Subthreshold Change in Glycated Hemoglobin and Body Mass Index After the Initiation of Second-Generation Antipsychotics Among Patients With Schizophrenia or Bipolar Disorder:

A Nationwide Prospective Cohort Study in Japan

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ABSTRACT

Objective: The risk of diabetes development has been reported to differ among second-generation antipsychotics (SGAs). However, few studies have focused on the subthreshold change in glycated hemoglobin (HbA_{1c}). Therefore, this study examined the subthreshold change in HbA_{1c} and change in body mass index (BMI) 3 months after patients initiated one of 6 SGAs widely prescribed in Japan.

Methods: This is a prospective cohort study of patients followed up based on the Japanese blood glucose monitoring guidelines for patients with schizophrenia. We collected eligible patients' demographic data, medication history, blood tests, and weight measurements both at baseline and 3 months after recruitment, between April 2013 and March 2015. In the 378 patients with schizophrenia, schizoaffective disorder, and bipolar disorder based on *ICD-10*, we compared the subthreshold change in HbA_{1c} and the change in BMI 3 months after antipsychotic initiation by using multivariate regression analysis.

Results: The subthreshold change in HbA_{1c} 3 months after initiating blonanserin was significantly lower compared with olanzapine ($B = -0.17$, 95% CI = −0.31 to −0.04). In addition, the change in BMI 3 months after initiating blonanserin and aripiprazole was significantly lower compared with olanzapine ($B = -0.93$, 95% CI = −1.74 to −0.12; $B = -0.71$, 95% CI = −1.30 to −0.12, respectively).

Conclusions: This is the first study to clarify the differences in the subthreshold change in HbA_{1c} among SGAs. Our results suggest that blonanserin is likely to be a favorable treatment for patients with high risk of diabetes.

Trial Registration: UMIN Clinical Trial Registry identifier: UMIN000009868

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Although the use of antipsychotic drugs decreases mortality versus nonuse,[1–3] they are associated with adverse effects such as glucose metabolism dysregulation and weight gain.[4–10] Because antipsychotic-induced glucose metabolism dysregulation and weight gain lead to reduced quality of life and premature death in psychiatric patients,[11,12] some preventive approaches to combat their effects are urgently needed. Given the differences in diabetes development among antipsychotics, several systematic reviews have shown that olanzapine and clozapine have a higher risk of increasing fasting blood glucose or diabetes development versus aripiprazole.[7,13]

Recently, the importance of a "subthreshold change" in glycated hemoglobin (HbA_{1c}), a subtle increase in HbA_{1c} less than the cutoff point for diabetes diagnosis, has been considered in the clinical setting from the viewpoint of the evaluation and early detection of the risk of diabetes development. Selvin et al[14] determined that the incidence rates of diabetes, coronary heart diseases, stroke, and death from any cause in non-diabetic adults were significantly increased in response to subthreshold increases in baseline HbA_{1c} levels. Although subthreshold increases in HbA_{1c} are not directly linked to the diagnosis of diabetes, they might be a clinically helpful and sensitive indicator of an increased risk of diabetes in psychiatric patients.[15–17] Thus, it is quite important to examine the impacts of individual antipsychotics on the subthreshold change in HbA_{1c}. However, to the best of our knowledge, the differences in the subthreshold change in HbA_{1c} among second-generation antipsychotics (SGAs) identified through a prospective cohort remain unknown.

Weight gain is another important factor that few prospective cohort studies have examined in terms of the differences among the multiple SGAs widely prescribed in Japan. Previous retrospective

Clinical Points

- This study focused on subthreshold change in glycated hemoglobin (HbA_{1c}) after initiation of a second-generation antipsychotic.
- The subthreshold increase in HbA_{1c} was smaller after initiation of blonanserin compared with olanzapine.
- Among the second-generation antipsychotics, blonanserin may be a favorable pharmacologic option for patients with high risk of diabetic progression.

cohort studies revealed that olanzapine is associated with a higher risk of weight gain than aripiprazole, quetiapine, and risperidone, although few target drugs were included in the analysis.[18,19] Specifically, these studies did not include blonanserin and perospirone.

Blonanserin and perospirone were originally manufactured in Japan and are widely prescribed in Asia. These two drugs have potent dopamine D_2 and serotonin $5\text{-}HT_{2a}$ antagonist properties but are nearly devoid of serotonin $5\text{-}HT_{2c,}$ histamine H_1, and muscarinic M_1 antagonist activities. They are well tolerated, and their safety profile compares favorably with that of haloperidol, particularly in terms of prolactin elevation and frequency of extrapyramidal symptoms.[20,21] Therefore, these two drugs are likely to have lower risks of weight gain due to their pharmacologic profiles. The results of a network meta-analysis also suggested that these drugs have smaller effects on weight gain than olanzapine.[22] Therefore, it is vitally important to examine the effects of SGAs, including blonanserin and perospirone, on weight gain through a prospective research design.

