A Pharmacoepidemiological Study of Diabetes Mellitus and Antipsychotic Treatment in the United States

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Introduction

- A number of reports describe increased prevalence of hyperglycemia and DM in patients with schizophrenia and major mood disorders, some preceding the era of modern psychopharmacology [1, 2, 3].
- With introduction of conventional antipsychotics, there have been additional reports of DM and hyperglycemia temporally associated with antipsychotic treatment [4, 5, 6].
- More recent reports describe onset of DM temporally associated with atypical antipsychotics [7, 8].
- Reports in the literature have primarily consisted of small case series and prevalence studies in relatively small population samples [9, 10, 11, 12].

Introduction cont.

- **The prevalence of DM in the US has been increasing rapidly[13] with recent prevalence estimates of 7.8%[14]. Large-scale epidemiological studies are the preferred method to evaluate actual rates of DM because of**
  - **Large sample size**
  - **Compared to clinical trials, results can be more easily extrapolated to the general population.**
  - **Subpopulations with common characteristics (e.g. age groups, gender, ethnic groups) can be studied with sufficient statistical power.**

Method

- **Database**
  - AdvancePCS prescription claim database processed over 300 million prescription claims per year for over 50 million members covered by over 2,000 employers and managed care plans nationwide. Ten percent of patients on antipsychotics are on Medicaid, with also some representation of the over 65 Medicare population.
- **Summary of Study Design**
  - This retrospective pharmacoepidemilogical study estimated the incidence and risk of developing DM among patients in the United States who received a single antipsychotic drug, irrespective of indication.
- **Definition of DM**
  - New onset of DM during antipsychotic exposure was identified by claim(s) for any medication(s) indicated for the treatment of DM, regardless of the route of administration.
- **Reference Cohort**
  - The general PCS patient population cohort was comprised of patients who did not receive antipsychotic treatment, did not make a claim for any PCS-covered benefit during a 2-month window, and had not made a claim for anti-diabetic drug(s) for at least 12 months before enrollment.

Method cont.

- **Inclusion criteria**
  - Prescription of an antipsychotic medication regardless of indication, for an uninterrupted period during a 6 month evaluation period.
  - Enrollment in PCS database for at least 12 months prior to antipsychotic prescription
  - Enrollment Window was Dec. 1, 1998 - Feb. 29, 2000
- **Exclusion criteria**
  - Age less than 18 years
  - Pre-existing history of DM, as evidenced by a prescription claim for any anti-diabetic medication during the 12-month period before enrollment
  - Prescription for a single antipsychotic during 6 month period prior to enrollment
- **Limitations**
  - Disease diagnostic information not available in the PCS database
  - Low mean daily doses of antipsychotics
  - Relatively short period of antipsychotic treatment
  - Findings can only be generalized to patient populations similar to those represented in the PCS database

