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The Association Between Weight Change And Symptom Reduction in the CATIE Schizophrenia Trial

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Conflict of Interest

Drs. Hermes and Davis report no competing interests.

Contributors

Dr. Hermes prepared the initial draft of the manuscript and worked with Dr. Rosenheck on the final preparation. Drs. Davis and Meyer performed the statistical analysis. Drs. Lieberman and Stroup led the CATIE Schizophrenia Study. All authors comprised a working group for data analysis and manuscript preparation.

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Abstract

Background—Weight gain and changes in metabolic indicators associated with some antipsychotics may be related to symptom improvement and thus an unavoidable correlate of clinical benefit.

Methods—Data from the CATIE schizophrenia trial comparing the effectiveness of perphenazine, olanzapine, risperidone, quetiapine and ziprasidone in a randomized, double-blind, trial over 18 months were used to evaluate the relationship between percent change in body mass index (BMI) and change in total serum cholesterol and triglycerides with the Positive and Negative Syndrome Scale (PANSS) score. Analysis of covariance for observations at 3 months and a mixed effects model for all observations up to 18 months adjusted for potentially confounding variables were used to examine these associations.

Results—In both models, there was a significant association ($p=0.001$) between change in PANSS total score and percent change in BMI, equating to a 0.28 and 0.21 point decrease in PANSS total score (range 30–210) per 1% increase in BMI respectively. Change in BMI accounted for 3% or less of variance for change in PANSS scores. There was no evidence that the association of symptoms and weight gain differed across medications in spite of substantial differences in weight gain and other metabolic measures. Neither total serum cholesterol nor triglyceride levels displayed a significant association with change in PANSS.

Conclusion—The magnitude of the relationship between change in BMI and PANSS was too small to be clinically important, indicating that switching medications to one with less metabolic risk is unlikely to result in meaningful loss of clinical benefit.

Keywords

antipsychotic agents; weight gain; lipids; schizophrenia; treatment outcome; body mass index

1. Introduction

Antipsychotic medications are the cornerstone of treatment for psychotic spectrum disorders and are increasingly used in the treatment of affective disorders. As in all pharmacologic treatment, the clinical benefits of these medications must be balanced against their risks. Weight gain, hyperglycemia and lipid abnormalities are associated with the use of a subset of these medications. These findings have sparked an extensive debate regarding the ratio of risks to benefits in their use (Allison et al., 1999).

First generation antipsychotics (FGAs) have long displayed efficacy in the treatment of psychosis. However, they are prone to neurological side effects that have made their use problematic due to compliance problems, the risk of stigmatization, and rarely disabling tardive dyskinesia (TD) (Miyamoto et al., 2004; Van Putten, 1974). Second generation antipsychotics (SGAs) have been thought to represent an improvement over FGAs due to their decreased risk of movement disorders and superior efficacy (Davis et al., 2003; Leucht et al., 2003). However, evidence of their superior efficacy in clinical treatment settings is not robust (Lieberman et al., 2005) and their superiority with respect to neurologic side effects has been difficult to confirm (Miller et al., 2008). In addition, many SGAs are associated

with significant weight gain, impairment of glucose metabolism and lipid abnormalities compared to other antipsychotics (Allison et al., 1999; Daumit et al., 2008).

The metabolic side effects associated with antipsychotics are variable and often clinically significant. The weight gain associated with FGAs generally varies according to potency. For example, the mid potency agent, perphenazine, was associated, in one study, with a 2.8 kg weight gain over 10 weeks (Blin and Micallef, 2001) and a mean weight loss in the CATIE trial (Lieberman et al., 2005). The effects of SGAs on weight are quite heterogeneous. Olanzapine and clozapine are associated with the greatest gains of 4.2 kg and 4.5 kg respectively over 10 weeks (Allison et al., 1999) and as much as 2.3 kg and 1.7 kg per month respectively. The same review found a mean gain of 1.8 kg per month for quetiapine, 1.0 kg per month for risperidone and 0.8 kg per month for ziprasidone (Wetterling, 2001). In addition, glucose and lipid metabolism are also affected to varying degrees (Lindenmayer et al., 2003; Meyer and Koro, 2004). Another method that has been used to judge the metabolic hazard of these medications is the estimated 10-year risk for coronary heart disease. Olanzapine and quetiapine display an increased risk of 0.5% and 0.3% respectively while a decreased risk of 0.5% has been estimated for perphenazine and 0.6% for risperidone and ziprasidone (Daumit et al., 2008).

