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# A retrospective comparison of BMI changes and the potential risk factors among schizophrenic inpatients treated with aripiprazole, olanzapine, quetiapine or risperidone

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ABSTRACT

The objective of this study was to evaluate weight gain and its potential risk factors among different second generation antipsychotics (SGAs). The study was conducted for Korean inpatients with schizophrenia in a university hospital in Seoul, between Jan 2000 and Dec 2007. Data were collected by reviewing the medical records of the patients, who were prescribed to one of the SGAs among aripiprazole, olanzapine, quetiapine or risperidone. The changes of weight and body mass index (BMI); risk of clinically significant weight gain (>7% gain to initial weight) and their associations with various clinical characteristics of such patients were analyzed. Five hundred and eighty-eight (588) and 294 subjects treated with one of the four SGAs for a duration of 1 month and 2 months were included, respectively. Olanzapine showed significantly greater weight and BMI increase at month 1 ($p=0.028$ for weight; $p=0.019$ for BMI) and month 2 ($p=0.032$ for weight; $p=0.029$ for BMI) than others. Females showed greater BMI increase change ($0.70\pm0.91$ kg/m$^2$, $p=0.008$) and were also more likely to experience clinically significant weight gain (odd ratio = 1.846, 95% CI = 1.098 to 3.105, $p=0.021$) at month 1.Younger patients (<45 years old) had significantly greater weight and BMI increase at both months 1 and 2. Younger patients also showed greater risk for clinically significant weight gain at month 2 (odd odd ratio = 2.567, 95% CI = 1.196 to 5.508, $p=0.016$). Low baseline BMI (<25 kg/m$^2$) was associated with greater weight gain at month 1 ($1.92\pm2.29$ kg, $p<0.001$) and month 2 ($4.07\pm3.56$ kg, $p<0.001$) and BMI increase at month 1 and month 2 ($p<0.001$ for both). Patients with low baseline BMI showed higher risk of clinically significant weight gain at both months 1 and 2 ($p<0.001$ for both). Olanzapine was shown to have higher metabolic risk than other SGAs in inpatients with schizophrenia. The individual's own clinical characteristics also exerted influence on weight gain effects of SGAs. Younger patients with lower baseline BMI were under greater risk of antipsychotic-induced weight gain. More studies are required to verify the role of gender on weight gain.



## 1. Introduction

People suffering schizophrenia are reported to have a 20% shorter life expectancy than the general population (Newman and Bland, 1991) with cardiovascular disease as the leading cause of death (Capasso et al., 2008; Fors et al., 2007). In light of the raised concerns, the metabolic side profiles of antipsychotics have been relatively well stated (American Diabetes Association, 2004; Bobes et al., 2003; Kelly et al., 2003; Newcomer et al., 2009) but schizophrenia itself had also been reported to predispose these patients to obesity (Allison et al., 1999; Ryan et al., 2004; Thakore, 2004). However, no differences in the prevalence of dyslipidemia and obesity (Verma et al., 2009) were shown and even lower BMI (Wetterling et al., 2004) was demonstrated in drug-naïve first-episode schizophrenia patients when compared with controls. In addition, the most frequent side effect of antipsychotics observed in drug-naïve first-episode schizophrenia patients was clinically significant weight gain (Perez-Iglesias et al., 2008). Considering the serious consequences of metabolic adversities, the recently suggested greater role of antipsychotics on obesity is particularly alarming.

*Abbreviations:* ANCOVA, analysis of covariance; ANOVA, analysis of variance; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; FFM, fat-free mass; GAF, global assessment of functioning; IRB, Institutional Review Board; RMR, resting metabolic rate; SGAs, second generation antipsychotics.

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While the relative metabolic side profiles of each SGA have been under extensive investigation, little attention had been paid to individual's own risks to antipsychotic-induced weight gain. Only a limited data exist to predict inter-individual's risk for antipsychotic-induced weight gain and even the existing data revealed conflicting results. For example, several studies reported low baseline body mass index (BMI) as a risk factor for accelerated antipsychotic-induced weight gain (Bai et al., 2009a; Basson et al., 2001; Boden et al., 2009; Saddichha et al., 2008). On the other hand, the effect of regression to the mean had been reported to contribute to the accelerated weight gain observed with lower baseline BMI in another study (Allison et al., 2009). The other studies that suggested higher metabolic risk in overweight patients (Bobes et al., 2003; Gebhardt et al., 2009) in contrast further escalate the pandemonium. Table 1 summarizes the potential risk factors proposed in previous studies for antipsychotic-induced weight gain.

