New-onset type-2 diabetes associated with atypical antipsychotic medications

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Abstract

Purpose: This study compared the one-year incidence of new-onset type-2 diabetes mellitus (DM) and changes in weight in patients with a variety of psychiatric diagnoses prescribed olanzapine, risperidone, or quetiapine, compared to a reference group receiving haloperidol and no other antipsychotic medication.
Research design and methods: Data was abstracted from charts of subjects newly initiated and then maintained for one year on olanzapine ($n=112$), risperidone ($n=100$), quetiapine ($n=100$), and haloperidol ($n=100$). Baseline and one-year DM status, height, and weight were collected, as well as concurrent psychotropic medications, medical and psychiatric comorbidities.
Findings: Using a multivariate model, logistic regression identified a significant association between olanzapine (but not other atypical agents) and the development of diabetes compared to haloperidol over the one-year period (odds ratio 8.4, 95% CI 1.8–38.7). Baseline obesity was independently associated with new-onset DM, but only marginally greater weight gain was found among olanzapine users.
Conclusions: The middle-aged American veterans in this study cohort were highly vulnerable to the diabetogenic effects of olanzapine, but a close correlation with weight change was not found. Patients administered olanzapine should receive careful laboratory monitoring for elevated plasma glucose in addition to weight measurement.
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Keywords: Atypical antipsychotic agents; Body mass index; Type-2 diabetes mellitus

1. Introduction

New generation "atypical" antipsychotic medications carry an increased risk of weight gain and new-onset type-2 diabetes mellitus (DM) (American Diabetes Association, 2004; Department of Veterans Affairs, 2002; Melkerson and Dahl, 2004; Cohen, 2004; Jin et al., 2002; Wirshing et al., 2002; Caro et al., 2002). While the association between atypical antipsychotics and these metabolic side effects is clear, especially in patients with schizophrenia, information about comparative risks of weight gain and diabetes between specific atypical medications, the exact relationship between weight gain and diabetes, and comparative risks for patients with diagnoses other than schizophrenia remain important areas of concern (Kornegay et al., 2002; Koro et al., 2002; Kropp et al., 2004; Beliard et al., 2003).

In the United States Department of Veterans Affairs Veterans Health Administration (VA), olanzapine, risperidone, and quetiapine are the most frequently prescribed atypical antipsychotic medications. Leslie and Rosenheck (2004), in a VA administrative data base study, found the risk for new-onset diabetes in schizophrenia patients was highest for clozapine (2.03%), with lower risks for quetiapine (0.80%), olanzapine (0.63%), and risperidone (0.05%) compared to a

reference cohort of patients on haloperidol. However, a high percentage of atypical use in VA care is for diagnoses other than schizophrenia: 34.8% of olanzapine, 14.7% of quetiapine, and 46.8% of risperidone prescriptions were for other disorders, such as posttraumatic stress disorder (PTSD), mood disorders, or dementia (Blow et al., 2003).

Characteristics of the VA population such as older age, polypharmacy, and pre-existing obesity may increase the risk for development of diabetes. Costs of additional weight gain and DM on health, quality of life, survival, and health care expenditures are enormous (Wolf and Colditz, 1998; Nasrallah, 2002). Given the need for information about the relative risk DM with this population, the current study was conducted to compare the incidence of new-onset DM in veterans with a variety of psychiatric diagnoses.

2. Methods

2.1. Study design

The study, conducted with Institutional Review Board (IRB) approval, was an electronic chart review of the occurrence of new-onset DM in patients maintained on olanzapine, risperidone or quetiapine for a one-year period compared to a haloperidol reference group. Data was collected from care episodes occurring between December 2000 and January 2003 in the greater North Texas catchment area, which includes three major VA mental health care settings. Change in weight and body mass index (BMI), (Gray and Fujioka, 1991) were also assessed.

2.2. Study criteria and patient population

Potential study charts were selected from a pharmacy list of patients newly initiated on the study medications who continued the medication for a full year as indicated by a minimum of four outpatient refills in the year following medication initiation. A baseline weight measurement was required in the medical record within two months of medication initiation and another within two months of the anniversary of medication initiation. A measurement of height was required as well as documentation of medical and psychiatric diagnoses. Exclusion criteria included concurrent prescription of any other study medication or death during the study year. The number of subjects per cell was determined a priori by a statistical power analysis indicating 100 subjects per cell would yield >80% power for detecting significant change in outcome variables of new-onset DM and weight change. To obtain subjects required by the protocol, 1034 olanzapine, 889 quetiapine, 987 risperidone, and 730 haloperidol records were screened in an identical manner applying study criteria in sequence by unique identifying number. Twelve olanzapine chart reviews unintentionally collected in excess of protocol due to an error in collection count between investigators were not discarded. Data was extracted from the electronic medical record applying a standardized study data collection form.

