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The type rather than the daily dose or number of antipsychotics affects the incidence of hyperglycemic progression

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Abbreviations[1]

[1] BMI, body mass index; CPZ, chlorpromazine equivalent; CI, confidence interval; GVIF, generalized variance inflation factor; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin; histamine 1, H_1; HR, hazard ratio; muscarinic 1, M_1; muscarinic 3, M_3; serotonin 2C, 5-HT_{2C}, s.d.; standard deviation.

ABSTRACT

There have been concerns that antipsychotics increase the incidence of hyperglycemic progression. Many factors have been suggested to contribute to the risk of antipsychotic-induced hyperglycemic progression, including the type, daily dose, and number of antipsychotics; however, few studies have examined these relationships. This study aimed to examine the affect of antipsychotic treatment-associated factors on hyperglycemic progression, after adjustment for the affect of background factors suggested to be associated with hyperglycemic progression. This was a nationwide, multicenter, prospective cohort study examining the incidence of hyperglycemic progression during a 12 mo period following the initiation of newly prescribed antipsychotic medication. Demographic data, medication history, and blood test values were collected from 631 study participants with normal blood glucose levels at baseline for 12 mo. The primary endpoint (incidence of hyperglycemic progression) was defined as progression from normal to prediabetic or probable diabetic status, and was evaluated based on the Japanese monitoring guidance in patients with schizophrenia. To further examine the affect of antipsychotics on glucose metabolism over time, we examined changes in HbA1c levels 3, 6, and 12 mo after the initiation of treatment with each antipsychotic. We found that treatment with zotepine and clozapine was associated with a significantly high incidence of hyperglycemic progression. Furthermore, changes in HbA1c levels 6 mo after the initiation of zotepine treatment were significantly higher than

those following blonanserin and haloperidol treatments. In contrast, there was no significant difference in the change in total cholesterol, triglycerides, HDL cholesterol, and BMI during the same period. Moreover, the “daily dose” and “number” of antipsychotics did not show an association with the incidence of hyperglycemic progression. However, in a post hoc analysis in which the antipsychotics were divided into two groups according to the strength of blockade of H_1, M_1, M_3, and 5-HT_{2C} receptors, the incidence of hyperglycemic progression was higher in the medium- and high-daily dose groups than in the low-daily dose group in the antipsychotic group with strong blockade of these receptors. Our study indicated that the type of antipsychotic had a greater affect on the incidence of hyperglycemic progression than the daily dose of antipsychotics or their number. Among these, zotepine was most likely to increase the incidence of hyperglycemic progression, suggesting the need for caution when these antipsychotics are prescribed.

Keywords: antipsychotics, zotepine, hyperglycemic progression, daily dose, polypharmacy

1. **INTRODUCTION**

Antipsychotics are widely used for the treatment of mental illnesses, such as schizophrenia and bipolar disorder (Huhn et al., 2019; Lindström et al., 2017). However, it has been reported that antipsychotics increase the risk of metabolic abnormalities, such as hyperglycemia, hyperlipidemia, and weight gain, consequently interfering with the mortality reduction effect of antipsychotics (Johnsen and Kroken, 2012; Olfson et al., 2015; Taipale et al., 2018; Zagozdzon et al., 2016).

Among the metabolic abnormalities, hyperglycemia is a major symptom of diabetes and metabolic syndrome, and its presence has been shown to lead to acute and chronic complications, increasing the mortality of patients and having a negative affect on the prognosis of patients treated with antipsychotics (Fizelova et al., 2014; Marcovecchio, 2017; Wu et al., 2015). Although the mechanisms underlying abnormalities in glucose metabolism caused by antipsychotics are still unknown, there are two major hypotheses about the mechanisms: 1) development of insulin resistance due to hyperinsulinemia, hypertension, and hyperlipidemia caused by obesity, and 2) reduction in insulin secretion due to direct action on pancreatic β-cells (Holt, 2019; Kowalchuk et al., 2019; Starrenburg and Bogers, 2009).