A body of research has emerged which seeks to identify an association between antipsychotic response and weight gain to determine whether the metabolic adverse effects are inescapable concomitants of clinical benefit. These studies have evaluated a limited number of agents and results have varied. Clozapine has been assessed in the most studies, which together suggest that weight gain is associated with greater improvement in psychopathology, and thus may warrant the medical risk (Bai et al., 2006; Bustillo et al., 1996; Czobor et al., 2002; Meltzer et al., 2003). Studies of olanzapine have also shown a positive association between clinical response and weight gain (Basson et al., 2001; Czobor et al., 2002; Gupta et al., 1999). Few studies have evaluated this association in risperidone treated patients and results have been mixed (Basson et al., 2001; Czobor et al., 2002). No study has evaluated ziprasidone and quetiapine in this regard. Studies with an FGA comparator have used the high potency agent haloperidol (Ascher-Svanum et al., 2005; Basson et al., 2001; Bustillo et al., 1996). None has evaluated mid-potency FGAs such as perphenazine which may have the potential to cause somewhat greater weight gain than haloperidol (Blin and Micallef, 2001).

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) is the largest trial to-date comparing the effectiveness of antipsychotic treatments. Secondary outcomes for the initial phases of this trial included weight and lipid measurements as well as an evaluation of schizophrenia symptoms (Stroup et al., 2003) with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Results for intention to treat population of the initial phase up to 18-months showed a mean increase of 4.3 kg for those treated with the SGA olanzapine compared to a loss of 0.9 kg for those treated with perphenazine (Lieberman et al., 2005). In addition, the same population showed a mean decrease of 8.9 points on the PANSS in the SGA group compared to a decrease of 8.3 for perphenazine treated patients, a non-significant difference (Rosenheck et al., 2006). The current study seeks to identify associations between weight gain and antipsychotic response through secondary analysis of data from the first phase of this trial.

2. Methods

2.1 Study Design

CATIE compared the effectiveness and cost-effectiveness of available SGAs [olanzapine (7.5 to 30 mg per day), risperidone (1.5 to 6.0 mg per day), quetiapine (200 to 800 mg per

day), and ziprasidone (40 to 160 mg per day)] and an FGA [perphenazine (8 to 32 mg per day)] in a large, 18-month, National Institute of Mental Health–funded, randomized double-blind trial at 57 US sites, including both academic and community providers. Details of the study design and entry criteria have been presented elsewhere (Lieberman et al., 2005; Stroup et al., 2003). The current study relied on data from phase 1/1A gathered at baseline through 18-month follow-up. Lieberman et al. (2005) provides a full description of the baseline characteristics of study participants. In short, mean baseline PANSS score for the population was 75.7 ± 17.6 SD with no significant difference between treatment groups at baseline. Overall baseline BMI was 29.8 ± 7.09 SD. The current study was limited to observations during the first phase of the CATIE trial during which patients were taking their originally assigned drug and had at least one baseline measurement.

2.2 Measures

The dependent measure of interest in the current study was change from baseline in the total PANSS score. The PANSS yields a total average symptom score, based on 30 items rated from one to seven (range=30–210), with higher scores indicating more severe symptoms) and also contains subscales reflecting positive, negative, and general psychiatric symptoms (Kay et al., 1987). Independent measures of interest included percent change from baseline in body mass index (BMI), serum triglyceride level and total serum cholesterol. PANSS and weight data were collected at baseline and at months 1, 3, 6, 9, 12, 15 and 18. Lipid profiles were collected at baseline and months 3, 6, 12 and 18.

2.3 Analysis

The association of percent change in BMI from baseline to 3 months with change in PANSS total score over the same period of time was evaluated using Analysis of Covariance (ANCOVA) with PANSS as the dependant variable and percent change in BMI as a predictor. The ANCOVA model adjusted for baseline PANSS and BMI, treatment assignment, and other covariates determined to be associated with change in PANSS total score. A partial correlation statistic was used to describe the amount of total variation in PANSS change that could be explained by the percent change in BMI after covariate adjustment.

