockers/thiazide diuretics</td>
<td>16.1 %</td>
</tr>
<tr>
<td>Lithium</td>
<td>5.6 %</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>1.5 %</td>
</tr>
<tr>
<td>Phenytoin/VPA</td>
<td>1.9 %</td>
</tr>
<tr>
<td><strong>DIABETES SCREENING</strong></td>
<td></td>
</tr>
<tr>
<td>No. Metabolic Panels (SD)</td>
<td>0.19 (0.77)</td>
</tr>
</tbody>
</table>
### Cox Proportional Hazard Model
**Reference: Any Typical (N=7009)**

<table>
<thead>
<tr>
<th>Hazard Ratios (95% CI)</th>
<th>Olanzapine (N = 5981)</th>
<th>Risperidone (N = 5901)</th>
<th>Quetiapine (N = 877)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>All Ages</em></td>
<td>1.47 (1.20, 1.80)</td>
<td>1.42 (1.16, 1.75)</td>
<td>1.50 (0.96, 2.37)</td>
</tr>
<tr>
<td><strong>Adjusted</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>All Ages</em></td>
<td>1.50 (1.22, 1.84)</td>
<td>1.47 (1.19, 1.81)</td>
<td>1.54 (0.98, 2.43)</td>
</tr>
<tr>
<td><strong>Adjusted</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>&lt;45</em></td>
<td>1.71 (1.10, 2.66)</td>
<td>1.91 (1.22, 2.98)</td>
<td>1.65 (0.64, 4.26)</td>
</tr>
<tr>
<td><em>45-54</em></td>
<td>1.75 (1.27, 2.40)</td>
<td>1.57 (1.13, 2.19)</td>
<td>1.19 (0.54, 2.61)</td>
</tr>
<tr>
<td><em>55-64</em></td>
<td>1.12 (0.67, 1.87)</td>
<td>1.50 (0.94, 2.37)</td>
<td>1.33 (0.46, 3.81)</td>
</tr>
<tr>
<td><em>65-74</em></td>
<td>1.14 (0.64, 2.02)</td>
<td>1.04 (0.56, 1.93)</td>
<td>2.53 (0.86, 7.48)</td>
</tr>
<tr>
<td><em>≥75</em></td>
<td>1.55 (0.57, 4.21)</td>
<td>1.32 (0.51, 3.39)</td>
<td>1.69 (0.19, 14.6)</td>
</tr>
</tbody>
</table>
Comparison to Previous Designs

- **Simple Cohort**
  - Cox Proportional Hazard Model

- **Case Control Study**
  - Conditional Logistic Regression Model
  - 12 and 52 week exposure window
## COMPARISON OF INCEPTION COHORT, SIMPLE COHORT AND CASE CONTROL ANALYSES

<table>
<thead>
<tr>
<th>AGENT</th>
<th>INCEPT. COHORT</th>
<th>SIMPLE COHORT</th>
<th>CASE CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td></td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td></td>
<td>N cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N controls</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 WEEK</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>52 WEEK</td>
</tr>
<tr>
<td>OLANZAPINE</td>
<td>N=5981</td>
<td>N=19,781</td>
<td>1.46 (1.32, 1.61)</td>
</tr>
<tr>
<td></td>
<td>1.50 (1.22, 1.84)</td>
<td>1.28 (1.19,1.38)</td>
<td>1.40 (1.23,1.60)</td>
</tr>
<tr>
<td>RISPERIDONE</td>
<td>N=5901</td>
<td>N=19,639</td>
<td>1.31 (1.18,1.45)</td>
</tr>
<tr>
<td></td>
<td>1.47 (1.19, 1.81)</td>
<td>1.16 (1.07,1.25)</td>
<td>1.45 (1.26,1.66)</td>
</tr>
<tr>
<td>QUETIAPINE</td>
<td>N=877</td>
<td>N=1578</td>
<td>1.50 (1.16,1.93)</td>
</tr>
<tr>
<td></td>
<td>1.54 (0.98, 2.43)</td>
<td>1.08 (0.82,1.44)</td>
<td>1.91 (1.34,2.72)</td>
</tr>
<tr>
<td>CLOZAPINE</td>
<td>Xxxxxxxxxxxxx</td>
<td>N=1293</td>
<td>1.41 (1.05,1.89)</td>
</tr>
<tr>
<td></td>
<td>Xxxxxxxxxxxxx</td>
<td></td>
<td>1.60 (1.09,2.33)</td>
</tr>
</tbody>
</table>

N = sample size; HR = hazard ratio; 95% CI = 95% confidence interval; OR = odd ratio; 95% CI = 95% confidence interval.
COMPARATIVE ANALYSIS

- Relative risk was increased with agents regardless of study design
- More variation in magnitude of relative risk among agents in simple cohort
STRENGTHS of PRIMARY STUDY

Current study design differs from previous studies by:

- Inception cohort design
  - Less influence of previous drug
  - Better exposure definition
  - Reduced selection bias
- Selection method of schizophrenic patients only
- Use of inpatient and outpatient data including medications
STRENGTHS

– Simultaneous adjustment for potential confounding:
  - Sociodemographic characteristics
  - Other diabetogenic medications
  - Diabetic screening tests (metabolic panels)
LIMITATIONS

- Database analysis vs prospective study
- Database design limits ability to adjust for other confounding factors:
  - family history
  - weight
  - diet
- Absence of additional clinical data
- Unable to evaluate other atypical antipsychotic agents
Olanzapine, risperidone and quetiapine have an increased risk of developing diabetes compared to typical antipsychotics. Quetiapine did not reach statistical significance.

Other agents were not evaluated:
- Clozapine - due to sample size
- Ziprasidone - newly marketed
- Aripiprazole - not available

Olanzapine and risperidone exposure in younger patients (< 45 years, 45-54 years) has a greater association with development of diabetes.
FUTURE ANALYSIS

- Phase II – weight gain study is ongoing
- Increase sample size for quetiapine
- Evaluate newer antipsychotic agents