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Prediction of long-term metabolic effects of olanzapine and risperidone treatment from baseline body mass index in schizophrenia and bipolar disorder

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ABSTRACT

Baseline body mass index (BMI), baseline BMI status (normal, overweight, obese) and early (1 month) BMI increases were tested as predictors of 6- and 12- month increases in glucose and lipid measures in 82 olanzapine (OLZ)- and 78 risperidone (RIS)-treated patients with schizophrenia, schizoaffective disorder, or bipolar disorder who participated in a 12-month randomized, prospective metabolic effects study. Baseline BMI predicted greater fasting glucose and HgbA1c levels at 12 months for both treatments. Early BMI change predicted fasting glucose levels at 6 months, but not HgbA1c or BMI, at either time point. For patients who received no concomitant mood stabilizers, early BMI change predicted 12 month HgbA1c values in the OLZ group, and 6- (but not 12-) month fasting glucose and HgbA1c values in the RIS group. Neither baseline BMI nor early BMI change consistently predicted increases in lipids with either drug. OLZ-treated patients with normal baseline BMI had greater increases in total cholesterol, triglycerides, and non-HDL-cholesterol than those who were overweight or obese. In conclusion, higher baseline BMI predicted adverse glycemic changes after 12 months with OLZ and RIS. Individuals with normal baseline BMI may be most susceptible to OLZ-induced hyperlipidosis. Frequency of metabolic screening should be independent of baseline BMI or rapid increases in BMI.

1. Introduction

Adverse metabolic changes associated with some antipsychotic drugs may be severe and can lead to increased risk of cardiovascular disease and death (Allison et al., 1999; Newcomer, 2005b; Drici and Priori, 2007). The risk of adverse metabolic effects varies considerably according to the individual drug. The propensities for clinically significant weight gain and adverse changes in glycemic and lipid profile appear to be parallel to one another, and are greatest for clozapine and olanzapine, relatively moderate for risperidone and quetiapine, and relatively low for aripiprazole and ziprasidone (Newcomer, 2005a). However, for each drug, there is still considerable inter-individual variability in adverse metabolic effect risk (Correll and Malhotra, 2004). Not all patients show these effects, even if treated with drugs that are associated with the greatest metabolic risk (Haddad, 2005). The ability to predict which patients will develop adverse changes in lipid and glycemic profile during longer-term antipsychotic treatment from baseline and early change in metabolic parameters (such as body mass index [BMI]) would be highly valued in clinical practice.

This is particularly true of olanzapine, a highly efficacious atypical antipsychotic drug that, along with clozapine, has been reported to produce the highest frequency of large increases in BMI, and is associated with the greatest risk of treatment-emergent hyperlipidemia, insulin resistance, and type 2 diabetes mellitus (2004). Among olanzapine-treated patients with schizophrenia and related psychoses, lower baseline BMI at the time of initiation of treatment predicts greater increases in body weight during short- and longer-term treatment (Basson et al., 2001; Kinon et al., 2001; Kinon et al., 2005b). Early changes in weight or BMI (over the first 3–6 weeks of treatment) have also been shown to predict greater weight gain in olanzapine-treated patients with schizophrenia and bipolar I disorder (Hennen et al., 2004; Kinon et al., 2005a).

The effects of baseline BMI and short term BMI change on glycemic and lipid profiles during longer-term treatment with olanzapine and other antipsychotic drugs has received far less attention. This is an important clinical question, given the known association between increased adiposity and greater risk of dysglycemia, atherogenic hyperlipidosis, and cardiovascular mortality in the general population. In the Kinon et al. (2001) study, body weight change was significantly but weakly related to changes in median non-fasting total cholesterol levels after an average 2.5 years of follow-up. However, there is a lack of data addressing relationships between baseline BMI/initial BMI change and subsequent changes in fasting glucose and lipid measures that are more closely related to insulin resistance and better predictors of cardiovascular risk. These include non-HDL-cholesterol and the TG/HDL ratio (Jeppesen et al., 2001c; Hirsch et al., 2002; McLaughlin et al., 2005d), the latter of which has recently been shown to be a superior

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predictor of insulin resistance compared to TG, HDL-, and LDL-cholesterol in antipsychotic-treated patients with schizophrenia or schizoaffective disorder, after adjusting for known confounding factors (Fan et al., 2011).