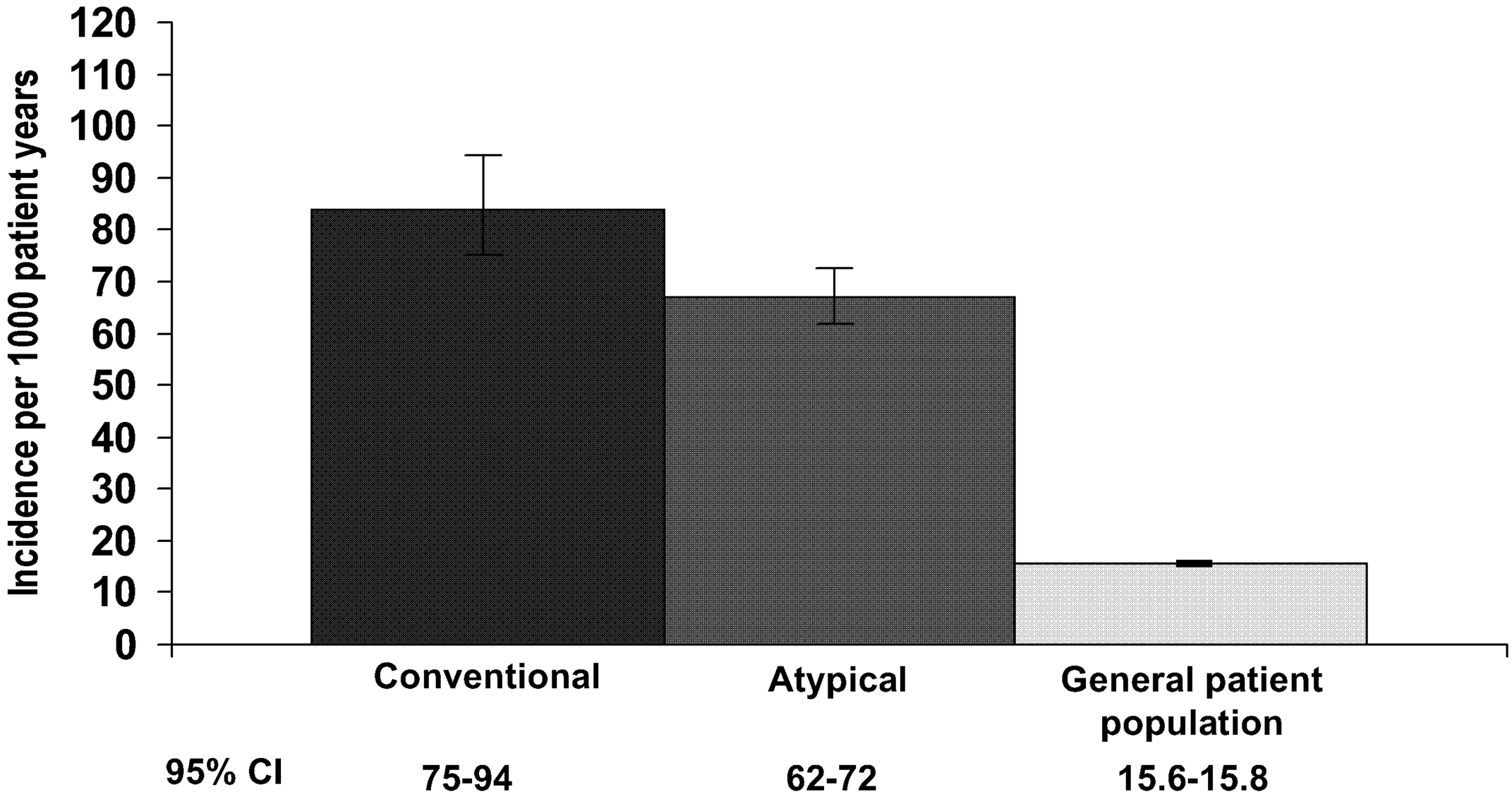
Method cont.

- **Statistical method**
  - **Cox Proportional Hazard (CPH) regression model (controlling for age and gender) to estimate the hazard of DM in patient cohorts by comparing**
    - **Antipsychotic cohorts to the general PCS patient population cohort**
    - **Combined conventional and combined atypical antipsychotic cohorts**
    - **Selected individual antipsychotic cohorts relative to each other**
  - **Given the wide dose ranges observed in the antipsychotic cohorts, HR's of DM were determined for each dose quartile, relative to the general PCS patient population.**
  - **CPH regression takes into account time to event (i.e. duration of antipsychotic exposure)**

