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# Weight gain over 4 months in schizophrenia patients: a comparison of olanzapine and risperidone

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**Abstract**

Weight gain frequently accompanies treatment with antipsychotics. In order to determine whether newer antipsychotic agents differ from each other with respect to weight gain, we compared two cohorts of patients with DSM-IV schizophrenia who had newly started treatment with either risperidone or olanzapine. After obtaining informed consent, data regarding body weight and height were culled from existing medical records of 100 patients (50 patients in each treatment group). Baseline body weight, close to the time of starting the new medication, and body mass index [BMI = weight (kg)/height (m) squared] were compared to the body weight and BMI following 4 months of treatment. There was no significant change in mean body weight or BMI in the group treated with risperidone (baseline weight = 83.1 kg ± 20.5, follow-up = 82.8 kg ± 19.9; matched pair $t = 0.66$, $P$ = n.s.; baseline BMI = 29.6 ± 9.4, follow-up = 29.5 ± 9.1; matched pair $t = 0.79$, $P$ = n.s.). However, in the group treated with olanzapine, there was a significant increase in both mean body weight and BMI (baseline weight = 84.9 kg ± 25.0, follow-up = 87.1 kg ± 25.1; matched pair $t = 4.62$, $P < 0.001$; baseline BMI = 29.5 ± 7.4, follow-up = 30.3 ± 7.5; matched pair $t = 4.43$, $P < 0.001$). In this naturalistic study, treatment with olanzapine was associated with a mean weight gain of about 2 kg from baseline, in patients with schizophrenia, while treatment with risperidone was associated with no mean weight change. 

*Keywords*: Atypical antipsychotic; Body mass index; Olanzapine; Risperidone; Weight gain

## 1. Introduction

With the exception of molindone and loxapine, most typical antipsychotic agents are associated with some degree of weight gain (Gardos and Cole, 1977; Doss, 1979; Stanton, 1995). While anecdotal evidence and some reports (Holden and Holden, 1970; Leadbetter et al., 1992) may support the historical belief that weight gain in patients with schizophrenia may be associated with a favorable outcome (Kraepelin, 1919), obesity-related health morbidities remains a significant concern. With the advent of novel 'atypical' antipsychotic agents like risperidone and olanzapine, there is renewed interest in determining whether treatment with these agents is associated with changes in body weight.

Weight gain associated with psychotropic medications has been attributed to an interference with serotonergic neuro-transmission (Garrattini et al., 1989) or their antihistaminic properties (Bernstein, 1988; Salomon, 1992). Weight gain has been reported more commonly in association with lower-potency antipsychotic medications, which have more inherent antihistaminergic and anticholinergic properties than

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higher-potency agents (Brady, 1989). Newer antipsychotic agents, which interfere with serotonergic neuro-transmission can also potentially influence body weight (Casey, 1996). An association between weight gain and the relative receptor affinities of novel antipsychotic agents for histamine H1 has also been proposed (Wirshing et al., 1999). Indeed, the prototypical 'atypical' antipsychotic agent, clozapine, has been linked to a significant increase in body weight in patients with schizophrenia (Umbricht et al., 1994). Data regarding weight gain with risperidone or olanzapine treatment are sparse and come primarily from the initial industry-sponsored clinical trials. Some studies have reported weight gain with risperidone treatment comparable to that observed with typical antipsychotic medications (Claus et al., 1992; Wetterling and Mubigbrodt, 1999) but considerably less than that observed with clozapine (Daniel et al., 1996). Other studies have failed to find any weight gain with risperidone (Ceskova and Svestka, 1993; Min et al., 1993). Treatment with olanzapine, too, has been associated with a dose-related increase of 2–3 kg over baseline body weight, especially in those patients who were underweight prior to beginning treatment (Beasley et al., 1996, 1997a,b). Longer follow-up periods of exposure to olanzapine have reportedly led to a mean weight gain of over 12 kg after a year of exposure (Nemeroff, 1997). In a clinical trial reporting a head-to-head comparison of olanzapine and risperidone (Tran et al., 1997), patients treated with olanzapine gained almost twice as much weight ($4.1 \pm 5.9$ kg) as those treated with risperidone ($2.3 \pm 4.8$ kg). In another study that examined changes in body weight with five different drug treatments (clozapine, olanzapine, risperidone, haloperidol and sertindole), a greater weight gain liability was associated with olanzapine as compared to risperidone (Wirshing et al., 1999). In a recently published meta-analysis, treatment with olanzapine was associated with almost twice as much weight gain (4.15 kg) compared to treatment with risperidone (2.10 kg, Allison et al., 1999a,b). The majority of data regarding weight gain with either risperidone or olanzapine, however, are derived primarily from controlled clinical trials. This study examined changes in body weight in two cohorts of patients with schizophrenia in a naturalistic setting, who had (newly) started treatment with risperidone or olanzapine as part of the usual clinical care at the Western Psychiatric Institute and Clinic, Pittsburgh, PA.