Here, we examined the subthreshold change in HbA_{1c} and change in body mass index (BMI) 3 months after the initiation of one of 6 SGAs widely prescribed in Japan—aripiprazole, blonanserin, perospirone, risperidone, quetiapine, and olanzapine—using data from our nationwide, multisite, prospective cohort study.[23]

METHODS

Study Design

The details of this prospective cohort study have been reported previously.[23] This study was registered with the University Hospital Medical Information Network (UMIN) clinical trial register system (registration number: UMIN000009868). We recruited 1,323 patients who newly initiated antipsychotics from 44 nationwide sites (24 general hospitals, 17 psychiatric hospitals, and 3 psychiatric clinics). This study was approved by each site's institutional review board and was conducted in accordance with the principles of the Declaration of Helsinki and its later amendments. All participants were fully briefed on the study procedures and provided written informed consent before participating in the study. We followed up the patients based on the Japanese blood glucose monitoring guidelines for patients with schizophrenia.[24] In the current study, we used data regarding participants' demographic characteristics and medication histories at baseline and blood test and weight measurements at baseline and 3 months after recruitment.

Study Population

First, we recruited participants diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder by psychiatrists in charge based on *International Classification of Diseases*, 10th Revision criteria[25] between April 2013 and March 2015 who had started treatment with a first- or second-generation antipsychotic (by either a medication change or the addition of a new medication) and who had a clear history of the use of psychotropic drugs for at least 1 year prior to enrollment, as reported previously.[23]

Second, we excluded patients according to the following criteria: (1) probable diabetes or prediabetes at baseline screening (probable diabetes defined as fasting blood glucose > 125 mg/dL, postprandial blood glucose > 179 mg/dL, or HbA_{1c} > 6.4%; prediabetes defined as fasting blood glucose 110–125 mg/dL, postprandial blood glucose 140–179 mg/dL, or HbA_{1c} 6.0%–6.4%); (2) receipt of a treatment for diabetes (antidiabetic drugs and/or exercise therapy and/or dietary therapy) during the 3-month follow-up period; (3) use of antipsychotics administered at baseline for less than 3 months; (4) lack of HbA_{1c} and/or BMI data at either baseline or 3 months after recruitment; and (5) use of antipsychotics other than the 6 target SGAs (aripiprazole, blonanserin, perospirone, risperidone, quetiapine, and olanzapine) at baseline.

Subthreshold Change in HbA_{1c} Level and Change in BMI

To examine the subthreshold change in HbA_{1c} and change in BMI 3 months after the initiation of individual SGAs in psychiatric patients with normal glucose levels at baseline, we first calculated the ΔHbA_{1c} and ΔBMI for each patient using the following formulas:

$$\Delta HbA_{1c} = HbA_{1c3M} - HbA_{1cBaseline}$$
$$\Delta BMI = BMI_{3M} - BMI_{Baseline}$$

where HbA_{1c3M} and BMI_{3M} were obtained at the 3-month follow-up visit and $HbA_{1cBaseline}$ and $BMI_{Baseline}$ were obtained at the baseline. Based on previous studies, we estimated that olanzapine would have the highest likelihood to cause an increment in the subthreshold change in HbA_{1c} and change in BMI.[3,13] Thus, we defined olanzapine as the reference category when comparing the differences in the ΔHbA_{1c} and ΔBMI among SGAs.

Other Variables

We selected target SGAs that were reported in previous studies as being relatively frequently prescribed in Japan: aripiprazole, blonanserin, perospirone, quetiapine, risperidone, and olanzapine.[23,26,27] All 6 of these SGAs

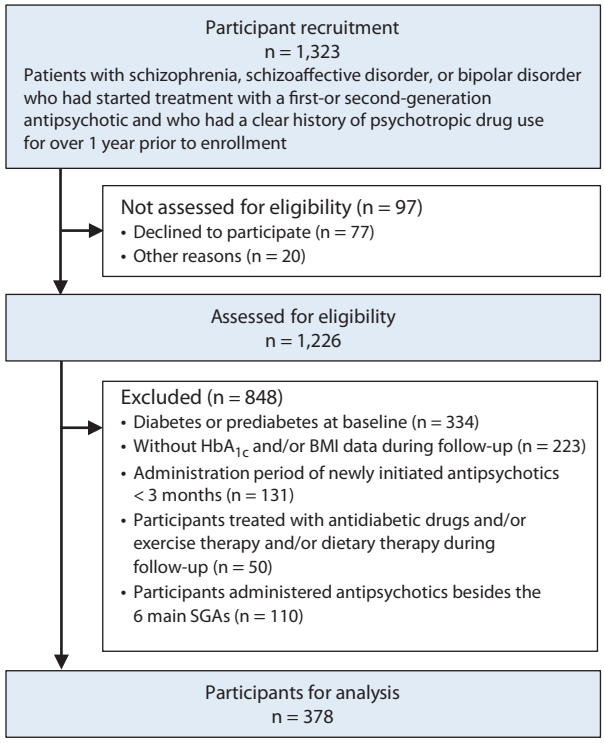
are approved by the Pharmaceutical and Medical Devices Agency in Japan, which is the counterpart of the US Food and Drug Administration, for the treatment of schizophrenia, schizoaffective disorder, and bipolar disorder. HbA_{1c} is a valuable marker of the glucose state and generally reflects the 1- to 2-month average blood sugar level.[28–30] Japanese blood glucose monitoring guidelines for patients with schizophrenia[24] recommend measuring HbA_{1c} at 3-month, 6-month, and 12-month visits in the first 1 year in patients with a normal diabetic type after newly initiating antipsychotics. Therefore, measurement of HbA_{1c} at the first 3-month visit is a reasonable and useful approach. Moreover, a 3-month follow-up period was also considered sufficient to detect changes in glucose metabolism in psychiatric patients based on a previous large cohort study in Denmark.[31]