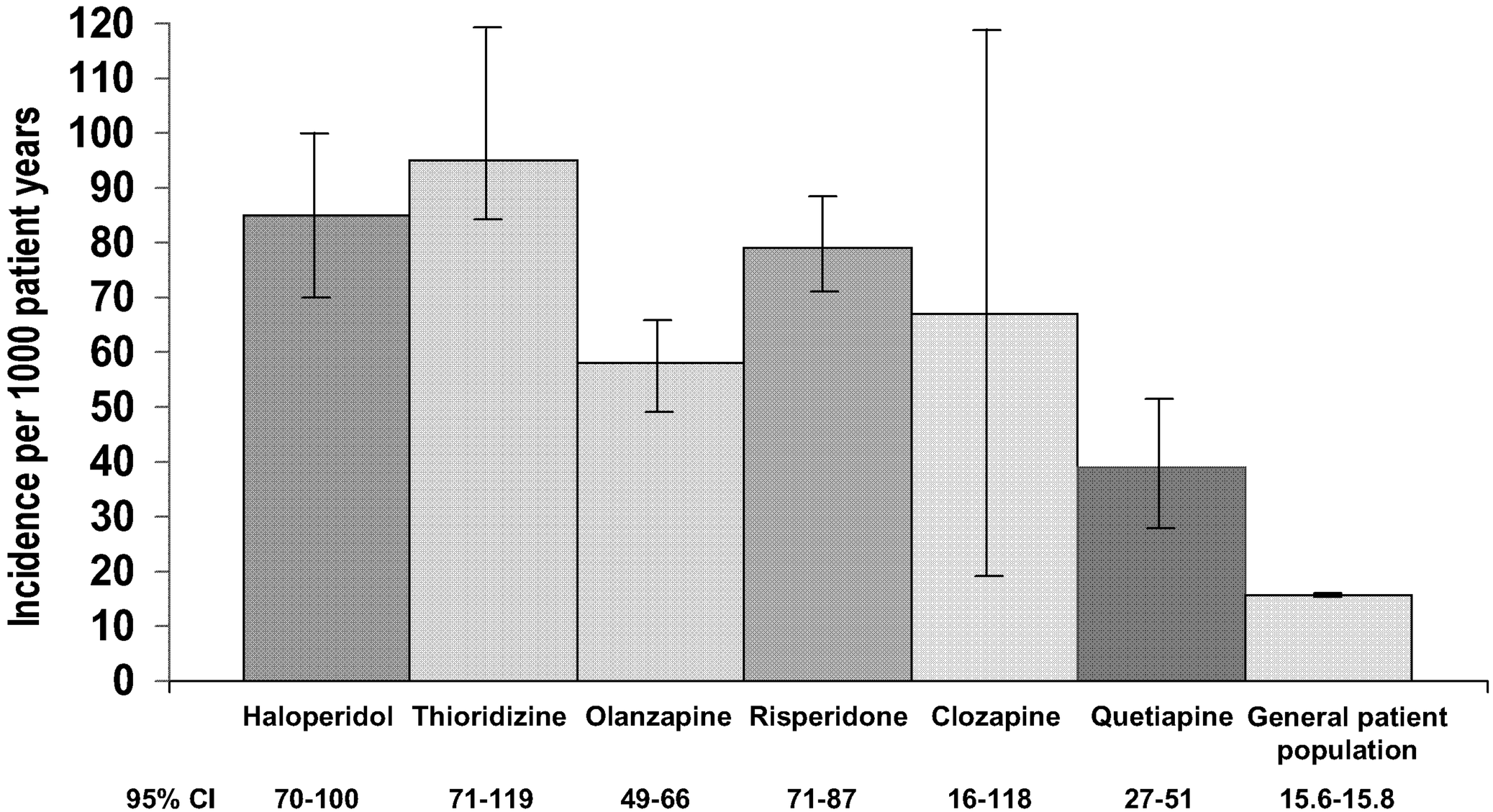
Cohort Characteristics

		CONVENTIONAL ANTIPSYCHOTIC			ATYPICAL ANTIPSYCHOTIC				
	General Patient Population	All Agents	Haloperidol	Thioridazine	All Agents	Olanzapine	Risperidone	Clozapine	Quetiapine
Number of subjects in cohort	5,816,473	19,782	8,476	3,133	38,969	13,863	20,633	277	4,196
Mean Age (years)	52	64	72	61	60	55	64	55	55
% Male	37%	44%	41%	38%	38%	39%	37%	53%	37%
Average duration of antipsychotic treatment (days) (SD)	--	67 (74)	68 (70)	76 (81)	90 (83)	89 (85)	90 (82)	137 (125)	89 (79)
Mean dose of antipsychotic (mg) (SD)	--	NA	2.5 (5.2)	43.9 (54.6)	NA	5.1 (4.2)	1.2 (1.0)	183.1 (198.6)	79.9 (96.7)

Annualized Incidence of DM in Antipsychotic Treatment Cohorts



Annualized Incidence of DM in Specific Antipsychotic Treatment Cohorts



Hazard Ratios of DM in Antipsychotic Cohorts Relative to the General PCS Patient Population

COHORT	Hazard Ratio		
	Ratio	95% CI	P value
Conventional Antipsychotics			
All agents combined	3.5	3.1 – 3.9	≤0.0001
Haloperidol	3.1	2.6 – 3.7	≤0.0001
Thioridazine	4.2	3.2 – 5.5	≤0.0001
Atypical Antipsychotics			
All agents combined	3.1	2.9 – 3.4	≤0.0001
Olanzapine	3.0	2.6 – 3.5	≤0.0001
Risperidone	3.4	3.1 – 3.8	≤0.0001
Quetiapine	1.7*	1.2 – 2.4	0.002
Clozapine	3.3	1.4 – 8.0	0.007

- HR and 95% CI values rounded to first decimal place
- CPH regression controlling for age and gender.