## 2. Methods

The subjects for this study were consecutive inpatients who began treatment with risperidone or olanzapine for the first time at the Western Psychiatric Treatment and Clinic (WPIC), Pittsburgh, PA, and who consented to be studied. These antipsychotic agents have been the most frequently prescribed 'newer' medications for patients with psychotic illnesses. We identified those patients who had not previously been on either risperidone or olanzapine and asked for consent to monitor their weight prospectively. Written informed consent was obtained using a consent form approved by the University of Pittsburgh Biomedical Institutional Review Board. Information regarding body weight and height was culled from the dictated history and physical examination that patients had received at the time of hospitalization. The second measurement of body weight (approximately 4 months later) was obtained only on those patients who had continued to receive the same antipsychotic medication that they had been prescribed at the time of hospitalization. These data were obtained from multiple sources. All patients in this sample who were hospitalized at WPIC received their follow-up care at the Schizophrenia Treatment and Research Center (STRC). The STRC is a comprehensive clinic that offers outpatient, partial hospital, vocational rehabilitation and primary care services at the same location. Body weights are routinely obtained at the partial hospital and primary care clinics, and these data were extracted by reviewing the appropriate medical chart. In the few instances where there was more than one follow up weight recorded, we used the weight that was closest in time to the end of the follow-up period.

Statistical analyses were carried out using SPSS (for Windows). In addition to weight (in pounds or kilograms), the body mass index [BMI = weight (kg)/height (m) squared] was also calculated based on the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults released by the National Heart, Lung and Blood

Table 1
Demographic characteristics of study sample

| Medication group | *N* | *n* | Age (years) (mean ± S.D.) | Gender | Race | Duration of treatment (days) (mean ± S.D.) |
|---|---|---|---|---|---|---|
| Risperidone | 50 | 50 | 40.1 ± 10.0 | Males = 29<br>Females = 21 | Caucasian = 27<br>African-American = 22<br>Other = 1 | 125.3 ± 11.7 |
| Olanzapine | 50 | 50 | 42.5 ± 11.1 | Male = 28<br>Female = 22 | Caucasian = 30<br>African-American = 16<br>Other = 4 | 115.5 ± 19.1 |

Institute in June 1998 (NHLBI, 1998). Correlational and contingency statistics were employed to compute the relationship between demographic and clinical variables and weight or BMI. The Bonferroni correction for multiple comparisons was also applied.

## 3. Results

The sample consisted of 100 patients with DSM-IV schizophrenia (or schizoaffective disorder) who had received treatment with either risperidone or olanzapine ($n = 50$ in each group) for approximately 4 months. The demographic characteristics of the study sample are presented in Table 1. There were similar proportions of male and female subjects in the two medication groups. There were no significant differences in the mean age of patients or the proportion of racial subgroups. Body weight was obtained in either pounds or kilograms and height in meters, and the BMI was computed by using the following formula: BMI = [weight (kg)/height (m) squared)]. The results of body weight and BMI at the time of starting the new medication, and approximately 4 months later are presented in Table 2. While there were no differences between the baseline and the follow-up weights, or BMI in the group treated with risperidone, significant increases from baseline in body weight and BMI were observed in the group treated with olanzapine. These changes were also reflected in both male and female patients separately in the two groups (Table 3).