Although the effect of a variety of different factors of antipsychotics, such as “type”, “daily dose”, and “number”, on glucose metabolism have been examined in patients treated with antipsychotics, the results have not been consistent. Regarding the types of

antipsychotics, all antipsychotics have been found to contribute to the incidence of abnormal glucose metabolism, although previous studies have reported that the incidence of abnormal glucose metabolism varies according to the type of antipsychotics (Carnovale et al., 2021; Holt, 2019; Marvanova, 2013; Pillinger et al. 2020; Zhang et al., 2017). Regarding the daily dose of antipsychotics, several studies have reported that some antipsychotics increase the risk of diabetes in a dose-dependent manner (Tu et al., 2019; Ulcickas Yood et al., 2011). In contrast, other studies have reported no clear relationship between daily dose and the incidence of diabetes in patients treated with antipsychotics (Henderson, 2001; Bechara, 2001). Regarding the number of antipsychotics, several studies have reported an association between increased risk of diabetes and antipsychotic polypharmacy (Kessing et al., 2010; Mamakou et al., 2018; Kato et al., 2015). In contrast, other studies have reported a lack of any significant difference in the prevalence of diabetes between polypharmacy and monotherapy with either first-generation antipsychotics or second-generation antipsychotics (Ijaz et al., 2018; Correll et al., 2007).

Most of these studies have examined the risk of diabetes; however, few studies have focused on hyperglycemia as a pre-stage of diabetes. Focusing on hyperglycemia progression (progression from normoglycemia to prediabetes or probable diabetes) is important because an intervention before the development of diabetes and metabolic syndrome is critical to prevent their occurrence (McKenzieet al., 2021; Tabák et al., 2012). For these reasons, we

decided to examine the affect of "type", "daily dose", and "number" of antipsychotics on the incidence of hyperglycemic progression. When examining the association between antipsychotics and incidence of hyperglycemic progression, it is necessary to consider both antipsychotic-related factors and the effects of glucose metabolism-related background factors, such as age, sex, exercise, diet, and coadministration of non-antipsychotics (Guo et al., 2006; Kusumi et al., 2018; Padwal et al., 2004; Preiss et al., 2011; Steardo et al., 2019; Sugai et al., 2018; Vancampfort et al., 2016). Therefore, the present study examined the affect of antipsychotic treatment-associated factors, such as type, daily dose, and number of drugs on the incidence of hyperglycemic progression after adjusting for the affect of background factors suggested to be associated with glucose metabolism using data from a nationwide, multisite, prospective cohort study.

2. METHODS

2.1. Study design and population

This was a nationwide prospective, observational cohort study registered at the University Hospital Medical Information Network (UMIN) clinical trial register system (registration number: UMIN000009868). Overall, 1323 patients with schizophrenia and schizoaffective disorder, or bipolar disorder, who recently initiated treatment with

antipsychotics, were recruited from 44 sites in Japan (24 general hospitals, 17 psychiatric hospitals, and 3 psychiatric clinics) as the study cohort between May 2013 and March 2015.

2.2. Definitions and criteria

Study participants were diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder by their physicians based on ICD-10 criteria (World Health Organization, 2013). Inclusion criteria were (i) initiation of a first- or second-generation antipsychotic medication, (ii) a 12 mo history of medication prior to enrollment, and (iii) no diagnosis of diabetes before baseline screening. Exclusion criteria were (i) patients with probable diabetes or prediabetes at baseline screening. This study was conducted according to the guidelines of the Declaration of Helsinki. All participants were fully briefed on study procedures and provided written informed consent.

2.3. Measurements

The initial screening captured the demographic characteristics of the participants, including age, sex, duration of illness, outpatient and inpatient status, smoking and drinking status, family history of illness (schizophrenia, bipolar disorder, major depressive disorder, diabetes, and dyslipidemia), coexisting medical diagnoses (hypertension, heart disease, and dyslipidemia), therapeutic interventions (dietary therapy, exercise therapy, and medical

therapy), and 12 mo medication history prior to enrollment and during the study period. Baseline measurements, which included blood glucose (fasting or postprandial) or glycated hemoglobin (HbA1c), serum lipids (total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides), body weight, body mass index (BMI), were obtained prior to the initiation of treatment with new antipsychotics. Baseline medication included the administration of new antipsychotics, number of coadministered antipsychotics, daily dose of antipsychotics, and coadministration of mood stabilizers, antidepressants, antilipidemic agents, and antihypertensives.