* HR in the top quetiapine dose quartile was 3.1 (CI: 1.9-5.1; p≤0.0001)

Hazard Ratios of DM in Antipsychotic Cohort Dose Quartiles Relative to the General PCS Patient Population

COHORT		Mean dose/quartile ± SD	Hazard ratio		
			Ratio	95% CI	p-value
Conventional					
Haloperidol	Q1	0.6 ± 4	2.6	1.9 - 3.7	≤0.0001
	Q2	1.5 ± .07	2.9	2.0 - 4.2	≤0.0001
	Q3	3.5 ± 1.7	2.9	2.0 - 4.1	≤0.0001
	Q4	17.4 ± 10.7	4.3	3.1 - 5.9	≤0.0001
Thioridazine	Q1	11.8 ± 7.6	2.1	1.0 - 4.5	0.0453
	Q2	26.2 ± 10.5	3.0	1.7 - 5.4	≤0.0001
	Q3	47.3 ± 17.0	2.9	1.6 - 5.2	0.0005
	Q4	133.4 ± 175.3	8.9	6.2 - 12.7	≤0.0001
Atypical					
Olanzapine	Q1	1.8 ± 1.0	3.4	2.6 - 4.5	≤0.0001
	Q2	3.5 ± 0.6	2.6	1.9 - 3.6	≤0.0001
	Q3	5.7 ± 1.8	2.5	1.9 - 3.3	≤0.0001
	Q4	11.3 ± 9.6	3.6	2.8 - 4.7	≤0.0001
Risperidone	Q1	0.5 ± 0.3	3.7	3.0 - 4.5	≤0.0001
	Q2	0.9 ± 0.2	3.0	2.4 - 3.8	≤0.0001
	Q3	1.4 ± 0.4	3.0	2.5 - 3.7	≤0.0001
	Q4	3.1 ± 2.7	4.0	3.3 - 4.8	≤0.0001
Quetiapine	Q1	18.8 ± 10.0	1.8	0.9 - 3.4	0.0957
	Q2	39.8 ± 14.0	1.4	0.7 - 2.9	0.3347
	Q3	76.1 ± 30.4	0.6	0.2 - 1.8	0.3938
	Q4	226.3 ± 244.6	3.1	1.9 - 5.1	≤0.0001

- HR and 95% CI values rounded to first decimal place
- CPH regression controlling for age and gender.
- Low sample size of the clozapine cohort (277 subjects with 7 cases of DM) was not sufficient for a meaningful quartile analysis.

Hazard Ratio of DM Comparing Selected Antipsychotic Cohorts

TREATMENT COHORT	No. of new Cases	No. of subjects in cohort	Hazard ratio		
			Ratio	95% CI	p-value
Atypical	641	38,969	1.0	0.8 - 1.1	0.6261
Vs. Typical	307	19,782	-	-	-
Clozapine *	7	277	1.3	0.6 - 2.9	0.496
Olanzapine	194	13,863	1.1	0.9 - 1.4	0.4786
Quetiapine	40	4,196	0.7	0.5 – 1.0	0.0327
Risperidone	400	20,633	1.2	1.0 - 1.5	0.0396
Vs. Haloperidol	133	8,476	-	-	-
Olanzapine	194	13,863	0.9	0.8 - 1.1	0.2344
Vs. Risperidone	400	20,633	-	-	-

- HR and 95% CI values rounded to first decimal place
- CPH regression controlling for age and gender

* Low sample size of the clozapine cohort was likely of insufficient power to detect a difference, if a difference existed.