To address these gaps in the current knowledge base, we conducted a secondary analysis of data from a recently completed randomized, prospective, 12-month comparison of the metabolic effects of olanzapine (OLZ) and risperidone (RIS) in patients with schizophrenia, schizoaffective disorder and bipolar disorder (Meltzer et al., in press). In that study, significantly greater increases in BMI, HgbA1c, total cholesterol, triglycerides (TG) and TG/HDL ratio were observed over time in the olanzapine- compared to the risperidone-treated patients. In this paper, we examined the relationships between baseline BMI and early BMI change and longer-term changes in glycemic and lipid profile during OLZ and RIS treatment.

2. Subjects and methods

2.1. Subjects

Sample characteristics, recruitment, and entry criteria for this study have been described in detail elsewhere (Meltzer, 2005; Meltzer et al., inpress). In brief, 193 patients (ages 18–64 years) who met Diagnostic and Statistical Manual, 4th Edition (DSM-IV) (American Psychiatric Association, 1994) criteria for schizophrenia (SCH), schizoaffective disorder (SCH-AF) or bipolar disorder (BPD) were recruited between September 2000 and June 2006 from six community-based clinical centers in North America. All were outpatients at the time of study entry and provided written informed consent.

Patients treated with OLZ, RIS or clozapine within 1 month of trial initiation, or who received in the past a ≥3 month trial of either OLZ or RIS, were excluded from the study. Patients with pre-existing diabetes mellitus were permitted to participate. The proportions of patients taking no psychiatric medication, monotherapy with antipsychotic drugs, mood stabilizers or antidepressants, or combinations of these, did not differ significantly between treatment groups (data not shown). The study protocol was approved by the institutional review boards of Vanderbilt University School of Medicine and other participating sites.

2.2. Treatment

After completing baseline assessments, patients were randomized to receive open, flexibly-dosed OLZ (5–20 mg/day) or RIS (2–6 mg/day) over 12 months. Patients receiving mood stabilizers and antidepressants were permitted to participate. Subjects were maintained on their assigned study antipsychotic drugs during their entire period of follow-up. Switching between treatment groups was not allowed.

2.3. Metabolic and anthropometric measures

Body weight (kg), BMI (kg/m^2), fasting blood glucose (FBG), fasting lipids (total cholesterol, HDL-cholesterol [HDL], LDL-cholesterol [LDL], triglycerides [TG]) and glycosylated hemoglobin (HgbA1c) were assessed at baseline and at 1, 3, 6 and 12 months after randomization. The ratio of TG/HDL(TG/HDL) and non-HDL-cholesterol (non-HDL-C) were included as endpoints based on their close association with ischemic heart disease risk, and/or insulin resistance (Frost et al., 1996a; Jeppesen et al., 1998a; Jeppesen et al., 2001b; Bittner et al., 2002a; Lu et al., 2003; McLaughlin et al., 2005a). All laboratory samples were drawn after a 12–14 hour fast and were analyzed by the Clinical Laboratory of Vanderbilt University Hospital. Weight was assessed in the fasting state during morning hours, in light clothing.

2.4. Data analysis

The analysis included 82 OLZ- and 78 RIS-treated subjects who had data from baseline and at least one subsequent study visit. Only a small proportion of patients were excluded from the analysis because they had data only at baseline (OLZ, 16.3% vs. RISP, 16.8%, P = NS). Relationships between baseline BMI/early BMI change (defined as change in BMI during the first month of treatment, obtained by subtracting baseline BMI from BMI measured 1 month after study drug initiation) and BMI at 6- and 12 months were assessed with Pearson correlation. Multiple regression was used to assess the relationship between baseline BMI/early BMI change (defined as above) and metabolic measures at 6 and 12 months, adjusting for baseline values of dependent variables. Because a small proportion of patients received concomitant mood stabilizer treatment, a sensitivity analysis was performed that excluded such patients.

Continuous outcome measures were dichotomized into high- and low-risk groups based on the National Cholesterol Education Program's Adult Treatment Panel III definition of metabolic syndrome (Grundy et al., 2004). Logistic regression models were used to examine the relationship between baseline BMI/early BMI change and these dichotomized metabolic measures at 6 and 12 months. The following cutoff values were used: FBG (≥110 mg/dL), TG (≥150 mg/dL) and HDL (males, <40 mg/dL; females, <50 mg/dL). A TG/HDL of ≥3.5 was chosen based on its ability to identify insulin resistant individuals and those at increased CVD risk (Jeppesen et al., 1998c; Jeppesen et al., 2001a; McLaughlin et al., 2005b). All analyses were adjusted for baseline values for dependent measures.