2.3. Measures

The dependent variables included new-onset DM and change in weight. New-onset DM was defined by American Diabetic Association (1997) criteria of a fasting plasma glucose of 126 mg/dl or higher, indication of a new diagnosis of DM in any medical progress note, or initiation of an anti-diabetic medication during the follow-up period. New-onset DM was classified as a dichotomous variable (yes/no). Change in weight in pounds over the study period was determined. Baseline and follow-up weights and BMI were recorded.

2.4. Statistical analyses

2.4.1. Independent variables and covariates

The independent variable of primary interest was type of antipsychotic medication: olanzapine, quetiapine, risperidone, or the reference medication haloperidol. Potential covariates included medical comorbidity, psychiatric diagnoses associated with weight loss, concurrent psychotropic medications associated with weight gain, baseline obesity, and demographic characteristics (age, gender, and race). Based on literature review of co-administered psychiatric medications associated with significant weight gain (Thompson Healthcare, 2004), a dichotomous marker (yes vs. no weight gain) was created for co-administered psychotropic medications. Dichotomous indicators (any vs. none) for baseline medical comorbidity and psychiatric conditions associated with weight loss were applied to assess possible influences of comorbidity. To designate these comorbid conditions, a panel of 5 academic psychiatrists rated the likelihood of weight loss associated with each of the diagnoses found in the study sample. The consensus results were used to develop the dichotomous indicators. A final indicator denoted pre-existing obesity defined by a baseline BMI of 30 or higher. Three age categories were devised: young (age 21–35), middle (age 36–50), and older (age 50–88). Other demographic variables included gender and race, coded white vs. non-white; non-white was primarily Black with one Asian and 12 Hispanic patients.

2.4.2. Multivariate model refined for the analyses

Frequencies and means were calculated to provide descriptive information about the sample. Multivariate models that included gender, race, and psychiatric and medical comorbid diagnoses associated with weight loss were tested but these measures were found to have no effect ($p > 0.40$). Accordingly, these variables were omitted from the analyses to conserve power. A diagnosis of schizophrenia may be a risk factor for diabetes, (Ryan et al., 2003; Citrome et al., 2005), so a preliminary analysis of the effect of schizophrenia was performed. Finding no association, schizophrenia was not used in subsequent models. Therefore, a logistic regression model was refined that determined the association of antipsychotic medication with development of diabetes, controlling for gender, race, age, baseline obesity, and use of weight-gain medications. This analysis was necessarily restricted to patients without pre-existing diabetes ($n = 332$). Analysis of

Table 1
Demographic and clinical characteristics of patients on antipsychotic medications (n=412)

Characteristic	Percent (n)	Mean (SD)	Range
Age		55.4 (12.3)	24–88
Age group			
Young (21–35 years)	3% (14)		
Middle-aged (36–50 years)	30% (125)		
Older (51–88 years)	66% (273)		
Race			
White	70% (288)		
Black	27% (110)		
Other	3% (13)		
Female	13% (53)		
Other weight-gain associated psychiatric medication	23% (96)		
Baseline weight in pounds		198 (41.7)	98–331
Baseline body mass index		29.1 (6.0)	14–51
Baseline obesity (BMI≥30)	42% (173)		
Pre-existing diabetes	19% (80)		
New-onset diabetes	6.9% (23 of 332)		
Comorbid medical diagnosis	87% (360)		

Table 3
Estimated odds ratios for factors predicting new-onset diabetes among veterans taking antipsychotic medications in comparison to haloperidol (n=332)

Effect	Odds ratio estimates	
	Point	95% Wald
	Estimate	Confidence limits
Olanzapine	8.7[a]	1.9–40.5
Quetiapine	2.7	0.5–14.7
Risperidone	0.5	0.0–5.7
Obese at baseline	5.2[a]	1.9–14.4
WeightGainMeds	1.5	0.5–4.5
PsyDxWgtLoss	1.0	0.4–2.6
Female	0.4	0.1–2.2
White	1.7	0.5–5.5
Age	1.0	<1.0–1.1

[a] Statistically significant effects.

co-variance (ANCOVA) was used to determine differences in weight change among patients taking the four antipsychotic medications, controlling for age, baseline obesity, baseline diabetes (based on BMI), and use of weight-gain medications (n=412). Dummy variables were created for the three atypical antipsychotic medications compared to patients on haloperidol. Post hoc pair-wise comparisons assessed differences in weight by antipsychotic medication using Tukey's adjustment for multiple comparisons. We report both significant ($p<0.05$) and trend ($p<0.10$) results from the analysis of variance of weight.