The Japanese monitoring guidance in patients with schizophrenia (Kusumi et al., 2011) classifies blood glucose levels as follows: (i) normal (fasting blood glucose <110 mg/dL, postprandial blood glucose <140 mg/dL, or HbA1c <6.0%), (ii) prediabetes (fasting blood glucose of 110–125 mg/dL, postprandial blood glucose of 140–179 mg/dL, or HbA1c of 6.0–6.4%), and (iii) probable diabetes (fasting blood glucose > 125 mg/dL, postprandial blood glucose > 179 mg/dL, or HbA1c > 6.4%). Blood tests were scheduled in accordance with the Japanese guidelines for blood glucose monitoring in patients with schizophrenia and were conducted at 3, 6, and 12 mo for patients with normal blood glucose levels (Kusumi et al., 2011).

2.4. Statistical analyses

The primary endpoint was hyperglycemic progression during 12 mo after new initiation of antipsychotic medication. The incidence of hyperglycemic progression was defined as progression from normal to prediabetes or probable diabetes according to the blood glucose criteria described in the "Measurements" section of the methods. Time-to-event was defined as the time interval between the date of new initiation of antipsychotic medication and the date of hyperglycemic progression or the censor date of the last follow-up period. We used Cox proportional hazard regression models (Cox, 1972) to assess whether the affect on hyperglycemic progression differed between each factor associated with antipsychotic medication (type, daily dose, and number of antipsychotics) in multivariable analysis adjusted for available background factors reported to have an affect on hyperglycemic progression (Kusumi et al., 2018; Koller and Doraiswamy, 2002; Mukherjee et al., 1996; Sweileh et al., 2013).

Participant data associated with antipsychotic medication included newly initiated antipsychotic medication (type of antipsychotics), number of antipsychotics, and daily dose of antipsychotics in chlorpromazine equivalent (CPZ) (Inada et al., 2015). Participant data related to hyperglycemic progression included sex, age, diagnosis (schizophrenia and schizoaffective disorder or bipolar disorder), duration of illness, treatment status (out-patient or in-patient), smoking status (current smoker or not), drinker status (current drinker or not),

family history of schizophrenia, bipolar disorder, major depression, diabetes, and heart disease, coexisting diagnoses of dyslipidemia, hypertension, and heart disease, therapeutic interventions and concomitant medication, baseline measurements including BMI (< 25 versus ≥25), total cholesterol (<220 versus ≥220 mg/dL), HDL cholesterol (<40 versus ≥40 mg/dL), and triglycerides (<150 versus ≥150 mg/dL) (Kusumi et al., 2018). These variables were acquired for each participant at baseline by psychiatrists in charge. Hazard ratios (HR) and 95% confidence intervals (CI) for the Cox univariate factors were calculated using a Cox proportional hazards model with each of the following groups as the reference group. The reference group for the type of antipsychotics was initiation of aripiprazole, which is considered to have the lowest risk of hyperglycemic progression among the antipsychotics included in the study (Pillinger et al. 2020; Zhang et al., 2017; Carnovale et al., 2021). The number of coadministered antipsychotics and the daily dose (as CPZ) of antipsychotics were classified into three levels based on previous reports (Mamakou et al., 2018; Wubeshet et al., 2019), and the reference group was the number of coadministered antipsychotics = 0 and 300 <daily dose (as CPZ) of antipsychotics, which is considered to have the lowest incidence of hyperglycemic progression. We checked the multicollinearity of the independent variables to assess their validity. Multicollinearity was assessed by calculating the degree of freedom adjusted for generalized variance inflation factors (GVIF) (Fox and Monette, 1992). To