The conflicting results on antipsychotic-induced weight gain indicate a strong need to elucidate the potential risk factors. Enhanced understanding of the risks may provide a useful ground for better targeted pharmacotherapy and in turn, more control over antipsychotic-induced weight gain. The fact that almost all studies took place in outpatient settings may have contributed to those aforementioned contradicting results. Various factors such as medication adherence, diets and physical activities can influence weight gain. Thus, failure of controlling these biasing factors may have complicated the results. However, inpatient investigation may reduce such biases with fewer variations in the daily calorie intakes, missing of antipsychotic doses, or factors as subtle as the difference in efforts when making an outpatient clinic visit.

In literature review, only a few inpatient studies were found with each having significant limitations. Three studies, carried out in small samples of hospitalized children, lacked specificity to schizophrenia (Khan et al., 2009; Martin et al., 2000; Ratzoni et al., 2002). In another inpatient study, lower admission body weight, smoking, male gender and prescriptions of SGAs showed associations with weight gain (Megna et al., 2006), but it also lacked specificity to schizophrenia. Furthermore, the study had a major limitation by allowing concomitant use of major psychotropics, which may exert influence on weight. Two investigations compared changes of weight, glucose and lipid profiles in inpatient with schizophrenia, but they analyzed only one patient demographic as a potential risk factor (Krakowski et al., 2009; Meyer, 2002). Other two retrospective studies of Chinese patients with schizophrenia have yet best addressed the inter-individual risk factors (Bai et al., 2009a,b). However, the allowance of concomitant antipsychotics or mood stabilizers hindered the efforts to correlate risk factors to antipsychotic use. Moreover, sampling biases could have occurred by the over-represented refractory cases in the samples.

To our knowledge, this is the first and the largest study to assess various potential risk factors of antipsychotic-induced weight gain for inpatients with schizophrenia, receiving different monotherapies of SGAs. In order to avoid over-represented refractory cases, the metabolic effects of various SGAs except clozapine were analyzed. The authors grouped and compared the sample by different SGAs and also by discrete baseline characteristics to look for potential risk factors associated with weight gain. The hospitalized setting and the careful design, which is presented later, would hopefully reduce the confounding factors that have contributed to those conflicting results in the previous studies and also provide a better opportunity to observe pure net effects of SGAs on weight.

**Table 1**
Reported risk factors of antipsychotic-induced weight gain.

| Variables |
|---|
| Younger age (Basson et al., 2001; Meyer, 2002; Safer, 2004; Strassnig et al., 2007; Bai et al., 2009a) |
| Gender |
| — Male (Basson et al., 2001) |
| — Female (Bobes et al., 2003) |
| Nonwhite Race (Basson et al., 2001; Krakowski et al., 2009) |
| Types of antipsychotics |
| Clozapine ~ Olanzapine > Quetiapine ~ Risperidone > Aripiprazole ~ Ziprasidone (Kelly et al., 2003; American Diabetes Association, 2004; Newcomer et al., 2009) |
| Baseline BMI |
| — lower BMI (Basson et al., 2001; Saddichha et al., 2008; Boden et al., 2009) |
| — Higher BMI (Bobes et al., 2003; Gebhardt et al., 2009) |
| More Negative Symptoms at baseline (Strassnig et al., 2007) |
| Better Clinical Outcome (Basson et al., 2001) |
| Undifferentiated Schizophrenia (Saddichha et al., 2008) |

BMI, body mass index.

## 2. Method

### 2.1. Design and data collection

A retrospective analysis was done by reviewing the medical records of the patients, who were prescribed to one of the SGAs (aripiprazole, olanzapine, quetiapine or risperidone) while being admitted to the psychiatric ward of Seoul St. Mary's hospital, Catholic University of Korea between Jan 2000 and Dec 2007. Admission settings are described subsequently to give a better picture of our study.

After hospitalization, the patients are confined to a locked ward unless they had been evaluated by the resident in charge as being stabilized enough to have off ward pass privileges. The off ward passages are allowed one to three times for a maximum of 30 min each. In the ward, patients can utilize indoor-bicycle or treadmill for exercise. They are provided with three meals per day with 2000 cal and 90 g of protein each and can order snacks once a day. If the patients have underlying diabetes mellitus (DM), a meal of calculated calorie, based on the patient's weight and physical activity, is provided instead and snacks would be prohibited.

The study included patients of any age with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) diagnosis of schizophrenia at both admission and discharge. Taking advantage of the retrospective nature, this study was conducted without age limitation in order to explore age's potential effects on weight in a full range. Patients with a history of severe physical illness requiring acute medicosurgical interventions, history of substance abuse or dependence and other axis I psychiatric comorbidities were excluded. To reduce other medications' influence on weight, the study also excluded those who received any kind of antidepressants, mood stabilizers, steroids or more than one different types of antipsychotic. We did not include subjects with a record of antipsychotic usage within one month prior to the admission. Other concurrent medications were allowed.