According to the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults published by the NHLBI in June 1998 (NHLBI, 1998), overweight is defined as a BMI of 25–29.9 kg/m$^2$, and obesity as a BMI >30 kg/m$^2$. The number of patients in each category at baseline and follow-up in the risperidone and olanzapine groups are presented in Table 4. In the risperidone group, the status of one male patient switched from normal weight to overweight, and another male patient from overweight to normal weight. The status of female patients on risperidone remained unchanged. In the olanzapine group, the status of one male patient changed from normal weight to overweight, and one female patient from normal weight to obese. However, a comparison of absolute weight gained or lost in the two treatment groups revealed

Table 2
Changes in body weight (kg) and BMI in treatment groups[a]

| Medication group | Baseline (mean ± S.D.) | Follow-up (mean ± S.D.) | *t* | Significance |
|---|---|---|---|---|
| Body weight | | | | |
| Risperidone | 83.1 ± 20.5 | 82.8 ± 19.9 | 0.66 | n.s. |
| Olanzapine | 84.9 ± 25.0 | 87.1 ± 25.1 | 4.62 | $P < 0.001$ |
| BMI | | | | |
| Risperidone | 29.6 ± 9.4 | 29.5 ± 9.1 | 0.79 | n.s. |
| Olanzapine | 29.5 ± 7.4 | 30.3 ± 7.5 | 4.43 | $P < 0.001$ |

[a] Significance values are based on matched-pair *t*-tests, baseline versus follow-up.

Table 3
Changes in body weight and BMI in male and female subjects

| Medication group | Baseline (mean ± S.D.) | Follow-up (mean ± S.D.) | *t* | Significance |
|---|---|---|---|---|
| Body weight (male) | | | | |
| Risperidone (29) | 84.4 ± 18.4 | 84.9 ± 18.2 | 0.86 | n.s. |
| Olanzapine (28) | 91.2 ± 27.9 | 92.9 ± 28.2 | 3.4 | 0.002 |
| BMI (male) | | | | |
| Risperidone (29) | 28.8 ± 7.4 | 28.9 ± 7.4 | 0.99 | n.s. |
| Olanzapine (28) | 30.5 ± 8.2 | 31.0 ± 8.3 | 3.5 | 0.002 |
| Body weight (female) | | | | |
| Risperidone (21) | 81.3 ± 23.4 | 79.8 ± 22.2 | 1.8 | n.s. |
| Olanzapine (22) | 76.9 ± 18.2 | 79.8 ± 18.6 | 3.3 | 0.004 |
| BMI (female) | | | | |
| Risperidone (21) | 30.8 ± 11.8 | 30.2 ± 11.2 | 1.9 | n.s. |
| Olanzapine (22) | 28.3 ± 6.1 | 29.5 ± 6.5 | 3.1 | 0.005 |

dramatic differences (Fig. 1). Sixty-six per cent of the patients in the risperidone group had lost weight, or their weight had remained unchanged in comparison to 26% of patients in the olanzapine group. Thirty-six per cent of patients in the olanzapine group had gained more than 2 kg in comparison to 26% in the risperidone group.

Correlational statistics (Pearson's *r*) were employed to examine the effect of duration of treatment on weight and BMI change in the two treatment groups. Two new variables, *delta* weight (follow-up weight − baseline weight) and *delta* BMI (follow-up BMI − baseline BMI), were employed for this analysis. The results are presented in Table 5. In the group treated with risperidone, there was a significant inverse correlation between baseline BMI and *delta* BMI.