192 further confirm the robustness of the results, the same tests were conducted in the groups
193 stratified by the duration of newly initiated antipsychotic medication (3, 6, and 12 mo).
194 Furthermore, we conducted two post hoc analyses to further assess the affect of type
195 of antipsychotic on hyperglycemic progression. A post hoc analysis was conducted to
196 determine whether the affect of daily dose and number of antipsychotics on hyperglycemic
197 progression depends on the pharmacological properties of the antipsychotics.
198 Pharmacological properties related to abnormalities in glycolipid metabolism were defined as
199 blocking effects on histamine 1 (H_1), muscarinic 1 (M_1), muscarinic 3 (M_3), and serotonin 2C
200 (5-HT_{2C}) receptors from previous reports (Chen et al., 2017; Montastruc et al., 2015;
201 Reynolds and Kirk, 2010; Silvestre and Prous, 2005; Starrenburg and Bogers, 2009; Weston-
202 Green et al., 2013). Clozapine, olanzapine, quetiapine, zotepine, and levomepromazine were
203 defined as antipsychotics with high affinity for H_1, M_1, M_3 and 5-HT_{2C} receptors, while
204 aripiprazole, blonanserin, risperidone, perospirone, paliperidone, fluphenazine, haloperidol,
205 and sulpiride were defined as antipsychotics with low affinity for these receptors (Kusumi et
206 al., 2014; Silvestre and Prous, 2005). The participants were divided into two groups: those
207 newly prescribed antipsychotics with high affinity for these receptors and those newly
208 prescribed antipsychotics with low affinity for these receptors. Subsequently, Cox regression
209 analysis was performed for each group in the same way as the main analysis. Another post
210 hoc analysis was conducted to assess the affect of each antipsychotic medication on

abnormalities in glycolipid metabolism over time. This analysis examined differences in changes over time in markers related to glycolipid metabolism (HbA1c, total cholesterol, HDL cholesterol, triglycerides, and BMI) at 3, 6, or 12 mo after initiation of each antipsychotic medication. In this analysis, the significance of the differences in changes in markers between antipsychotics at each timepoint was assessed using the Kruskal-Wallis test and Steel-Dwass post-test. All statistical analyses were performed using the dplyr packages run on R statistics 4.0.2. All probability values were two-tailed, and the significance level was set at $P < 0.05$.

3. RESULTS AND STATISTICAL ANALYSES

3.1. Participants and baseline characteristics

The cohort recruited 1323 participants with schizophrenia and schizoaffective disorder or bipolar disorder who had started treatment with a first- or second-generation antipsychotic. Among them, 77 declined to participate, 41 failed to meet the inclusion criteria, and 3 were rejected as duplicate enrolments. Additionally, 160 participants were excluded as prediabetes or probable diabetes cases, while 407 participants were excluded due to missing data at baseline monitoring, and 4 participants were excluded because they were initiated on antipsychotics (chlorpromazine and fluphenazine), which are rarely prescribed. Finally, 631 participants were included in the analysis, as shown in Figure 1.