When eligible criteria were satisfied, the following data were obtained in the review of the medical charts. Gender and age were collected as demographic data. Clinical data such as schizophrenia subtypes; global assessment of functioning (GAF) scales upon admission and discharge; presence of DM or hypertension; duration of admission; types of antipsychotics used; height; weight and calculated BMI ($kg/m^2$; calculated accordingly with the weights checked at designated interval and the heights of the corresponding patients acquired at baseline) at the admission, 1 month and 2 month after the treatment initiation with a SGA were also gathered. Weights recorded within $\pm 5$ days of the designated interval were allowed. The diagnosis of schizophrenia and its subtyping was made by a

psychiatric resident and confirmed at discharge by an attending psychiatrist in charge of the patients.

Of the 1246 charts reviewed, 658 were excluded and 588 subjects were included for analysis. 407 subjects were excluded for not being diagnosed as schizophrenia or having other comorbid axis I diagnoses. 126 subjects were excluded for exposure to antipsychotics within 1 month prior to the admission or due to switch of SGA for any reason during the admission. 109 subjects were excluded for concurrent medications that were not allowed (antidepressant, mood stabilizer, steroids, or more than one antipsychotic). 5 subjects were excluded for severe physical illness. 4 subjects with catatonic schizophrenia subtype were excluded due to lack of statistical power. 7 subjects were excluded for missing records of weight. The Institutional Review Board (IRB) of the hospital approved the study (IRB approval number: KC10RISE0034).

### 2.2. Statistical analyses

We have performed continuous variable for the normality for distribution. The Kolmogorov–Smirnov and Shapiro–Wilk Tests have shown normal distribution of clinical variables included in the analyses (for instance, Kolmogorov–Smirnov Z: for age = 2.031, for weight at admission = 1.571 and for BMI at admission = 1.709). Analysis of variance (ANOVA) was carried out for between-group comparisons of baseline characteristics among the four different SGAs (aripiprazole, olanzapine, quetiapine, and risperidone), using post-hoc analyses by Tukey's method and chi-squared test for non-continuous and categorical variables. Since many of our demographic and clinical variables could be interrelated, we used analysis of covariance (ANCOVA) to adjust potential confounding factors. Changes of weight and BMI were defined as dependent variables and comparison of between potential risk factors was performed. Whenever there were available additional data, analyses on changes in weight and BMI after 2 months of SGA treatment were also carried out. Pearson correlation was additionally performed between the changes in weight and BMI and the GAF at discharge to explore whether better clinical outcome is associated with greater weight gain as previously reported (Basson et al., 2001). Multivariate Binary Logistic Regression was carried out to find whether a particular variable increases the risk for clinically significant weight gain. The variables, which showed a significant difference in the ANCOVA, were selected as independent variables. The binary dependent variable was categorized into weight gain of less than 7% and equal or greater than 7% from the baseline. All data were analyzed using the SPSS version 12.0 (SPSS Inc., Chicago, Ill.) for windows and two-tailed significance level of less than 0.05 was selected for all tests.

When we calculated the sample power of the present study using the results of olanzapine-treated group and risperidone-treated group (Table 3), group sample sizes of 363 and 128 achieve almost 100% power to detect a difference of 1.4 between olanzapine and risperidone-treated groups, given that the mean of olanzapine-treated group is 3.8 and risperidone-treated group is 2.4 with estimated standard deviations for each of 1.8 and 1.4, respectively, with a significance level (alpha) of 0.05000 using a two-sided two-sample t-test.

## 3. Results

### 3.1. Baseline patients' characteristics

Patients' baseline demographic and clinical characteristics for each of the SGAs are shown in Table 2. The four SGA groups showed significant differences for baseline weight, BMI, diagnosis subtypes and the comorbidity of hypertension. The olanzapine group had lower baseline weight ($p = 0.003$), BMI ($p = 0.001$) and comorbid hypertension ($p = 0.041$). Although our result indicated statistical difference in GAF scale ($p = 0.034$) among the four SGA groups, no difference was found between the SGAs in the post-hoc analysis. There were no other significant difference in baseline characteristics among the SGA groups.

### 3.2. Weight and BMI changes

After one month of SGA treatment, weight records of 588 patients were obtained. Additional analysis was done with the weight records of 294 patients, when they were available at month 2. With collected weight data, corresponding BMI were calculated. Table 3 shows the changes of weight and BMI after 1 month and 2 months of treatment by the four different SGAs. These results were attained after adjusting variables – types of SGAs, sex, age, GAF scale, BMI and schizophrenia diagnoses – which were not homogenous between treatment groups in Table 2.

