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Understanding the relationship between baseline BMI and subsequent weight change in antipsychotic trials: Effect modification or regression to the mean?

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ABSTRACT

The purpose of this study was to examine whether prior evidence of an inverse relationship between initial body weight and subsequent antipsychotic-induced weight change represents true effect modification or a statistical artifact, regression to the mean (RTM). We conducted a post-hoc analysis after pooling seven randomized, placebo- or active-controlled trials of ziprasidone and other antipsychotic agents. ANCOVA was applied to evaluate treatment-by-baseline body mass index (BMI) range interaction effect on weight change. Regression analysis was applied to estimate the potential bias due to RTM. Statistical interaction tests between baseline BMI ranges and treatment assignments (haloperidol, olanzapine, risperidone, or ziprasidone, versus placebo) were not significant within studies or across studies. Correlation between baseline and follow-up measurements of body weight in placebo-treated subjects was less than perfect ($r = 0.87$, 6-month cohort), leading to RTM. Consistent with predictions based on RTM, the greatest weight change, on average, was observed in subgroups with baseline weights differing the most from the population mean. Our findings suggest that the previously observed correlation between baseline BMI and weight change subsequent to antipsychotic treatment reflects in part RTM, and not effect modification. This class of drugs appears to cause similar weight gain in both high and low baseline BMI groups.

1. Introduction

Differential drug-induced weight gain attributable to antipsychotic medications has been reported in previous studies (Allison et al., 1999; Lieberman et al., 2005; Newcomer, 2005). Allison et al. (1999) noted that weight gain was greatest with clozapine and olanzapine and least with molindone and ziprasidone. In contrast to earlier atypical antipsychotic agents, ziprasidone and aripiprazole have a relatively low propensity for weight gain (ADA, 2004; Newcomer, 2005). Given that weight gain is an important adverse effect of some antipsychotics and obesity is highly prevalent among individuals with schizophrenia (ADA, 2004), the potential moderating effect of baseline weight on weight change following antipsychotic treatment is of particular interest and importance. Several previous studies have shown an inverse relationship between baseline BMI and the magnitude of subsequent weight gain during antipsychotic treatment (Ratzoni et al., 2002; Lane et al., 2003; Lee et al., 2004; Appendix B Table: v, vi, vii). These studies have reported that subjects with higher initial body weight (or BMI) gained less weight than those with lower baseline weight, following treatment with antipsychotic medication. Limitations of these previous findings generally include the lack of a control group, use of analyses that ignored the biasing effects of regression to the mean (RTM) on measurement of change in body weight over time, and absence of an appropriate statistical interaction test to determine if baseline BMI affected or modified the extent to which antipsychotic agents cause weight changes (Allison 1977).

Body weight measurements obtained before and after treatment in a clinical setting are often influenced by measurement error, biological variation, intra-subject variability and other changes not related to the study drug. As a result, the correlation between serial weight measurements made on an untreated or placebo-treated subject at different time points is generally less than perfect, leading to RTM (Galton 1886; Yudkin and Stratton 1988; Rogers and Nicewander, 1988; Shepard and Finison, 1993; Bland and Altman, 1994, Campbell and Kenny, 1999; Tu and Gilthorpe 2007). The principle of RTM predicts greater mean weight change will occur in those subjects with more extreme baseline body weight. That is, there will be an inverse association between baseline body weight and expected weight change even in the absence of any treatment effect. This RTM confounds the interpretation of weight change, especially in those

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subjects whose baseline weight differs most from the population mean.

In this report, we analyzed double-blind, placebo- or active-controlled studies to evaluate the relationship between initial body weight and subsequent weight change following antipsychotic treatments, as well as the impact of RTM.

2. Methods

Analysis datasets were obtained by pooling seven long-term, randomized, double-blind or open-label, placebo- and active-controlled trials of ziprasidone and other antipsychotic agents (haloperidol, olanzapine, and risperidone) from the ziprasidone schizophrenia clinical trial database (Table 1). To control for the potential confounding effects of variations in the duration of treatment exposure (Allison et al., 1999). 6-month and 1-year follow-up cohorts were defined. The treatment-by-baseline BMI interaction effect was evaluated in 470 subjects who received active antipsychotic treatment for 1 year (treatment duration 330–390 days after study randomization). In addition, RTM was illustrated in (1) all subjects ($N=31$) who received placebo over a 6-month treatment period (treatment duration 150–210 days after study randomization in the ziprasidone schizophrenia clinical trial database); (2) all placebo-treated subjects ($N=76$) from a 1-year, double-blind, randomized study (S303 in Table 1). Institutional review board approval for the underlying studies was obtained at each investigational site. Written informed consents were obtained from subjects before any study-related procedure was conducted.

2.1. Statistical methods

To address the research question of whether drug-induced weight gain was moderated by baseline BMI, the treatment-by-baseline BMI range interaction effect was analyzed. Raw data from each study were available for analysis. We applied an ANCOVA model which included terms for treatment-by-baseline BMI interaction, treatment, baseline BMI range, studies, treatment-by-studies interaction, and treatment-by-studies-by-baseline BMI interaction (Hedges and Olkin, 1985). Baseline BMI was adjusted in the ANCOVA model. The primary objective was to test the significance of any treatment-by-baseline BMI interaction effect on body weight; in other words, the extent to which drug-induced weight gain was moderated by baseline BMI. The *F*-test for treatment-by-studies-by-baseline BMI interaction assessed if any such interaction depended on the protocol effect.