We included the following variables: demographic variables, including sex, age, diagnosis (schizophrenia, schizoaffective disorder, or bipolar disorder); duration of illness; treatment status (outpatient vs inpatient); smoking status (current smoker or not); drinking status (current drinker or not); family histories of schizophrenia, bipolar disorder, major depression, diabetes, and heart disease; coexisting diagnoses of dyslipidemia, hypertension, and heart disease; baseline measurements, including weight, BMI (< 25 vs ≥ 25), total cholesterol (< 220 vs ≥ 220 mg/dL), HDL cholesterol (< 40 vs ≥ 40 mg/dL), and triglycerides (< 150 vs ≥ 150 mg/dL); and antipsychotic monotherapy (only newly initiated antipsychotics) or not. These variables were acquired for each patient at baseline by the psychiatrists in charge.

Statistical Analysis

We report continuous variables as the mean (standard deviation [SD]) and nominal variables as the number of patients (%). Next, to examine the impact of variables (age, sex, duration of illness, diagnosis, patients' status, smoking status, drinking status, family history, coexisting diagnoses, baseline measurements, and baseline medication) on the ΔHbA_{1c} or ΔBMI, we calculated partial regression coefficients (*B*) and the 95% confidential intervals (CIs) of *B* by using simple regression analysis. Finally, to examine the linear associations of all aforementioned variables and the ΔHbA_{1c} or ΔBMI, we calculated the *B* and 95% CI using multiple regression analysis for 216 participants in whom all of the explanatory variables were available. Specifically, for baseline medications, we calculated the *B* and 95% CI of each SGA for the ΔHbA_{1c} or ΔBMI using a multiple regression model, with olanzapine serving as reference in the main results, and we performed sensitivity analysis using models with reference to SGAs other than olanzapine in the supplementary results. We conducted the same analysis for "combination of antipsychotics with newly initiated antipsychotics," with "monotherapy of antipsychotics" as reference. In the baseline diagnosis, we used the schizophrenia group as reference. We performed all statistical analysis with R version 3.4.1[32] and considered *P* values less than .05 to be statistically significant.

Figure 1. Flow Diagram of Study Participants



Abbreviations: BMI = body mass index, HbA_{1c} = glycated hemoglobin, SGA = second-generation antipsychotic.

RESULTS

Characteristics of the Study Participants

We performed inclusion screenings on 1,323 patients with schizophrenia, schizoaffective disorder, or bipolar disorder who had started treatment with a first- or second-generation antipsychotic and who had a clear history of psychotropic drug use for over 1 year prior to enrollment. Of these patients, 77 declined to participate and 20 were not assessed for eligibility due to other reasons. We excluded the following patients: those who were classified as probably diabetic or prediabetic at baseline monitoring (n = 334), those without HbA_{1c} and/or BMI data during the 3-month follow-up period (n = 223), those whose administration period of the baseline antipsychotics was shorter than 3 months (n = 131), those who were treated with antidiabetic drugs and/or exercise therapy and/or dietary therapy during the follow-up period (n = 50), and those who were administered other antipsychotics besides the 6 target SGAs (n = 110). Finally, 378 participants were analyzed in this study (Figure 1).

The characteristics of the study participants are shown in Table 1. Of the patients, 311 (82.3%) were diagnosed with schizophrenia or schizoaffective disorder and 67 (17.7%) were diagnosed with bipolar disorder. Aripiprazole was the most frequently initiated drug of the 6 antipsychotics examined (31.7%), followed by perospirone (21.2%).