In addition, a mixed model examined the same associations for all available data up to 18-months utilizing a random subject effect with a spatial power covariance structure to adjust for the correlation of observations from the same individuals. The mixed model included terms for baseline PANSS, time (treated as a classification variable), and a term representing the baseline PANSS with time interaction which adjusts for difference in baseline values of patients who dropped out early and are less well represented at later time points. Additionally, the mixed model adjusted for baseline BMI, treatment, and the same potential confounders used in the ANCOVA model.

In order to identify these potentially confounding covariates, the association of change in PANSS with gender, race, Hispanic ethnicity, age, investigator site, site type, duration of illness, baseline antipsychotic, baseline substance abuse, ziprasidone cohort and TD status were analyzed in separate ANCOVA models. All variables significant at $p \leq 0.10$ were placed in the final model and those no longer significant ($p > 0.05$) were removed in a stepwise fashion. Interactions between percent change in BMI and these covariates were also investigated. If an interaction was identified, then the relationship between percent change in BMI and change in PANSS total score was compared descriptively among levels of the covariate using additional models.

Similar ANCOVA models at 3 months of treatment were performed to examine the relationship between change in total serum cholesterol and fasting serum triglycerides with PANSS outcomes while adjusting for baseline values, baseline PANSS, treatment, investigator site, age and duration of illness.

To compare the effect of clinically significant change in BMI ($>7\%$) with small changes ($0-7\%$) and reductions in BMI ($<0\%$), unadjusted mean changes in the PANSS were calculated for each of these three categories after 3 months of treatment.

3. Results

The ANCOVA for individuals completing 3 months of treatment included data from 865 subjects while the mixed effects model included data from 1245 subjects. Of all covariates considered, only age, duration of illness and investigator site were determined to be significant potential confounders and included in both models. Statistically significant symptom improvement (i.e. greater reduction in PANSS scores) was associated with increased BMI ($p=0.001$) in both of the analyses. (Table 1) However, partial r-squared in the 3-month analysis was small, accounting for only 1% of the variance in PANSS change. While partial r-squared is not available from the mixed model, the slope estimate represents a 0.21 decline in PANSS for each 1 percent increase in BMI, a smaller estimate than that of the 3-month model (-0.28).

The models contained significant interactions between percent change in BMI baseline PANSS (in both models) as well as duration of illness (in the 3 month model) and are presented in Table 2 for each level of stratification. When stratified by baseline PANSS the slope estimate increased in the more symptomatic group (baseline PANSS greater than 75) such that there was a 0.42 and 0.25 decline in PANSS for each 1 percent increase in PANSS in both the 3-month and mixed model analysis respectively. When stratified by duration of illness in the 3-month model, the change for those with a shorter duration of illness, less than 13 years, increased to a 0.39 point change in PANSS for every one percent change in PANSS. In the analysis of both interactions, the partial r-squared results remained low, 2%.

No significant interaction was found between randomly assigned medication and the percent change in BMI in the prediction of PANSS change for either the 3-month or mixed effects model indicating there was no significant difference between treatment groups in estimating the association of PANSS with change in BMI. (Table 2) Estimates stratified by medication are presented for descriptive purposes.

The 3-month model showed significant effects for olanzapine and perphenazine but not for quetiapine, risperidone or ziprasidone reflecting in part, sample size differences. With the greater power of the mixed model, the association of symptoms and weight gain using 18 months of data was significant for all drugs except perphenazine. However, the slope estimates were smaller in these models compared to the 3-month models for olanzapine, perphenazine and quetiapine, but larger for risperidone and ziprasidone. In each case a 1% increase in BMI was associated with a less than 0.6 point decrease in PANSS, which corresponds on average to a 6 point decrease for a 10% of weight gain from baseline.

Examination of changes in PANSS associated with categorized percent change in BMI for all treatments at 6 months suggests a difference of 8.5 points between those who lost weight (PANSS mean change of $-5.6 \pm 16.2SD$) and those who gained more than 7% of their baseline weight (PANSS mean change of $-14.1 \pm 15.7SD$). These changes represent a 12% decrease in PANSS scores from the mean baseline value ($75.7 \pm 17.6SD$) after 6 months of treatment.