Types of SGA showed significant effect on weight and BMI changes. The olanzapine group had significantly greater weight ($1.84 \pm 2.37$ kg, $p = 0.028$) and BMI increase ($0.69 \pm 0.90$ kg/m$^2$, $p = 0.019$) than other SGAs after one month of treatment. The olanzapine also showed significantly greater weight ($3.80 \pm 3.89$ kg, $p = 0.032$) and BMI increase ($1.40 \pm 1.46$ kg/m$^2$, $p = 0.029$) at month 2 than the rest.

Gender exerted a significant influence on metabolic parameters. Males showed greater increase of weight ($3.87 \pm 3.70$ kg, $p = 0.039$) at month 2 but such difference was not found in BMI at the same time ($p = 0.390$). Interestingly, females had numerically greater increase in

**Table 2**
Demographic and clinical characteristics' comparison among SGAs.

| Characteristics | Olanzapine (n = 363) | Quetiapine (n = 31) | Risperidone (n=128) | Aripipralzole (n = 66) | p value |
|---|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) | |
| Sex | | | | | 0.409 |
| Female | 205 (56.5) | 15 (48.4) | 68 (52.7) | 42 (63.6) | |
| Schizophrenia diagnosis | | | | | 0.001 |
| Paranoid | 221 (60.9) | 24 (77.4) | 58 (45.3) | 34 (51.5) | |
| Undifferentiated | 142 (39.1) | 7 (22.6) | 70 (54.7) | 32 (48.5) | |
| Medical comorbidity | | | | | |
| Diabetes mellitus | 9 (2.5) | 2 (6.5) | 7 (5.4) | 4 (6.1) | 0.236 |
| Hypertension | 6 (1.7) | 1 (3.2) | 8 (6.2) | 4 (6.1) | 0.041 |
| | Mean ± S.D. | Mean ± S.D. | Mean ± S.D. | Mean ± S.D. | |
| Age (years) | 35.98 ± 11.92 | 36.10 ± 10.37 | 39.21 ± 12.11 | 37.36 ± 11.33 | 0.062 |
| Baseline weight (kg) | 61.52 ± 12.42 | 68.30 ± 13.63 | 64.09 ± 13.02 | 65.41 ± 12.44 | 0.003 |
| Baseline BMI (kg/m$^2$) | 22.88 ± 4.04 | 25.08 ± 4.13 | 23.83 ± 4.22 | 24.58 ± 4.22 | 0.001 |
| Duration of admission (days) | 53.77 ± 26.79 | 57.19 ± 30.00 | 50.69 ± 24.09 | 47.06 ± 21.72 | 0.144 |
| GAF | 57.82 ± 18.02 | 57.90 ± 6.16 | 57.23 ± 5.13 | 63.27 ± 7.28 | 0.034 |

SGA, second generation antipsychotic; BMI, body mass index; GAF, Global Assessment of Functioning.