Advance PCS - Summary

- Comparable increases in incidence and risk of DM were observed in patients treated with both conventional and atypical antipsychotics relative to a reference patient population.
- Although the risk of DM relative to the general PCS patient population was numerically lower in the quetiapine cohort, the risk of DM in the top quetiapine dose quartile was comparable to the risk observed in the other antipsychotic treatment cohorts. This finding may be related the quetiapine cohort's smaller sample size, or may reflect differences in diagnostic entities and illness severity across antipsychotic treatment cohorts.
- On direct comparison of the three largest individual antipsychotic treatment cohorts:
  - The risk of DM was comparable between the haloperidol and olanzapine cohorts and between the risperidone and olanzapine cohorts.
  - However, there was a moderate and statistically greater risk of DM in the risperidone treatment cohort compared to the haloperidol treatment cohort.

Conclusions

- **This study is consistent with previous observations of elevated risk of diabetes in patients treated with antipsychotic drugs.**
- **What remains unclear is whether the observed increases in incidence and risk of DM may be related to factors intrinsic (psychiatric condition, including genetic vulnerability) or extrinsic (environmental, including treatment-related) to those psychiatric disorders commonly treated with antipsychotic drugs.**
- **Additional factors which are not available in the PCS database would need to be evaluated regarding their association with the risk of developing DM (e.g. psychiatric diagnosis, ethnicity, obesity).**
- **Several years of cumulative clinical use of a given antipsychotic drug are needed for enough patients to be available for this type of epidemiological analyses. Therefore, caution should be exercised in making conclusions regarding the presence or absence of an increased risk of DM in patients treated with more recently introduced or future antipsychotic agents.**

References

1. Lorenz WF: Sugar tolerance in dementia praecox and other mental disorders. Arch Neurol Psychiatry 1922; 8:184-196.
2. Braceland RJ, Meduna LJ, Vaichulis JA: Delayed action of insulin in schizophrenia. Am J Psychiatry 1945; 102:108-110.
3. Freeman H: Resistance to insulin in mentally disturbed soldiers. Arch Neurol Psychiatry 1946; 56:74-78.
4. Thonnard-Neumann E: Phenothiazines and diabetes in hospitalized women. Am J Psychiatry 1968; 124:138-14.
5. Charatan FBE, Bartlett NG: The effect of chlorpromazine ("Largactil") on glucose tolerance. J Mental Sci 1955; 101:351-353.
6. Korenyi C, Lowenstein B: Chlorpromazine-induced diabetes. Diseases of the Nervous System 1968; 827-828.
7. Wirshing DA, Spellberg BJ, Erhart SM, and Wirshing WC. Novel antipsychotics and new onset diabetes. Biol Psychiatry 44: 778-783, 1998.
8. Liebzeit KA, Markowitz JS, Caley CF: New onset diabetes and atypical antipsychotics. Eur Neuropsychopharmacol 2001; 11:25-32.

References cont.

9. Wilson D, DeSouza L, Sarkar W, Newton MA, Hammond C, Glucose intolerance with atypical antipsychotics. Presented at American Psychiatric Association Meeting, May 5-10, 2001 New Orleans , LA (NR519).

10. Meyer JM, One-year comparison of lipids, glucose and weight with Olanzapine or Risperidone. Presented at American Psychiatric Association Meeting, May 5-10, 2001 New Orleans, LA (NR490).

11. Casey DE, Danielson EM, Fishman NB, Prevalence of Diabetes in schizophrenia patients treated with antipsychotics. Presented at American Psychiatric Association Meeting, May 5-10, 2001 New Orleans, LA (NR315).

12. Sernyak MJ, Rosenheck RA, Leslie D, Association of Diabetes Mellitus with atypical neuroleptics. Presented at American Psychiatric Association Meeting, May 5-10, 2001 New Orleans, LA (NR506).

13. Mokdad AH. Ford ES. Bowman BA. Nelson DE. Engelgau MM. Vinicor F. Marks JS. Diabetes trends in the U.S.: 1990-1998. Diabetes Care. 23(9):1278-83, 2000 Sep.

14. Harris MI, Goldstein DE, Flegal KM, Little RR, Cowie CC, Wiedmeyer H, Eberhardt, MS, Byrd-Holt DD. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US Adults: the third national health nutrition examination survey. Diabetes care. 21(4):518-524, 1998.