Table 1. Participant Characteristics and Baseline Monitoring and Medication

	Value	n
Baseline characteristics		
Man/woman, n (%)	167 (44.2)/211 (55.8)	378
Age, mean (SD), y	48.0 (16.1)	378
Duration of illness, mean (SD), y	18.0 (15.5)	353
Diagnosis (schizophrenia/schizoaffective disorder/bipolar disorder), n (%)		
Schizophrenia	278 (73.5)	378
Schizoaffective disorder	33 (8.7)	378
Bipolar disorder	67 (17.7)	378
Outpatient/inpatient, n (%)	180 (47.6)/198 (52.4)	378
Smoking, n (%)	112 (29.9)	374
Drinking, n (%)	59 (15.8)	373
Family history, n (%)		
Schizophrenia	50 (15.3)	327
Bipolar disorder	12 (3.8)	318
Major depression	38 (12.1)	315
Diabetes	62 (20.2)	307
Dyslipidemia	19 (6.8)	280
Coexisting medical diagnoses, n (%)		
Dyslipidemia	27 (7.2)	375
Hypertension	31 (8.3)	374
Heart disease	18 (4.8)	374
Monitoring at baseline, ΔBMI and ΔHbA_{1c}		
Body weight, mean (SD), kg	61.3 (14.8)	378
Body mass index, mean (SD), kg/m^2	23.3 (4.6)	378
Body mass index ≥ 25, n (%)	114 (30.2)	378
ΔBMI, mean (SD), kg/m^2	0.2 (1.5)	378
Fasting blood glucose, mean (SD), mg/dL	86.3 (8.8)	129
Postprandial blood glucose, mean (SD), mg/dL	97.3 (14.6)	245
HbA_{1c}, mean (SD), %	5.3 (0.3)	378
ΔHbA_{1c}, mean (SD), %	0.0 (0.2)	378
Total cholesterol, mean (SD), mg/dL	189.4 (39.1)	366
Total cholesterol ≥ 220, n (%)	77 (21.0)	366
HDL cholesterol, mean (SD), mg/dL	58.3 (18.5)	364
HDL cholesterol < 40, n (%)	36 (9.9)	364
Triglyceride, mean (SD), mg/dL	114.4 (81.1)	370
Triglyceride ≥ 150, n (%)	72 (19.5)	370
Baseline medication		
Newly initiated antipsychotics, n (%)		
Aripiprazole	120 (31.7)	378
Blonanserin	55 (14.6)	378
Perospirone	80 (21.2)	378
Quetiapine	41 (10.8)	378
Risperidone	40 (10.6)	378
Olanzapine	42 (11.1)	378
Combination of antipsychotics with newly initiated antipsychotics, n (%)	110 (29.1)	378
Monotherapy of antipsychotics (only newly initiated antipsychotics), n (%)	268 (70.9)	378

Abbreviations: BMI = body mass index, HbA_{1c} = glycated hemoglobin, HDL = high-density lipoprotein.

Table 2. Multiple Regression Analysis for the Subthreshold Change in HbA_{1c}

	Multivariate analysis (n = 216)		
		95% CI	
	B	Lower	Upper
Baseline characteristics			
Female sex	0.02	−0.05	0.08
Age	0.00	0.00	0.00
Diagnosis (schizophrenia/schizoaffective disorder/bipolar disorder)			
Schizoaffective disorder vs schizophrenia	0.08	−0.01	0.18
Bipolar disorder vs schizophrenia	0.06	−0.05	0.17
Duration of illness, years	0.00	0.00	0.01
Inpatient/outpatient, inpatient	−0.02	−0.08	0.05
Smoking, yes	0.00	−0.07	0.07
Drinking, yes	−0.04	−0.13	0.05
Family history			
Schizophrenia, yes	0.05	−0.05	0.15
Bipolar disorder, yes	−0.08	−0.26	0.10
Major depression, yes	0.04	−0.07	0.14
Diabetes, yes	−0.04	−0.13	0.05
Dyslipidemia, yes	−0.04	−0.18	0.10
Coexisting diagnoses			
Dyslipidemia, yes	−0.06	−0.20	0.07
Hypertension, yes	−0.09	−0.22	0.04
Heart disease, yes	0.12	−0.04	0.28
Baseline measurements			
Body mass index ≥ 25 kg/m^2	0.03	−0.05	0.10
Total cholesterol ≥ 220 mg/dL	−0.04	−0.13	0.04
HDL cholesterol < 40 mg/dL	0.01	−0.12	0.13
Triglyceride ≥ 150 mg/dL	0.02	−0.07	0.11
Baseline medication			
Newly initiated antipsychotics			
Aripiprazole vs olanzapine	−0.05	−0.15	0.05
Blonanserin vs olanzapine	−0.17	−0.31	−0.04
Perospirone vs olanzapine	0.00	−0.13	0.12
Quetiapine vs olanzapine	−0.04	−0.17	0.08
Risperidone vs olanzapine	−0.09	−0.22	0.05
Combination of antipsychotics with newly initiated antipsychotics vs monotherapy of antipsychotics (only newly initiated antipsychotics)	0.02	−0.05	0.09

[a]Multiple regression analysis. Adjusted $R^2 = -0.005$.
Abbreviations: HbA_{1c} = glycated hemoglobin, HDL = high-density lipoprotein.

Effects of SGAs on the Subthreshold Change in HbA_{1c}

The results of simple regression analysis are shown in Supplementary Table 1. Significant positive associations were detected between the ΔHbA_{1c} and patients with schizoaffective disorder and with heart disease as a coexisting diagnosis ($B = 0.09$, 95% CI = 0.02 to 0.15; $B = 0.12$, 95% CI = 0.01 to 0.23, respectively). In contrast, a significant negative association was found between the ΔHbA_{1c} and patients who newly initiated blonanserin at baseline compared with olanzapine ($B = -0.09$, 95% CI = −0.18 to −0.01). Multivariate regression analysis revealed a significant negative association between the ΔHbA_{1c} and patients who newly initiated blonanserin at baseline compared with olanzapine ($B = -0.17$, 95% CI = −0.31 to −0.04) (Table 2). The results of sensitivity analysis using models with reference to SGAs other than olanzapine are shown in Supplementary Table 2.