**Table 3**
Correlations of potential risk factors with changes in weight and BMI after 1 and 2 months of treatment.

| Potential risk factors | Weight change (kg) | | | | BMI change (kg/m$^2$) | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 month | | 2 Months | | 1 month | | 2 months | |
| | Mean ± S.D. | p value | Mean ± S.D. | p value | Mean ± S.D. | p value | Mean ± S.D. | p value |
| Types of SGAs | | 0.028 | | 0.032 | | 0.019 | | 0.029 |
| Olanzapine | 1.84 ± 2.37 (n = 363) | | 3.80 ± 3.89 (n = 203) | | 0.69 ± 0.90 (n = 363) | | 1.40 ± 1.46 (n = 203) | |
| Quetiapine | 1.67 ± 2.37 (n = 31) | | 2.43 ± 2.97 (n = 19) | | 0.63 ± 0.86 (n = 31) | | 0.91 ± 1.09 (n = 19) | |
| Risperidone | 1.43 ± 2.02 (n = 128) | | 2.41 ± 2.85 (n = 56) | | 0.53 ± 0.75 (n = 129) | | 0.87 ± 1.04 (n = 57) | |
| Aripipralzole | 0.99 ± 2.31 (n = 66) | | 2.38 ± 4.53 (n = 16) | | 0.37 ± 0.85 (n = 66) | | 0.87 ± 1.63 (n = 16) | |
| Sex | | 0.184 | | 0.039 | | 0.008 | | 0.390 |
| Male | 1.51 ± 2.34 (n = 259) | | 3.87 ± 3.70 (n = 130) | | 0.51 ± 0.79 (n = 259) | | 1.32 ± 1.26 (n = 130) | |
| Female | 1.76 ± 2.28 (n = 329) | | 2.97 ± 3.72 (n = 164) | | 0.70 ± 0.91 (n = 329) | | 1.18 ± 1.50 (n = 164) | |
| Age | | <0.001 | | <0.001 | | 0.001 | | 0.001 |
| <45 years old | 1.83 ± 2.34 (n = 453) | | 3.77 ± 3.65 (n = 229) | | 0.68 ± 0.87 (n = 453) | | 1.38 ± 1.33 (n = 229) | |
| ≥45 years old | 1.03 ± 2.07 (n = 135) | | 1.92 ± 3.69 (n = 65) | | 0.40 ± 0.83 (n = 135) | | 0.75 ± 1.51 (n = 65) | |
| BMI at baseline | | <0.001 | | <0.001 | | <0.001 | | <0.001 |
| <25 kg/m$^2$ | 1.92 ± 2.29 (n = 401) | | 4.07 ± 3.56 (n = 201) | | 0.72 ± 0.86 (n = 401) | | 1.51 ± 1.33 (n = 201) | |
| ≥25 kg/m$^2$ | 1.07 ± 2.23 (n = 187) | | 1.84 ± 3.66 (n = 93) | | 0.39 ± 0.84 (n = 187) | | 0.66 ± 1.37 (n = 93) | |
| Schizophrenia diagnosis | | 0.002 | | 0.945 | | 0.002 | | 0.916 |
| Paranoid | 1.90 ± 2.24 (n = 337) | | 3.35 ± 3.67 (n = 164) | | 0.71 ± 0.84 (n = 337) | | 1.23 ± 1.36 (n = 164) | |
| Undifferentiated | 1.31 ± 2.35 (n = 251) | | 3.38 ± 3.83 (n = 130) | | 0.49 ± 0.88 (n = 251) | | 1.25 ± 1.45 (n = 13) | |
| GAF | | 0.001 | | 0.016 | | 0.001 | | 0.010 |
| Correlation | 0.067 | 0.093 | 0.021 | <0.001 | 0.070† | 0.077 | 0.238 | <0.001 |

SGA, second generation antipsychotic; BMI, body mass index; GAF, Global Assessment of Functioning.
† Denotes Pearson coefficient of correlation.

weight (1.76 ± 2.28 kg, p = 0.184) and experienced significantly greater BMI change (0.70 ± 0.91 kg/m$^2$, p = 0.008) at month 1.

Age was revealed as a potential risk factor for weight and BMI increase in this study. Patients under 45 years old had significantly higher weight gain at month 1 (1.83 ± 2.34 kg, p<0.001) and month 2 (3.77 ± 3.65 kg, p<0.001). Younger patients also showed greater BMI increase (0.68 ± 0.87 kg/m$^2$, p = 0.001) at month 1 and at month 2 (1.38 ± 1.33 kg/m$^2$, p = 0.001).

Baseline BMI was a strong predictor of weight and BMI increase. Lower baseline BMI (<25 kg/m$^2$) was associated with significantly greater weight gain at month 1 (1.92 ± 2.29 kg, p<0.001) and month 2 (4.07 ± 3.56 kg, p<0.001) than the patients with higher baseline BMI (≥25 kg/m$^2$). Accelerated BMI increase was also observed with lower baseline BMI patients at month 1 (0.72 ± 0.86 kg/m$^2$, p<0.001) and month 2 (1.51 ± 1.33 kg/m$^2$ p<0.001).

Schizophrenia diagnosis subtypes also showed significant influence on weight and BMI initially. Diagnosis of paranoid schizophrenia had a statistically greater weight gain (1.90 ± 2.24 kg, p = 0.002) and BMI (0.71 ± 0.84 kg/m$^2$, p = 0.002) at month 1 but failed to maintain such trend at month 2 (p = 0.945 and 0.916 respectively).

The GAF scale at discharge demonstrated weak but significant positive correlation with increase of weight and BMI at month 2. No significant changes in weight or BMI were noted by medical comorbidities.

### 3.3. Risk of clinically significant weight gain among different factors

Table 4 summarizes the risks of clinically significant weight gain, defined as least 7% increase of weight from the baseline, between various SGA types, gender, age, baseline BMI, and diagnosis subtypes. In contrast to results of weight and BMI change analysis, types of SGAs failed to demonstrate statistically significant difference for clinically significant weight gain. However, the olanzapine group showed higher tendency of having clinically significant weight gain with odd ratios of 2.389 at month 1 and 2.507 at month 2. In line with our study results that showed greater BMI increase in females at month 1, likelihood for clinically significant weight gain was also increased in females at month 1 (odd ratio=1.846, 95% CI=1.098 to 3.105, p=0.021). However, such gap by the gender was not displayed by month 2. Patients under the age of 45 showed increased tendency for clinically significant weight gain at month 1 (odd ratio = 1.939, 95% CI = 0.960 to 3.917, p = 0.065) and were at significantly greater risk at month 2 (odd ratio = 2.567, 95% CI = 1.196 to 5.508, p = 0.016). Lower baseline BMI increased the likelihood of clinically significant weight gain at both month 1 (odd ratio = 5.078, 95% CI = 2.262 to 11.398, p<0.001) and month 2 (odd ratio = 7.866, 95% CI = 3.735 to 16.569, p<0.001). Schizophrenia diagnosis subtypes had no significant difference in the chance of having clinically significant weight gain.

