DIABETES ASSOCIATED WITH ANTIPSYCHOTIC USE IN VETERANS WITH SCHIZOPHRENIA

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This research project was supported in part by Bristol Myers Squibb

BACKGROUND

- **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**

BACKGROUND

- 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

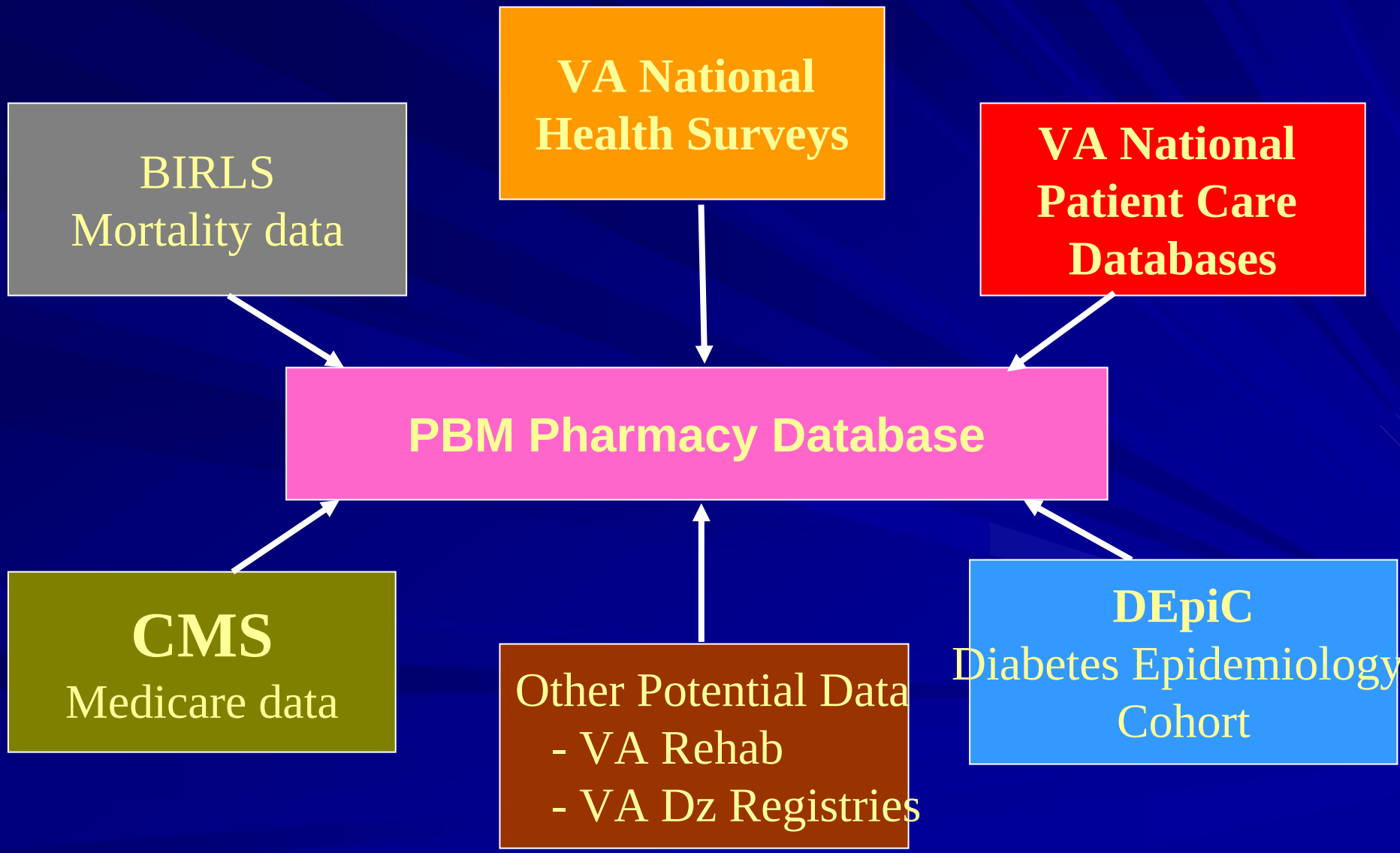
- Department of Veterans Affairs has a high prevalence of mental health disorders with schizophrenia approximately 5%

- 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



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
  - Oct 1998 – Sept 2001 (FY 1999-2001)
- 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

STUDY DESIGN

- 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

CHARACTERISTICS	OVERALL
AGE (mean ± SD)	51.0 (11.6)
GENDER (%)	
Male	94.2 %
Female	5.8 %
ETHNICITY (%)	
White	47.7 %
African-American	31.1 %
Other	21.2 %
DIABETOGENIC MEDS (%)	
B-Blockers/thiazide diuretics	16.1 %
Lithium	5.6 %
Corticosteroids	1.5 %
Phenytoin/VPA	1.9 %
DIABETES SCREENING	
No. Metabolic Panels (SD)	0.19 (0.77)

COX PROPORTIONAL HAZARD MODEL REFERENCE: ANY TYPICAL (N=7009)

HAZARD RATIOS (95% CI)	OLANZAPINE (N = 5981)	RISPERIDONE (N = 5901)	QUETIAPINE (N = 877)
UNADJUSTED *ALL AGES*	1.47 (1.20, 1.80)	1.42 (1.16, 1.75)	1.50 (0.96, 2.37)
ADJUSTED *ALL AGES*	1.50 (1.22, 1.84)	1.47 (1.19, 1.81)	1.54 (0.98, 2.43)
ADJUSTED			
<45	1.71 (1.10, 2.66)	1.91 (1.22, 2.98)	1.65 (0.64, 4.26)
45-54	1.75 (1.27, 2.40)	1.57 (1.13, 2.19)	1.19 (0.54, 2.61)
55-64	1.12 (0.67, 1.87)	1.50 (0.94, 2.37)	1.33 (0.46, 3.81)
65-74	1.14 (0.64, 2.02)	1.04 (0.56, 1.93)	2.53 (0.86, 7.48)
≥ 75	1.55 (0.57, 4.21)	1.32 (0.51, 3.39)	1.69 (0.19, 14.6)

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

AGENT	INCEPT. COHORT N HR (95%CI)	SIMPLE COHORT N HR (95%CI)	CASE CONTROL OR (95% CI) N cases N controls
			12 WEEK 3644 12,819 52 WEEK 2053 6656
OLANZAPINE	N=5981 1.50 (1.22, 1.84)	N=19, 781 1.28 (1.19,1.38)	12 WEEK 1.46 (1.32,1.61) 52 WEEK 1.40 (1.23,1.60)
RISPERIDONE	N=5901 1.47 (1.19, 1.81)	N=19, 639 1.16 (1.07,1.25)	12 WEEK 1.31 (1.18,1.45) 52 WEEK 1.45 (1.26,1.66)
QUETIAPINE	N= 877 1.54 (0.98, 2.43)	N=1578 1.08 (0.82, 1.44)	12 WEEK 1.50 (1.16,1.93) 52 WEEK 1.91 (1.34,2.72)
CLOZAPINE	XXXXXXXXXXXXX XXXXXXXXXXXXX XXXXXXXXXXXXX XXXXXXXXXXXXX	N=1293 1.99 (1.63, 2.42)	12 WEEK 1.41 (1.05,1.89) 52 WEEK 1.60 (1.09,2.33)

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

CONCLUSION
INCEPTION COHORT

- 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