Effects of SGAs on the Change in BMI

The results of simple regression analysis are shown in Supplementary Table 3. A significant positive association was detected between the ΔBMI and patients with schizoaffective disorder ($B = 0.45$, 95% CI = 0.04 to 0.85). In contrast, significant negative associations were shown between the ΔBMI and patients with a high BMI (≥ 25 kg/m^2) and patients who newly initiated aripiprazole, blonanserin, perospirone, and risperidone at baseline compared with olanzapine ($B = -0.51$, 95% CI = −0.84 to −0.18; $B = -0.55$, 95% CI = −0.97 to −0.13; $B = -0.96$, 95% CI = −1.52 to −0.40; $B = -0.78$, 95% CI = −1.34 to −0.21; $B = -0.61$, 95% CI = −1.17 to −0.04, respectively). Multivariate regression analysis

Table 3. Multiple Regression Analysis for the Change in BMI

	Multivariate analysis (n = 216)		
		95% CI	
	B	Lower	Upper
Baseline characteristics			
Female sex	−0.09	−0.49	0.31
Age	0.00	−0.02	0.02
Diagnosis (schizophrenia/schizoaffective disorder/bipolar disorder)			
Schizoaffective disorder vs schizophrenia	0.28	−0.32	0.88
Bipolar disorder vs schizophrenia	0.44	−0.22	1.09
Duration of illness, years	−0.02	−0.04	0.00
Inpatient/outpatient, inpatient	0.25	−0.18	0.67
Smoking, yes	0.04	−0.40	0.49
Drinking, yes	−0.04	−0.58	0.49
Family history			
Schizophrenia, yes	−0.13	−0.74	0.47
Bipolar disorder, yes	0.68	−0.42	1.78
Major depression, yes	0.53	−0.11	1.18
Diabetes, yes	−0.32	−0.87	0.22
Dyslipidemia, yes	−0.17	−1.01	0.67
Coexisting diagnoses			
Dyslipidemia, yes	−0.05	−0.86	0.75
Hypertension, yes	−0.16	−0.95	0.63
Heart disease, yes	0.32	−0.66	1.30
Baseline measurements			
Body mass index ≥ 25 kg/m^2	−0.14	−0.59	0.30
Total cholesterol ≥ 220 mg/dL	0.67	0.15	1.19
HDL cholesterol < 40 mg/dL	−0.48	−1.24	0.27
Triglyceride ≥ 150 mg/dL	0.01	−0.52	0.53
Baseline medication			
Newly initiated antipsychotics			
Aripiprazole vs olanzapine	−0.71	−1.30	−0.12
Blonanserin vs olanzapine	−0.93	−1.74	−0.12
Perospirone vs olanzapine	−0.76	−1.52	0.00
Quetiapine vs olanzapine	−0.36	−1.12	0.41
Risperidone vs olanzapine	−0.80	−1.61	0.01
Combination of antipsychotics with newly initiated antipsychotics vs monotherapy of antipsychotics (only newly initiated antipsychotics)	−0.39	−0.85	0.06

[a]Multiple regression analysis. Adjusted $R^2 = 0.058$.
Abbreviations: BMI = body mass index, HDL = high-density lipoprotein.

showed a significant positive association between the ΔBMI and patients with high total cholesterol (≥ 220 mg/dL) ($B = 0.67$, 95% CI = 0.15 to 1.19). In contrast, we observed a significant negative association between the ΔBMI and patients who newly initiated aripiprazole and blonanserin at baseline compared with olanzapine ($B = -0.71$, 95% CI = −1.30 to −0.12; $B = -0.93$, 95% CI = −1.74 to −0.12, respectively; Table 3). The results of sensitivity analysis using models with reference to SGAs other than olanzapine are shown in Supplementary Table 4.

DISCUSSION

The aim of this prospective cohort study was to assess the differences among SGAs in the subthreshold change in HbA_{1c} and change in BMI in patients with schizophrenia, schizoaffective disorder, and bipolar disorder, an aspect explored by few studies. We found that the increase in HbA_{1c} 3 months after the initiation of blonanserin was significantly lower than that of olanzapine. Similarly, the weight gain 3 months after the initiation of blonanserin and aripiprazole was significantly lower than that of olanzapine. To the best of our knowledge, this study is the first to clarify the differences among SGAs in the subthreshold change in HbA_{1c}.