## 4. Discussion

Considering the limitations of outpatient assessment on antipsychotic-induced weight gain, inpatient investigation may provide advantages with fewer variations in diet, medication adherence and activity. This study, to the best of our knowledge, is the first and the largest study to investigate the potential risk factors that could influence weight gains by different monotherapies of SGAs among inpatients with schizophrenia. Our meticulous attempts to exclude the potential confounding factors, stated in the methodology of our study, enabled more accurate identification of risk factors for the antipsychotic-induced weight gain.

Since obesity is a major risk factor for cardiovascular, metabolic diseases and excess mortality, a greater proposed role of the

**Table 4**
Risk of Clinically significant weight gain after 1 and 2 months of SGA treatment.

| Weight gain ≥ 7% | 1 Month | | | 2 Months | | |
|---|---|---|---|---|---|---|
| | OR | p value | 95%CI | OR | p value | 95% CI |
| Types of SGAs | | | | | | |
| Olanzapine | 2.389 | 0.085 | 0.887–6.436 | 2.507 | 0.195 | 0.625–10.052 |
| Quetiapine | 1.418 | 0.661 | 0.298–6.748 | 1.163 | 0.866 | 0.202–6.688 |
| Risperidone | 1.680 | 0.357 | 0.557–5.072 | 0.817 | 0.797 | 0.176–3.805 |
| Aripipralzole | | | | | | |
| Sex | | | | | | |
| Female | 1.846 | 0.021 | 1.098–3.105 | 0.960 | 0.884 | 0.557–1.656 |
| Age | | | | | | |
| <45 years old | 1.939 | 0.065 | 0.960–3.917 | 2.567 | 0.016 | 1.196–5.508 |
| BMI at baseline | | | | | | |
| <25 kg/m$^2$ | 5.078 | <0.001 | 2.262–11.398 | 7.866 | <0.001 | 3.735–16.569 |
| Schizophrenia diagnosis | | | | | | |
| Paranoid | 1.195 | 0.491 | 0.720–1.985 | 0.850 | 0.866 | 0.488–1.480 |

SGA, second generation antipsychotic; BMI, body mass index; CI, confidence interval.

antipsychotics on weight gain raises a particular concern. Apart from medical health, the antipsychotic-induced weight gain also causes significant problems in treatment adherence (Weiden et al., 2004) and quality of life in individuals with schizophrenia (Allison et al., 2003; De Hert et al., 2006).

Considering the aforementioned adversities, clinicians should bear in mind the metabolic effects of SGAs when making a choice in antipsychotic treatment. SGAs' differential metabolic side profiles have been relatively well reviewed (Barnett et al., 2007; Newcomer, 2007), providing a useful ground in selecting antipsychotics.

### 4.1. Effects of SGAs on weight

In this study, varying degrees of weight gain effects by SGA types were again observed. Contrary to earlier literature (Barnett et al., 2007; Newcomer, 2007), our results found no increased risk of weight gain for risperidone, when compared with aripiprazole. However this result is consistent with the recent meta-analysis, which found no significant difference among the two agents (Rummel-Kluge et al., 2010). Olanzapine displayed greater propensity for weight gain, in line with the previous findings (Kahn et al., 2008; Newcomer, 2007; Rummel-Kluge et al., 2010).

The olanzapine group in our study had lower baseline BMI and comorbid hypertension. This may reflect the prescribers' consideration of relatively high metabolic adversity of olanzapine (American Diabetes Association, 2004; Kelly et al., 2003; Komossa et al., 2010; Koro et al., 2002a,b; Newcomer et al., 2009). Such lower baseline BMI of the olanzapine group, which would be discussed soon as a predisposing factor of weight gain, could have possibly exerted influence on highest weight gain propensity of olanzapine. However, olanzapine remained as the most potent SGA to cause weight gain even after baseline BMI adjustment.