Change in glycemic and lipid measures over time were compared according to drug and baseline BMI category, based on clinically established cut-points (normal, BMI<25 kg/m^2; overweight, BMI 25–30 kg/m^2; obese, BMI≥30 kg/m^2), using a mixed model repeated measures (MMRM) analysis, also adjusted for baseline values of dependent measures. Relationships between categorical variables were analyzed using chi-square analysis. All main effects were tested at a two-tailed α level of 0.05. Analyses were performed using SAS™ (SAS Institute, Inc., Cary, NC, USA) statistical software.

3. Results

Table 1 presents the baseline demographic and clinical characteristics of the study sample (OLZ, n = 82, RIS, n = 78). Slightly more than half of the patients had a diagnosis of BPD. The patients were predominantly male and Caucasian. Seven patients (8.5%) had a history of diabetes. Prior to study entry, 52 patients (63.4%) in the OLZ group and 54 (75.0%) in the RIS group, mostly bipolar, were not taking any antipsychotic drug. Seventeen (20.7%) of the OLZ- and 8 (10.2%) of the RIS-treated patients were taking typical antipsychotic drugs at the time of study entry. The remainder were taking quetiapine (n = 21, combined), ziprasidone (n = 5, combined), or other antipsychotics. Approximately two-thirds of the sample was either overweight or obese at baseline. There was no significant difference between OLZ- and RIS groups in this regard. A total of 26 patients in the OLZ group and 28 patients in the RIS group received concomitant mood stabilizers (predominantly valproic acid in both groups). These subjects were included in the main analysis and excluded in sensitivity analyses.

Mean 6- and 12-month doses were 12.3 ± 5.2 mg/day and 11.0 ± 5.3 mg/day in the OLZ group, and 3.1 ± 2.1 mg/day and 2.9 ± 1.3 mg/day in the RIS group. There were no significant between-group (OLZ vs. RIS) differences in dropout rate at 3- (8.8% vs. 10.6%, P = NS), 6- (19.4% vs. 21.9%, P = NS), or 12 months (30.0% in both groups).

During treatment, the mean baseline to endpoint changes in BMI for OLZ- and RIS-treated patients were +1.9 ± 2.7 kg/m^2 (6.7% increase) and +0.8 ± 3.5 kg/m^2 (3.9% increase), respectively (P = 0.03, Fig. 1). There was a significant drug × time interaction effect for BMI [F(4,426) = 6.5, P = 0.0001], due to greater increases in the OLZ group, most of which occurred during the first 6 months of treatment. BMI changes during the first 6 months of the study were independent

Table 1
Baseline demographic and clinical characteristics of study sample.

Characteristics	Olanzapine (n = 82)	Risperidone (n = 78)
Age, yrs.	40.7 (10.7)	40.4 (11.1)
Gender (no., %)		
Male	47 (57.3)	38 (48.7)
Female	35 (42.7)	40 (51.3)
Race (no., %)		
Caucasian	53 (64.6)	52 (66.7)
African-American	25 (30.5)	25 (32.0)
Other	4 (4.9)	1 (1.3)
Diagnosis (no., %)		
Schizophrenia, Schizoaffective disorder	37 (45.2)	33 (42.4)
Bipolar disorder	45 (54.8)	45 (57.6)
Duration of illness, yrs.	16.7 (11.4)	17.2 (10.8)
Prior hospitalizations, no.	4.0 (6.0)	4.6 (9.2)
Body weight, lbs.	184.5 (49.6)	192.5 (41.5)
Body mass index, kg/m^2	28.4 (7.1)	29.9 (6.3)
Body mass index category (no., %)		
Normal (BMI<25 kg/m^2)	22 (27.5)	17 (22.7)
Overweight (BMI 25–29.9 kg/m^2)	27 (33.8)	25 (33.3)
Obese (BMI≥30 kg/m^2)	31 (38.8)	33 (44.0)
Drug treatment during study		
Antipsychotic, no concomitant mood stabilizers	56 (68.3)	50 (64.1)
Antipsychotic, with concomitant mood stabilizers	26 (31.7)	28 (35.9)

All values are mean (S.D.) unless otherwise specified.
Key: BMI = Body mass index (kg/m^2).