The increase in HbA_{1c} 3 months after the initiation of blonanserin was significantly smaller than that of olanzapine, unlike other SGAs. Moreover, results obtained from a model with reference to SGAs other than olanzapine indicated that blonanserin may be favorable in terms of the increment in HbA_{1c} compared with aripiprazole and perospirone (Supplementary Table 2). In this study, we included blonanserin and perospirone as target drugs, which few previous studies have included as analytic targets, and we are the first to report differences among SGAs in the subthreshold change in HbA_{1c}. Blonanserin has a low affinity for serotonin 5-HT_{2c}, histamine H_1, and muscarinic M_1 receptors, and their antagonism is associated with increased appetite and basal metabolism depression.[20] These pharmacologic profiles might be partly related to the favorable effects of blonanserin on the subthreshold change in HbA_{1c}. In support of this, the results of the meta-analysis by Kishi et al[33] suggested that blonanserin might have lower risk than haloperidol and risperidone regarding an increase in blood glucose. Interestingly, in the present study, the HbA_{1c} increase 3 months after the initiation of aripiprazole, quetiapine, and risperidone seemed slightly, although nonsignificantly, lower than that of olanzapine. Several studies revealed that aripiprazole, quetiapine, and risperidone were associated with a significantly lower risk of an increase in fasting blood glucose or HbA_{1c} than olanzapine and clozapine.[31,34–36] Thus, our findings may not be fully consistent with the results of previous research. This is partly because the present work consists of an observational study of a real-world population rather than randomized controlled trials. The differences among drugs are likely to be diminished in an observational study that is accompanied by prescription preference compared with experimental settings, such as in a randomized trial.[37] Specifically, because the prescription of quetiapine and olanzapine for patients with diabetes is contraindicated in Japan, clinicians tend to avoid prescribing quetiapine and olanzapine and instead prefer to prescribe aripiprazole for patients with high risk of diabetic progression. Similar to previous research,[23] these prescription preferences might have reduced our ability to identify the superiorities of aripiprazole, quetiapine, and risperidone over olanzapine. Thus, our findings suggest that blonanserin has favorable effects on a subthreshold change in HbA_{1c}. In future studies, it is essential to investigate the effects of blonanserin on glucose metabolism from the standpoint of both basic studies focusing on its pharmacologic profile and clinical studies focusing on a comparison with antipsychotics with known favorable effects on glucose metabolism, such as aripiprazole.

In addition, the BMI increase 3 months after the initiation of blonanserin and aripiprazole was significantly smaller than that of olanzapine. Moreover, there were no significant

differences in the increase in BMI between blonanserin and other SGAs besides olanzapine (Supplementary Table 4). In this study, we included blonanserin and perospirone as target drugs and applied, for the first time, a prospective research design to the analysis of the differences among multiple SGAs in terms of weight gain. Weight gain associated with antipsychotic use has been reported in several studies.[36,38,39] In a recent systematic review and a network meta-analysis, aripiprazole was associated with a significantly smaller weight gain than olanzapine, quetiapine, and risperidone.[34,35] Furthermore, another systematic review and network meta-analysis revealed that blonanserin was associated with a significantly smaller weight gain than olanzapine,[22] although no direct comparison was performed of blonanserin and olanzapine. The evidence that aripiprazole and blonanserin are superior to olanzapine, mainly obtained from the results of randomized trials, is consistent with the results of the present nationwide cohort study, performed with adjustment for confounding factors. Thus, the superiority of blonanserin and aripiprazole over olanzapine regarding weight gain may be validated both internally and externally. Furthermore, in a previous network meta-analysis, blonanserin was associated with the lowest risk of weight gain, with aripiprazole the second-ranked antipsychotic.[22] Thus, blonanserin is likely to have a lower risk of weight gain than aripiprazole. We expect that blonanserin and aripiprazole will be directly compared in future work.

Similar to a previous study,[23] the major strengths of this study were its large and nationwide sample and the strict monitoring of participants based on Japanese guidelines in a real-world clinical setting. In particular, the strict monitoring contributed to the early detection of glucose metabolism abnormalities. However, our results should be interpreted within the context of several limitations. First, this study did not evaluate psychiatric symptoms or severity. These factors may be related to the subthreshold change in HbA_{1c} and change in BMI.[40]

Second, we focused on only the first 3 months after the initiation of individual SGAs. Based on the Japanese blood glucose monitoring guidelines for patients with schizophrenia,[24] it is strongly recommended that HbA_{1c} be measured at 3-month, 6-month, and 12-month visits in the first 1 year when encountering patients with a normal diabetic type after newly initiating antipsychotics. Moreover, hyperglycemic progression related to SGAs is thought to happen following complicated pathophysiologic changes, such as an increase in appetite and body weight. Therefore, HbA_{1c} and BMI are estimated to be modulated in parallel. From this point of view, our result that blonanserin is favorable in terms of both HbA_{1c} and BMI compared with olanzapine is reasonable. Thus, we believe that a follow-up period of 3 months was optimal for our study, and the results we obtained should be useful for clinicians in real-world settings. However, the effects of SGAs on the subthreshold change in HbA_{1c} and change in BMI might differ from the present findings in a longer follow-up period.

Third, we focused only on antipsychotics and did not include other types of medication such as mood stabilizers and antidepressants. These drugs might also affect the subthreshold change in HbA_{1c} and change in BMI. Fourth, we could not include patients with treatment-resistant unipolar depression because only aripiprazole was approved for the treatment of unipolar depression in Japan, whereas other SGAs were approved in western countries. Therefore, our results cannot be interpreted in patients with unipolar depression.