When prescribing an antipsychotic, differential metabolic side profiles are increasingly taken into account in accordance to heightened awareness of metabolic burden of SGAs (Smith et al., 2008). However, weight changes in individuals may show varying degrees of response in the same given SGA. Thus, the individual's proneness to weight gain should also be reflected when prescribing an antipsychotic. Unfortunately apart from medications' own side profiles, individual's risk factors that make patients more prone to antipsychotic-induced weight gain had not been studied extensively. Through analysis of various potential risk factors, baseline BMI, age, gender, GAF scale at discharge and schizophrenia subtypes were found to be in association with increased weight and/or BMI changes.

### 4.2. Effects of baseline BMI on weight

Low baseline BMI had been suggested as a predisposing factor for antipsychotic-induced weight gain (Bai et al., 2009a; Basson et al., 2001; Boden et al., 2009; Megna et al., 2006; Saddichha et al., 2008). The same results were obtained in our study, with low baseline BMI showing strong association with greater increase of weight, BMI and clinically significant weight gain. Baseline BMI was significantly associated with weight and BMI increase at both months 1 and 2. In contrast, two studies suggested that initial weight status has a positive correlation with weight gain (Bobes et al., 2003; Gebhardt et al., 2009). Gebhardt et al. observed initial acceleration of weight gain in subjects with low baseline BMI, but eventually greater weight gain occurred in subjects with higher baseline BMI at the end. They hypothesized that accelerated BMI increase in lower baseline BMI could have been biased by the short observation periods. However, in an 8-year study, baseline BMI lower than 25 resulted in greater weight gain ($10.98 \pm 8.48$ kg) compared to baseline BMI equal or greater than 25 ($1.17 \pm 13.29$ kg, $p = 0.004$)(Bai et al., 2009a). Therefore, the clinical significance of accelerated weight gain, observed in patients with lower baseline BMI, should not be overlooked and it would be wise to track these healthy BMI patients until changes of weight reach plateaus.

### 4.3. Effects of gender on weight

Like contradictory existing literatures, mixed results were also drawn in our study for the role of gender in antipsychotic-induced weight gain. Whereas females were more likely to experience clinically significant BMI increase for the first month of SGA treatment, males showed greater weight gain but not with BMI at month 2. Since no significant difference in BMI was observed, greater absolute increase of weight in males may not necessarily indicate extra weight gain burden at month 2. In contrast, females displayed greater risk of clinically significant weight gain at month 1 (odd ratio = 1.846, 95% CI = 1.098 to 3.105, $p = 0.021$).

Therefore females may be more biologically prone to metabolic adversities of antipsychotics. Higher plasma concentrations of clozapine and olanzapine were demonstrated in female gender (Tang et al., 2007; Weiss et al., 2005) and metabolic outcomes showed dose–response relationship with serum concentrations of clozapine and olanzapine (Simon et al., 2009). However in our naturalistic settings, schizophrenic inpatients would have been likely to be encouraged for physical activity. Since females response better to brief cognitive behavior therapy in schizophrenia (Brabban et al., 2009), there is a chance that females could have benefited more from behavioral activation as psychotic symptoms improved. The aforementioned hypothesis may be one of the underlying reasons for loss of predictive value in females over metabolic outcomes by month 2. Further studies are indicated to elucidate contribution of gender in antipsychotic-induced weight gain.

### 4.4. Effects of age on weight

Aging encompasses various physiologic changes such as compositions of body (Manini, 2010), hormones, appetites (Chapman, 2007) and so on. Resting metabolic rate (RMR), responsible for 60–80% of an individual's total energy expenditure (Manini, 2010), was reported to decline by 5.0 and 3.0% per decade in males and females, respectively (Luhrmann et al., 2009). Differences in fat-free mass (FFM) alone explained 63% of the variation in RMR and the changes in the FFM was a main contributor to the changes in RMR (Johnstone et al., 2005). Therefore, this study stratified the subjects by age of 45 since the mean FFM peaked in 35 to 44 years old for males and 45 to 54 years old for females and declined thereafter (Kyle et al., 2001).

The patients younger than 45 years old were under significantly greater metabolic risk by SGAs. Younger patients showed greater weight and BMI increase at both months 1 and 2 in our study. As energy expenditure is not increased but rather falls by aging (Luhrmann et al., 2009), diminished metabolic effect of SGAs in elderly may result from attenuated influence of SGAs on energy intake. We hypothesize that with aging, energy intake would not surge as much as the younger counterparts by SAGs. It is possible that 'the anorexia of aging' may underlie the decreased metabolic risk observed in the older patients. The anorexia of aging, the age-associated physiologic reduction in appetite and food intake, may serve a 'protective' role against antipsychotic-induced weight gain. Consequently, this study indicates a need for closer monitoring on metabolic outcomes when prescribing SGAs to younger patients. Further studies should follow to verify our hypothesis and determine the underlying mechanism for the metabolic vulnerability of younger patients.