To illustrate the RTM effect, we performed regression analyses of baseline and follow-up weight measurements for all placebo-treated subjects in the 6-month follow-up cohort ($N=31$, treatment duration 150–210 days after study randomization) as well as in a separate placebo cohort ($N=76$) taken from a 1-year, double-blind, randomized study (S303 in Table 1). Least squares slope and Pearson correlation coefficient (denoted by ρ) between the two serial measurements of body weight were estimated for both cohorts.

RTM is observed when an extreme subgroup is selected based on a baseline variable and measurements are made of the same variable at subsequent time points, unless $\rho=1$ (perfect correlation between the serial measurements) (Galton 1886; Yudkin and Stratton 1988; Rogers and Nicewander, 1988; Bland and Altman, 1994; Campbell and Kenny, 1999). The amount of RTM thus increases when the correlation is weaker and/or the cutoff selection value for the extreme subgroup moves further from the population average of baseline measurement. The expected weight change due to this statistical artifact for the subgroup with high baseline body weight can be estimated by the following formula (see Appendix A for details):

RTM effect ={baseline difference between subgroup mean and its population mean} × {deviation from perfect correlation between baseline and follow−up measurements} × {ratio of standard deviation of follow−up to baseline measurements}

$$\mathrm{RTM}_{\rho<1} = \left(\bar{w}_{b\,>\,C} - \overline{W}_b^{\mathrm{Pop}}\right)(1-\rho)\frac{\sigma_y}{\sigma_b}. \quad (1)$$

The three factors in (Eq. (1)) show that:

- The $(\bar{w}_{b>C} - \bar{W}_b^{\mathrm{Pop}})$ factor measures the extent to which the baseline mean weight for the subgroup with values greater than the selected cutoff ($\bar{w}_{b>C}$) differs from its population mean ($\bar{W}_b^{\mathrm{Pop}}$).
- The $(1-\rho)$ factor measures how far the observed correlation (ρ) between baseline (with standard deviation σ_b) and follow-up measurements (with σ_y) of body weight in the total population deviates from the perfect correlation ($\rho=1$) (Campbell and Kenny, 1999).

Table 1
Double-blind study analysis database description.

Study	Year	Drug dose	Number of subjects	Study duration (weeks)	Median age (years)	Findings	1-year cohort (treatment days 330–390)
S570 (Simpson et al., 2005)	2001	Olanzapine 5–15 mg once daily Ziprasidone 40–80 mg BID	133	26	39	"Olanzapine was associated with significant within group increases from acute-study baseline in mean body weight (4.97 kg) ($P<0.01$) and body mass index (1.31) ($P<0.01$) at continuation-study endpoint; however, ziprasidone was associated with significant between-group reductions in weight (−0.82 kg) ($P=0.0008$) and body mass index (−0.59) ($P=0.002$). Kaplan–Meier estimates of probability of weight gain ≥7% after first dose showed a higher probability of rapid weight gain associated with olanzapine than with ziprasidone (respectively, 0.03 versus 0.02 at day 7, 0.4 versus 0.05 at day 28, and 0.68 versus 0.23 at day 154) ($P=0.001$, log-rank test)."	$n=28$
S303 (Arato et al., 2002)	1997	Placebo Ziprasidone 20mg, 40 mg, 80 mg BID	294	52	53	"There was a small mean reduction in body weight of 3.6, 2.7. 3.2 and 2.9 kg in the placebo and ziprasidone 40, 80 and 160 mg/day groups, respectively."	$n=116$
S307 (Data on file)	1999	Placebo Ziprasidone 40–60 mg once daily Ziprasidone 80–100 mg once daily	190	52	47	"Median baseline values of body weight were comparable for the three treatment groups. Median changes from baseline to last visit were small and clinically insignificant. There were few occurrences of clinically significant changes: mean body weight increased for 2 (3.2%), 5 (8.1%), and 3 (4.8%) of subjects and decreased for 14 (22.2%), 19 (30.6%), and 23 (36.5%) subjects in the 40–60 mg QD ziprasidone, 80–100 mg QD ziprasidone, and placebo groups, respectively."	$n=79$
S108E (Potkin et al., 2009)	2002	Haloperidol 5–20 mg daily Ziprasidone 40–80 mg BID Ziprasidone 80–120 mg daily	186	156	40	"The percent of subjects showing a significant change (±7% change in body weight) was comparable for all three treatment groups."	$n=16$
S301E (Data on file)	1999	Haloperidol 5mg, 10 mg BID Ziprasidone 20 mg, 60 mg, 100 mg BID	117	40	35	"Twenty-four (8, 4, 5, 1, 6) subjects had a clinically significant increase (>=7%) in weight; 21 (2, 4, 5, 5, 5) subjects had a clinically significant decrease (<=7%) in weight."	$n=43$
S302E (Addington et al., 2009)	1999	Risperidone 3–5 mg BID Ziprasidone 40–80 mg BID	139	44	37	"A smaller proportion of ziprasidone-treated subjects than risperidone-treated subjects experienced a clinically significant increase (>=7%) in body weight (25.0%, 35.5%) and a greater proportion of ziprasidone-treated subjects than risperidone-treated subjects experienced clinically significant decreases (<=7%) in body weight (16.7%, 3.9%)."	$n=54$