3. Results

Demographic and clinical data are presented in Table 1. Patients ranged in age from 24 to 88 with a mean of 55 (±12)

Table 2
Comparison of patient characteristics by type of antipsychotic agent

	Haloperidol n=100	Olanzapine n=112	Quetiapine n=100	Risperidone n=100
Age in years	56.0	53.8	54.2	57.8
No pre-existing DM (%)	88	83	75	76
New-onset diabetes (%)	2	13	5	1
Pre-treatment weight (lb)	193.7	197.0	205.5	196.5
Post-treatment weight (lb)	196.0	203.7	208.2	200.9
Average weight change (lb)	2.3	6.7	2.7	4.4
Lost more than 10 lb (%)	7	11	12	15
Gained >10–20 lb (%)	13	14	12	17
Gained more than 20 lb (%)	4	18	11	13

years. Only 3.4% (n=14) were young adults aged 21–35. Thirteen percent (n=53) were females and 27% (n=110) were African-American. A total of 19.4% (n=80) subjects had pre-existing DM; 332 (80.6%) had no history of DM and therefore were at risk for new-onset DM. Overall, 23 (6.9%) of 332 subjects without pre-existing diabetes developed new-onset diabetes (Table 1). Table 2 presents absolute change in weight and BMI, and change in weight and BMI as a percent of baseline for each medication groups, as well as raw differences in new-onset diabetes between the medication groups.

Controlling for age, race, gender, baseline obesity, and weight-gain medications, there was a strong association between the use of olanzapine (compared to haloperidol) and the development of diabetes over the one-year period. Table 3 presents odds ratios for factors predicting new-onset diabetes, indicating a significant risk effect for olanzapine (odds ratio 8.7, 95% CI, 1.9–40.7). Quetiapine and risperidone were not associated with increased risk of the onset of diabetes. Demographic characteristics and weight-gain medications were not associated with the development of new-onset DM. The only other factor significantly related to diabetes onset was baseline obesity (odds ratio 5.2; 95% CI, 1.9–14.4). Similarly controlling for age, baseline diabetes, baseline obesity, and weight-gain medications, the association of type of antipsychotic with weight change was only marginally significant in the analysis of variance (omnibus $F=2.56$; $df=8$, 403; $p=0.01$). Young age, weight-gain medications, and baseline obesity were significantly associated with changes in weight. Examination of adjusted means revealed that baseline obesity was associated with less gain in weight over the year while youthful age was associated with more.

4. Discussion

4.1. Key findings

The key finding was the effect of olanzapine exposure on the risk of developing DM over a one-year period, while quetiapine and risperidone showed no effect relative to haloperidol. Weight change was not strongly associated with risk of new-onset DM. Clearly, patients prescribed olanzapine

should receive careful laboratory monitoring for DM and relying on weight assessment alone is inadequate. Patients with additional risk factors, such as older age or pre-existing obesity should be very closely monitored for new-onset diabetes by baseline and repeat assessments of glucose status (fasting serum glucose, HbA1c).

In this study, subjects in all groups developed newly diagnosed DM at a higher rate (10 to 130 per 1000) than the annual incidence reported by the U.S. Department of Health and Human Services (2002) among the general U.S. population (6.3 per 1000). Olanzapine subjects had a higher rate of new-onset DM than that reported in a previous study of VA patients with schizophrenia: 7.3% over a 12–24 month follow-up period (Leslie and Rosenheck, 2004). This difference may in part be due to the high prevalence of pre-existing obesity in our subjects increasing DM risk. The U.S. Preventive Services Task Force (McTigue, 2003) designates a BMI of 30 or greater as "Class I Obesity." On average the study population was near the cutoff for Class I Obesity and 42% met criteria for Class I Obesity at baseline.

Atypical antipsychotic medications have many useful applications for patients other than those with schizophrenia. In our clinical experience, the mood-stabilizing and calming effects are useful in patients with mood disorders, PTSD, and in some patients with unstable personality disorder. Additional research is needed to identify the specific effect of diagnosis on relative risk of diabetes and weight gain with these medications. At the current time, only schizophrenia has been identified as frequently having an independent risk of type-2 DM (Citrome et al., 2005), although our analyses did not find an increased risk in this study.

Metabolic side effect screening guidelines for atypical antipsychotic medications, such as those based on the Mount Sinai Conference on the Pharmacotherapy of Schizophrenia, emphasize weight assessment (Marder et al., 2002). Monitoring weight alone may be insufficient to screen for DM risk. Further research needs to refine guidelines that adequately monitor adverse effects in light of the lack of a strong association between DM and weight gain.

4.2. Limitations and strengths of the study

Retrospective studies are limited by reliance on documented data. Surveillance bias may exist in the subject selection process as patients on certain atypical agents may have been more closely monitored for adverse effects. The subjects may not represent typical VA care in that extensive documentation was required for study inclusion. Data on family history of diabetes was not available for the analyses. However, detailed clinical information from individual patient charts improved the validity of the data compared to information derived from batch administrative databases.

5. Conclusion

The results indicate a high risk of new-onset DM associated with olanzapine in this VA population of individuals with a variety of psychiatric diagnoses, predominantly composed of late middle-aged overweight males. Good clinical practice should include frequent monitoring for new-onset diabetes, including baseline and repeat laboratory assessments of glucose status in veterans prescribed olanzapine. Further research is needed to clarify specific risk factors associated with DM in patients prescribed atypical antipsychotic medications.

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