### 4.5. Effects of diagnosis subtypes and clinical outcome on weight

Unlike an earlier report of undifferentiated schizophrenia associated with greater risk of weight gain (Saddichha et al., 2008), a different result was obtained in the present study. Patients with a diagnosis of paranoid schizophrenia had significantly greater weight and BMI increase for the first month. However, such statistical

differences were not maintained by month 2. It can be inferred that the patients with paranoid schizophrenia may show faster initial recovery from a previously underfed state due to the psychotic symptoms but they do not gain more in absolute amount than the patients with undifferentiated schizophrenia.

On the other hand, the positive correlation, demonstrated between the GAF scale at discharge and weight and BMI at month 2 in our study, supports the previous report of better clinical outcome in association with greater weight gain (Basson et al., 2001). However, the strength of correlation was weak ($r = 0.021$ and 0.238 for weight and BMI, respectively). Therefore, the effects of schizophrenia diagnosis subtypes or clinical outcome on antipsychotic-induced weight gain should be verified in future.

### 4.6. Limitations

When making a choice of prescription, clinicians consider many conditions: patients' overall symptoms, past medical and psychiatric histories, drug interactions and so on. By its naturalistic settings, we believe that our study have advantages in reflecting the clinical practice of the real-world. However, there are some limitations derived from the nature of retrograde investigation. First would be the lack of randomization. Our hospital is a university hospital located in an urban area. Although compensated by the large sample size, possibilities of selection bias exist due to the higher cost of hospitalization. Furthermore, the strength of our large sample size may have been weakened for the individual SGAs as various SGAs were included for the analysis and sampling bias could have occurred due to smaller sizes in each SGA. Thirdly, we were not able to control all the medications which were reported to have influence over weight gain like oral hypoglycemic agents, cyproheptadine and beta-blockers. Trend of concomitant prescription of propranolol with aripiprazole for akathisia control may have contributed to extra weight gains. Fourthly as polypharmacies were excluded in the study design, ultra-high risk patients, whose antipsychotics were switched for intolerable rapid weight gain, may have not been included in the analysis. Basically, the patients included in the present study were confined to a locked ward unit, by which the physical activities of the patients may be limited and may also affect the study outcomes. Hence, this point has to be also considered in future similar studies. The present study did not include potential clinical variables that might affect study outcomes such as individual activity level, nutrition behaviors, nicotine abuse, waist circumference, lipids, fasting glucose and weight changes before admission. Those factors have to be included in future studies to ensure more precise study outcomes. Multivariate regression analysis was performed to find whether a particular variable is associated with the risk to development of significant weight gain ($\geq 7\%$). Hence, clinical variables tested in the present study were all included in the model, by which the respective odd ratio has been eventually adjusted by the influences of the other variables. Therefore, we have to keep in mind that the non-significant effect of drug-groups may be also reflected by the regression model effects. Finally since all of our subjects were Koreans, studies on other ethnicities should be performed for generalization.

## 5. Conclusion

SGAs have been placed as a first-line treatment option for schizophrenia as risks for extra-pyramidal side effects and other undesirable adverse events such as tardive dyskinesia may be significantly reduced with SGAs treatment (Correll et al., 2004; Miller et al., 1998). However, the revealed cardiometabolic adversities of SGAs are alarming (Fontaine et al., 2001; Green et al., 2000) when considering the fact that cardiovascular disease was the leading cause of mortality in patients with schizophrenia (Capasso et al., 2008; Fors et al., 2007). Since patients with schizophrenia already suffer from higher prevalence of DM (Mukherjee et al., 1996; Okumura et al., 2010; Suvisaari et al., 2008), dyslipidemia (Suvisaari et al., 2007), smoking (Bobes et al., 2010; Volkow, 2009) and physical inactivity, an extra cardiometabolic burden caused by antipsychotics should not be overlooked. The increased mortality observed in the recent analyses of schizophrenia (Osby et al., 2000; Saha et al., 2007) may possibly stem from the increased prescriptions of SGAs.

In addition to considering the SGAs' own metabolic side profiles, predisposing metabolic risk factors of individuals should also be taken into account to reduce the excess mortality in schizophrenia. Younger patients with lower baseline BMI were under greater risk of antipsychotic-induced weight gain in this study. To improve predictive value of inter-individual risk factors for metabolic adversity, well controlled prospective studies are indicated. Further investigations clarifying the mechanism of potential risk factors interacting with antipsychotics will enhance our understanding for metabolic consequences of antipsychotics and in turn achieve better targeting of schizophrenia itself without causing unnecessary cost of life.

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