The adjusted 3-month models for the association of percent change in total serum cholesterol and triglycerides with change in PANSS were not significant for either independent variable.

4. Discussion

This study found that in a large, naturalistic analysis of data from a randomized trial of antipsychotic treatment in schizophrenia (Lieberman et al., 2005; Stroup et al., 2003) there was an inverse and statistically significant relationship between percent change in BMI and change in the PANSS total score for the entire sample albeit with small estimates representing no more than 3% or less of explained variance. Extrapolating from the coefficients in adjusted models, even those stratified by interacting, one would expect at most a 3.9 point (5% of baseline value) average change in PANSS with an increase in BMI of 7% which is conventionally considered to be clinically meaningful weight gain. Analysis of unadjusted 6 month data show an actual 8.5 point (12%) greater decline in PANSS among patients with a 7% gain in BMI compared to those with a 7% decrease in BMI. As discussed below, such declines in PANSS, even with substantial weight gain, are not likely to be clinically meaningful. Interaction analysis of specific antipsychotic agents and change in BMI did not reveal a statistically significant result, indicating that the relationship with symptom change associated with weight gain was no greater for any one antipsychotic compared to others even though differences in the degree of weight change between these medications have been clearly demonstrated (Lieberman et al., 2005). In addition, neither percent change in total cholesterol nor serum triglyceride levels displayed a significant association with change in PANSS.

Analyses of study results indicate that a clinically meaningful increase in BMI is unlikely to result in a change in PANSS score of clinically important magnitude. Several previous studies have investigated clinically meaningful change in PANSS score. Leucht et al. (2005) compared PANSS ratings with Clinical Global Impressions Score (CGI), a provider-rated score of global change in illness severity, and found “minimal improvement” on the CGI correlated to a 26% decrease in PANSS after 4 weeks of treatment. Another study comparing clinical improvement with PANSS score found patients judged as “improved” by clinicians to have a 21% decrease in PANSS (Cramer et al., 2001). Moreover, general biostatistical norms indicate effect sizes between 20 and 30% should be considered “weak” (Cohen, 1988). PANSS change associated with 7% weight gain in this study was well under these thresholds for clinically meaningful change.

Previous studies in the area of weight change and clinical response to antipsychotics have involved a limited number of agents and varying methods making comparison with this study difficult. A majority of studies have evaluated clozapine and olanzapine. Unfortunately, the current analyses did not involve clozapine, prohibiting comparison with this medication. Two studies of olanzapine have reported significant associations between change in weight and treatment efficacy reporting partial r-squared calculations in the 0.32 to 0.45 range (Czobor et al., 2002; Ritter et al., 2000). The difference in r-squared between these studies and the current effort can in part be explained by sample size and adjustment for potentially confounding covariates in the current study. A large study comparing olanzapine with haloperidol showed a significant relation between clinically significant improvement in the Brief Psychiatric Rating Scale (BPRS) and weight gain (Basson et al., 2001). Clinically significant improvement in BPRS corresponded to an average 0.5 kg gain in weight. A similar study involving olanzapine and risperidone showed average 1.5 kg increase in weight in those with clinically significant improvement in BPRS scores (Basson et al., 2001). The effect sizes in the prior studies can be considered relatively small and thus similar to the results of this study.

Similar studies of antipsychotics other than olanzapine and clozapine have failed to show a significant association between weight gain and clinical improvement. Two such studies have evaluated risperidone (Basson et al., 2001; Czobor et al., 2002). Other studies have used haloperidol as a comparator and have also failed to show a significant relationship between weight change and clinical response (Basson et al., 2001; Bustillo et al., 1996; Czobor et al., 2002). The CATIE study, in contrast, used perphenazine, which may cause more weight gain (Blin and Micallef, 2001), but failed to show a clinically meaningful association between BMI change and symptom reduction.

The CATIE study is the largest trial to date comparing the effectiveness of antipsychotic treatments. Its use of broad inclusion criteria, minimal exclusion criteria and a variety of clinical settings increases the generalizability of the results to real world practice. However, the current study is a secondary analysis of CATIE, which was not designed a priori to test these associations and results should be understood as a descriptive rather than hypothesis-testing analysis. Moreover, there was a high rate of treatment discontinuation in CATIE because of its relatively long duration (Lieberman et al., 2005) potentially introducing some attrition bias. However, the mixed model in the current study controlled for the effect of time in an effort to minimize this bias.