Lastly, the sample size of this cohort study was designed based on the confidence interval for the hyperglycemic progression rate over the course of 1 year for those who changed antipsychotic medications, as reported in our previous work.[23] However, the sample size of 216 used in this analysis was considered to be sufficient to achieve the purpose of this study because it could detect independent variables with a partial correlation coefficient of 0.33 or higher with a dependent variable with a power of 0.8 or higher under the condition of 26 independent variables and a significance level of .05 (Supplementary Table 5).[41] Furthermore, the number of newly initiated antipsychotics was uneven, ranging from 40 patients for risperidone to 120 patients for aripiprazole. In the present analysis, we did not perform regression analysis for each drug but simultaneously entered them into the model, so we do not expect any difference in the statistical power. However, if the number of people who changed to a particular drug was small (eg, risperidone), changes in outcome due to factors not measured in the study (eg, life events) that occur in some of these people may be reflected more strongly in the results. In such cases, more caution is needed in interpreting the results. However, we believe that this issue does not fatally compromise our results because it does not distort the results in any particular direction.

In conclusion, our novel results indicate differences among multiple SGAs, including blonanserin and perospirone, in the subthreshold change in HbA_{1c} and change in BMI. Blonanserin may be a favorable treatment option for patients with high risk of diabetic progression. To confirm the direction of causality, future studies should use larger samples and longer follow-up periods that include evaluations of psychiatric symptoms and severity with or without considering other types of medications.

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Supplementary Material

Article Title: Subthreshold Change in Glycated Hemoglobin and Body Mass Index After the Initiation of Second-Generation Antipsychotics Among Patients With Schizophrenia or Bipolar Disorder: A Nationwide Prospective Cohort Study in Japan

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Supplementary Material

Supplementary Table 1. Simple regression analysis for the subthreshold change in HbA1c

		Simple analysis		
	n	B	95%CI	
Baseline factors				
Female sex	378	−0.01	−0.06	0.03
Age	378	0.00	0.00	0.00
Diagnosis (Schizophrenia / Schizoaffective disorder / Bipolar disorder)				
Schizoaffective disorder vs. Schizophrenia	378	0.09	0.02	0.15
Bipolar disorder vs. Schizophrenia	378	0.06	−0.02	0.15
Duration of illness, years	353	0.00	0.00	0.00
In-patient/Out-patient, In-patient	378	−0.01	−0.06	0.04
Smoking, Yes	374	−0.01	−0.06	0.05
Drinking, Yes	373	−0.03	−0.10	0.03
Family history				
Schizophrenia, Yes	327	−0.03	−0.10	0.05
Bipolar disorder, Yes	318	−0.03	−0.17	0.11
Major depression, Yes	318	0.01	−0.07	0.09
Diabetes, Yes	307	−0.03	−0.10	0.04
Dyslipidemia, Yes	280	−0.06	−0.17	0.05
Coexisting diagnoses				
Dyslipidemia, Yes	375	−0.01	−0.10	0.09
Hypertension, Yes	374	−0.03	−0.12	0.05
Heart disease, Yes	374	0.12	0.01	0.23
Baseline measurements				
Body mass index: ≥25 kg/m^2	378	−0.02	−0.07	0.04
Total cholesterol, ≥220 mg/dL	366	−0.06	−0.12	0.00
HDL-cholesterol, <40 mg/dL	364	0.03	−0.05	0.11
Triglyceride, ≥150 mg/dL	370	−0.02	−0.08	0.04
Baseline medication				
Newly initiated antipsychotics				
Aripiprazole vs. Olanzapine	378	0.00	−0.07	0.07
Blonanserin vs.Olanzapine	378	−0.09	−0.18	-0.01
Perospirone vs. Olanzapine	378	0.02	−0.07	0.11
Quetiapine vs. Olanzapine	378	−0.03	−0.11	0.05
Risperidone vs. Olanzapine	378	−0.04	−0.13	0.05
Combination of antipsychotics with newly initiated antipsychotics vs. Monotherapy of antipsychotics (only newly initiated antipsychotics)	378	−0.01	−0.06	0.05

Abbreviation: CI = confidence interval, HDL = high-density lipoprotein

Supplementary Table 2. Sensitivity analysis of multiple regression analysis in Table 2 for the subthreshold change in HbA1c with reference to SGAs other than olanzapine

	Reference				
	vs Blonanserin	vs Olanzapine	vs Perospirone	vs Quetiapine	vs Risperidone
Aripiprazole	0.12 (0.01 to 0.24)	–0.05 (–0.15 to 0.05)	–0.05 (–0.16 to 0.06)	–0.01 (–0.11 to 0.10)	0.04 (–0.08 to 0.16)
Blonanserin	-	–0.17 (–0.31 to –0.04)	–0.17 (–0.31 to –0.03)	–0.13 (–0.26 to 0.00)	–0.09 (–0.23 to 0.05)
Olanzapine	-	-	0.00 (–0.12 to 0.13)	0.04 (–0.08 to 0.17)	0.09 (–0.05 to 0.22)
Perospirone	-	-	-	0.04 (–0.09 to 0.17)	0.09 (–0.06 to 0.23)
Quetiapine	-	-	-	-	0.04 (–0.09 to 0.18)

[a] The B and 95%CI of B using multiple regression analysis are described in each cell.
[b] The model includes 26 explanatory variables: age, sex, duration of illness, diagnosis, patients' status, smoking status, drinking status, family history, coexisting diagnoses, baseline measurements, and baseline medication.
[c] Red color indicates statistically significant value of B for the increase in HbA1c.
[d] Cyan color indicates statistically significant value of B for the decrease in HbA1c.