## 4. Discussion

In this sample, treatment with risperidone was not associated with any weight gain or change in BMI in patients with schizophrenia. Treatment with olanzapine, however, was associated with an increase in both body weight [*delta* weight (kg) = 2.22 ± 3.4] and BMI [*delta* BMI (kg) = 0.81 ± 1.3] from baseline and was observed in both sexes. An association between low BMI at baseline and a subsequent change in weight was revealed only in the group treated with risperidone. It should be noted that the weight gained by the olanzapine patients was relatively modest (2.2 kg) but this may be accounted for by the fact that most of the patients had previously taken conventional antipsychotics and may have gained weight on the latter. Prior antipsychotic usage may also account for the lack of weight change in the risperidone group, and it is noteworthy that 30–40% of patients starting either drug were already categorically obese. In a recent study, Allison et al. (1999a,b) note that persons with schizophrenia tend to be at least as obese as the rest of the population, and thus additional weight gain associated with antipsychotics ought to be of concern.

There are several limitations as to what may be concluded from these data. Factors related to obesity

Table 4
Status change based on BMI criteria

| Medication group | Gender | Baseline | | | Follow-up | | |
|---|---|---|---|---|---|---|---|
| | | Normal | Overweight | Obese | Normal | Overweight | Obese |
| Risperidone | Male (29) | 10 | 11 | 8 | 10 | 11 | 8 |
| | Female (21) | 4 | 9 | 8 | 4 | 9 | 8 |
| Olanzapine | Male (28) | 9 | 6 | 13 | 8 | 7 | 13 |
| | Female (22) | 7 | 7 | 8 | 6 | 7 | 9 |