In conclusion, this study found a statistically significant but clinically insubstantial association between percent change in BMI and decrease in PANSS score. A methodological point illustrated by these findings is that researchers should not favor statistical significance, reflecting findings that are not merely due to chance, over relationships that reflect effect size or clinically meaningful change. The clinical implication of this finding is that in the presence of weight gain, clinicians need not fear that switching to a medication with less metabolic risk is likely to result in significant loss of clinical benefit since the two are not tightly linked.

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Table 1

Adjusted Regression Models Predicting The Association Of Percent Change In BMI On PANSS with Potentially Confounding Covariates

Treatment	3-Month Model ^a			All time points Model ^b		
	Slope Estimate	Partial R ²	P value	Slope Estimate	P value	P value
% Change in BMI	-0.28	0.01	<0.001	-0.21	<0.001	<0.001
Baseline PANSS	-0.35	0.13	<0.001	-0.61	<0.001	<0.001
Baseline BMI	-0.11	<0.01	NS	-0.07	NS	NS
Treatment ^c :						
Perphenazine	-0.31	<0.01	NS	0.28	NS	NS
Quetiapine	1.12	<0.01	NS	2.54	<0.001	<0.001
Risperidone	3.23	0.01	0.012	2.95	<0.001	<0.001
Ziprazidone	1.90	<0.01	NS	1.99	NS	NS
Age	-0.02	<0.01	NS	-0.07	NS	NS
Duration of illness	0.12	<0.01	0.036	0.16	0.010	0.010

Abbreviations: BMI, Body Mass Index; PANSS, Positive and Negative Syndrome Scale; NS, Non-significant

^a 3-month model is a fixed model of observations at 3 months and is additionally adjusted for investigator site which contains over 40 levels, the results of which are not presented here for space.

^b All time points model is a mixed effects model of observations at all time points up to 18 months which is additionally adjusted for investigator site and visit number, as well as interactions between baseline PANSS and visit number and Duration of illness and visit number, the results of which are not presented here for space.

^c Olanzapine used as reference group for treatment in both models.

Table 2
Models Predicting The Association Of Percent Change In BMI On PANSS Stratified by Interactions of Interest

Model ^a	3-Month Models ^b		All time points Models ^c	
	Slope Estimate	Partial R ²	Slope Estimate	P value
Treatment ^d				
Olanzapine	-0.37	0.02	-0.17	0.001
Perphenazine	-0.56	0.02	-0.10	NS
Risperidone	-0.04	0.00	-0.24	0.002
Quetiapine	-0.25	0.01	-0.18	0.017
Ziprasidone	-0.29	0.01	-0.31	0.005
Baseline PANSS ^e				
<75	-0.17	<0.01	-0.19	0.001
75	-0.42	0.02	-0.25	0.001
Duration of Illness ^f				
<13 years	-0.39	0.02	--	--
13 years	-0.21	0.01	--	--

BMI, Body Mass Index; PANSS, Positive and Negative Syndrome Scale; NS, Non-significant

^aModels predicting the association between percent change in BMI and PANSS score for each stratification level for interactions of interest.

^b3-month models are fixed models of observations at 3 months adjusted for baseline PANSS, baseline BMI, treatment, age, duration of illness, and investigator site.

^cAll time points models are mixed effects models of observations at all time points up to 18 months adjusted for baseline PANSS, baseline BMI, treatment, age, duration of illness, investigator site as well as interactions between baseline PANSS and visit number.

^dResults are presented by treatment type for descriptive purposes only. There was not a significant interaction between percent change in BMI and Treatment in either model

^eThere was a significant interaction between percent change in BMI and baseline PANSS in both models ($p=0.002$ 3-month model and $p=0.019$ all time points model). Estimates and Partial R² for percent change in BMI on PANSS in are presented here for both models stratified by baseline PANSS.

^fThere was a significant interaction between percent change in BMI and duration of illness in the three month model only ($p=0.015$ 3-month model, $p=0.322$ all time points model. Estimates and Partial R² for percent change in BMI on PANSS in are presented here for the 3-month model stratified by duration of illness.