Supplementary Table 3. Simple regression analysis for the change in BMI

		Simple analysis		
	n	B	95%CI	
Baseline factors				
Female sex	378	−0.01	−0.32	0.30
Age	378	−0.01	−0.02	0.00
Diagnosis (Schizophrenia / Schizoaffective disorder / Bipolar disorder)				
Schizoaffective disorder vs. Schizophrenia	378	0.45	0.04	0.85
Bipolar disorder vs. Schizophrenia	378	0.51	−0.03	1.05
Duration of illness, years	353	−0.01	−0.02	0.00
In-patient/Out-patient, In-patient	378	0.06	−0.25	0.37
Smoking, Yes	374	−0.20	−0.54	0.13
Drinking, Yes	373	0.25	−0.17	0.68
Family history				
Schizophrenia, Yes	327	−0.28	−0.74	0.17
Bipolar disorder, Yes	318	0.41	−0.47	1.29
Major depression, Yes	318	0.20	−0.30	0.71
Diabetes, Yes	307	0.02	−0.41	0.45
Dyslipidemia, Yes	280	0.50	−0.20	1.21
Coexisting diagnoses				
Dyslipidemia, Yes	375	0.00	−0.60	0.60
Hypertension, Yes	374	0.22	−0.34	0.78
Heart disease, Yes	374	0.20	−0.52	0.92
Baseline measurements				
Body mass index: ≥25 kg/m^2	378	−0.51	−0.84	−0.18
Total cholesterol, ≥220 mg/dL	366	0.10	−0.28	0.49
HDL-cholesterol, <40 mg/dL	364	−0.31	−0.83	0.22
Triglyceride, ≥150 mg/dL	370	−0.17	−0.56	0.23
Baseline medication				
Newly initiated antipsychotics				
Aripiprazole vs. Olanzapine	378	−0.55	−0.97	−0.13
Blonanserin vs. Olanzapine	378	−0.96	−1.52	−0.40
Perospirone vs. Olanzapine	378	−0.78	−1.34	−0.21
Quetiapine vs. Olanzapine	378	−0.11	−0.62	0.40
Risperidone vs. Olanzapine	378	−0.61	−1.17	−0.04
Combination of antipsychotics with newly initiated antipsychotics vs. Monotherapy of antipsychotics (only newly initiated antipsychotics)	378	−0.32	−0.65	0.02

Abbreviation: CI = confidence interval, HDL = high-density lipoprotein

Supplementary Table 4. Sensitivity analysis of multiple regression analysis in Table 3 for the change in BMI with reference to SGAs other than olanzapine

	Reference				
	vs Blonanserin	vs Olanzapine	vs Perospirone	vs Quetiapine	vs Risperidone
Aripiprazole	0.22 (–0.49 to 0.93)	–0.71 (–1.30 to –0.12)	0.05 (–0.63 to 0.74)	–0.35 (–1.01 to 0.31)	0.09 (–0.63 to 0.82)
Blonanserin	-	–0.93 (–1.74 to –0.12)	–0.17 (–1.01 to 0.67)	–0.57 (–1.39 to 0.24)	–0.13 (–0.99 to 0.73)
Olanzapine	-	-	0.76 (–0.00 to 1.52)	0.36 (–0.41 to 1.12)	0.80 (–0.01 to 1.61)
Perospirone	-	-	-	–0.40 (–1.20 to 0.39)	0.04 (–0.82 to 0.90)
Quetiapine	-	-	-	-	0.44 (–0.38 to 1.27)

[a] The B and 95%CI of B using multiple regression analysis are described in each cell.
[b] The model includes 26 explanatory variables: age, sex, duration of illness, diagnosis, patients' status, smoking status, drinking status, family history, coexisting diagnoses, baseline measurements, and baseline medication.
[c] Red color indicates statistically significant value of B for the increase in BMI.
[d] Cyan color indicates statistically significant value of B for the decrease in BMI.

Supplementary Table 5. Post-hoc simulation of the relationship between partial correlation coefficient and detection power in 26 independent variables, 216 sample size and a significance level of 0.05.

partial correlation coefficient	detection power
0.20	0.28
0.21	0.31
0.22	0.35
0.23	0.37
0.24	0.43
0.25	0.47
0.26	0.51
0.27	0.56
0.28	0.60
0.29	0.65
0.30	0.69
0.31	0.73
0.32	0.77
0.33	0.81
0.34	0.84
0.35	0.87
0.36	0.90
0.37	0.92
0.38	0.94
0.39	0.95
0.40	0.97