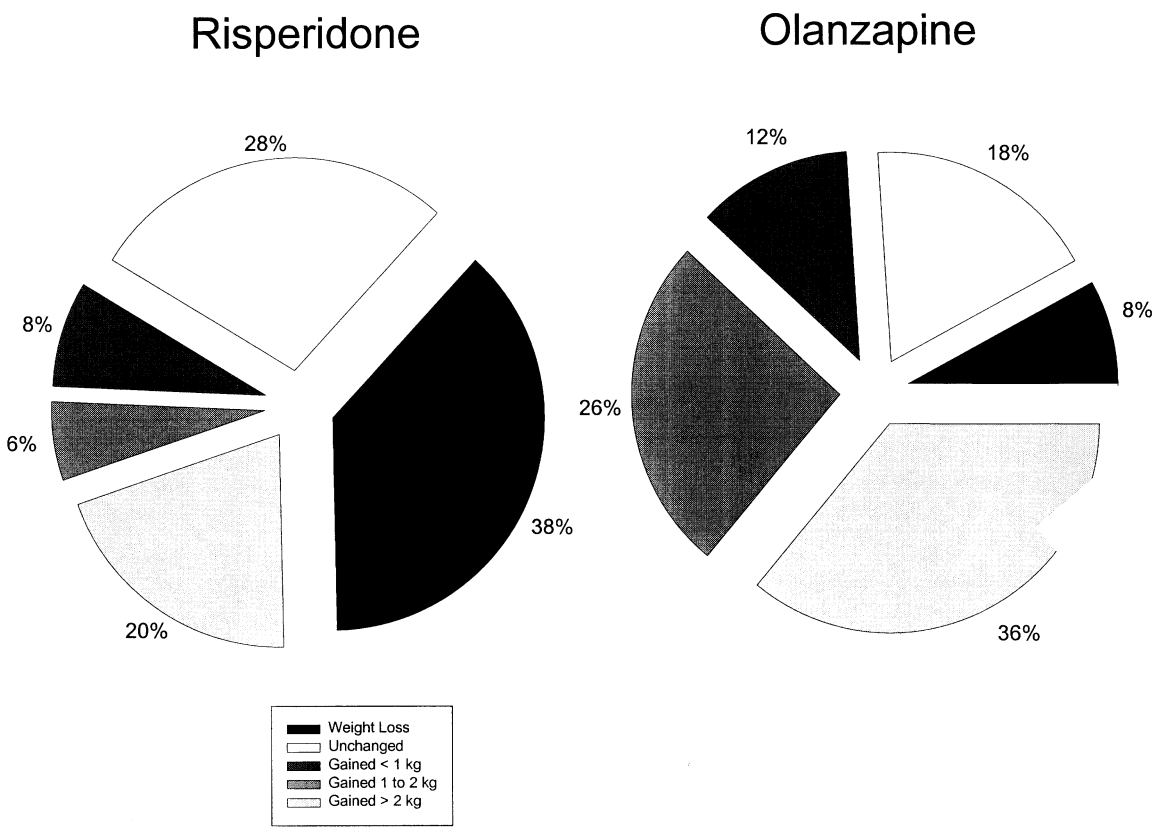


Fig. 1. Comparison of weight gained or lost in patients on treatment with risperidone or olanzapine.

including, dietary habits, medical illnesses, concomitant medications, smoking history, etc. were not taken into account. However, there was no reason to suspect that these factors were systematically associated with treatment with one or other of the novel medications. We did not obtain the dosage of either risperidone or olanzapine at the time of follow-up to examine whether weight change was dose-related. The effect

Table 5
Correlation matrix ($r$) for the risperidone group and olanzapine group[a]

| | Baseline weight | Baseline BMI | *delta* weight | *delta* BMI |
|---|---|---|---|---|
| Risperidone group | | | | |
| Age | 0.01 | 0.04 | −0.09 | −0.08 |
| Duration of treatment | −0.004 | 0.05 | 0.08 | 0.09 |
| Baseline weight | | 0.84** | −0.26* | −0.29* |
| Baseline BMI | | | −0.29* | −0.35** |
| Olanzapine group | | | | |
| Age | 0.09 | 0.14 | −0.23 | −0.21 |
| Duration of treatment | 0.15 | 0.16 | 0.12 | 0.12 |
| Baseline weight | | 0.91** | −0.04 | −0.07 |
| Baseline BMI | | | 0.04 | 0.03 |

[a] $r$ : correlation coefficient; * correlation is significant at the 0.05 level (two-tailed); ** correlation is significant at the 0.01 level (two-tailed).

of treatment duration on weight gain may not have been revealed in this study because of an a priori selection of study duration that was more or less similar for all patients. Furthermore, the absence of psychiatric assessments precluded analyses to test the hypothesized associations between weight gain and clinical improvement.

## 5. Conclusions

While this study was not aimed at determining the mechanism of weight gain in patients treated with risperidone or olanzapine, the results may clarify many important issues. Firstly, risperidone may be a good alternative for patients who either are switching treatment from typical antipsychotic agents, and are obese, or have obesity-related medical morbidities. Secondly, the absence of a ceiling effect with regard to increases in body weight with antipsychotic medication is also borne out in this study. As can be seen from these data, a large proportion of patients who experienced weight gain with olanzapine were 'obese', even before starting the medication. The absence of a ceiling effect with regard to weight gain has also been reported in association with clozapine (Umbricht et al., 1994).

It is difficult to speculate on the reasons on why risperidone may offer some advantages over olanzapine with regard to weight gain. While both drugs belong to the class of serotonin–dopamine antagonists, risperidone has a high affinity for dopamine ($D_2$) receptors, whereas olanzapine is a potent serotonin (5-$HT_2$) but somewhat weaker dopamine ($D_2$) receptor antagonist. These differences in pharmacological profiles, and the preferential affinity for serotonergic antagonism by olanzapine may interfere with the perception of satiety and result in weight gain in patients.

The non-interfering design of this study examined weight changes in a naturalistic environment of usual clinical practice. Given the current enthusiasm by clinicians to prescribe these novel agents, the additional information regarding the relative risk of gaining weight may be helpful in selecting the appropriate agent for each patient, particularly for those who are currently being treated with typical antipsychotic agents and who face obesity-related health morbidities. This study also underscores the importance of nutritional counseling for patients who are receiving these medications.

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