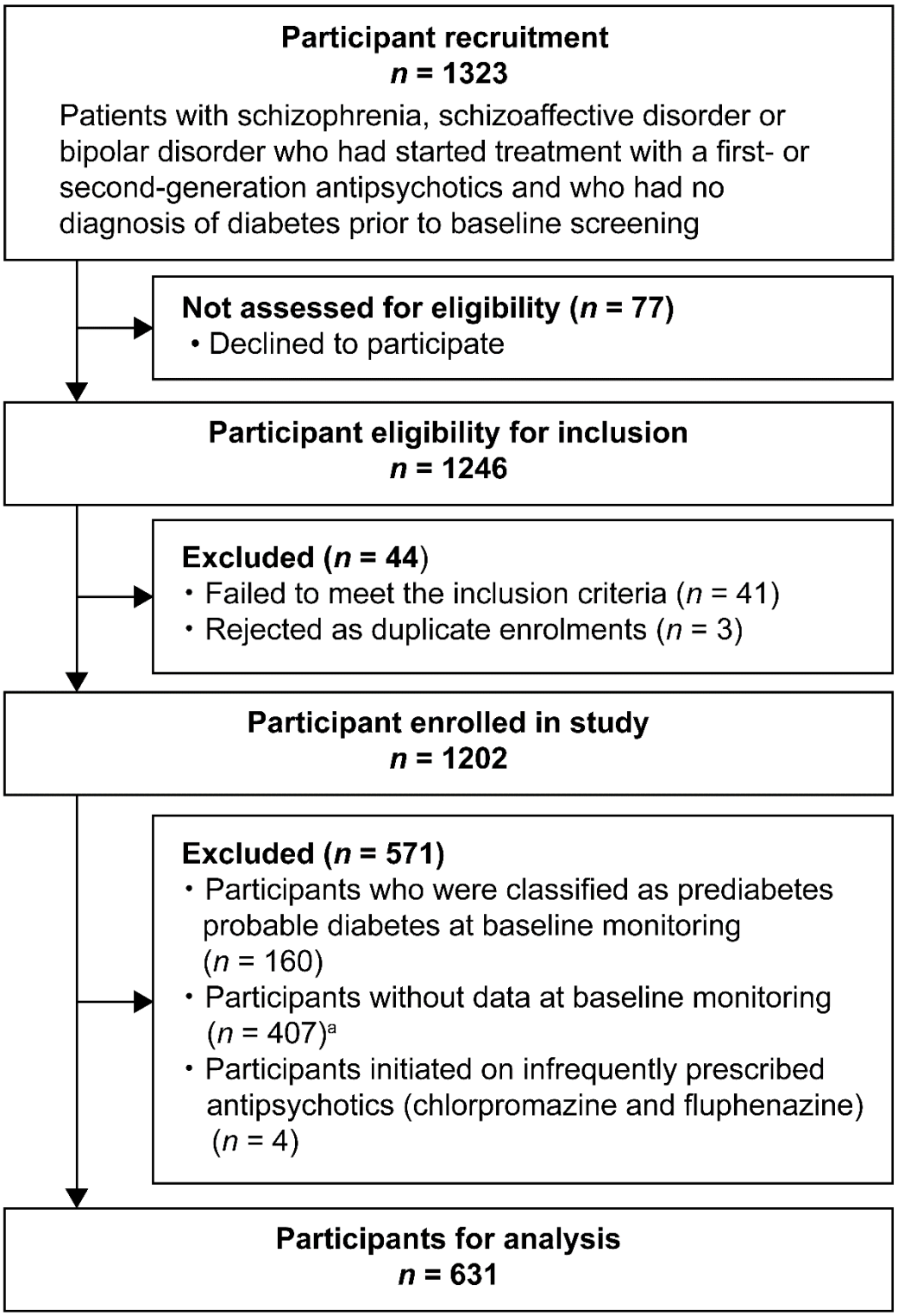

Figure 1. Flowchart of study participants. The number of participants excluded from the study due to missing data for each factor is shown. We noticed the overlap of exclusion

criteria in some study participants. Type and number of excluded data were duration of illness (n = 92), smoking (n = 20), drinking (n = 23), family history of schizophrenia and schizoaffective disorder (n = 113), family history of bipolar disorder (n = 127), family history of major depression (n = 131), family history of diabetes (n = 176), family history of dyslipidemia (n = 229), coexisting dyslipidemia (n = 5), coexisting hypertension (n = 6) coexisting heart disease (n = 6), dietary therapy (n = 2), exercise therapy (n = 1), total cholesterol (n = 25), HDL cholesterol (n = 50), triglycerides (n = 19), chlorpromazine equivalent dose (n = 52), and coadministered antilipidemic agents (n = 1).

The characteristics of participants are shown in Table 1. Of the 631 participants, we observed that 94 progressed to hyperglycemia during the study term. Among them, 523 (82.9%) participants were diagnosed with schizophrenia or schizoaffective disorder and 108 (17.1%) with bipolar disorder. Administered antipsychotics included aripiprazole (29.8%), olanzapine (14.4%), quetiapine (11.4%), risperidone (8.2%), blonanserin (7.4%), perospirone (7.1%), levomepromazine (6.8%), paliperidone (3.5%), haloperidol (3.3%), clozapine (3.2%), sulpiride (2.9%), and zotepine (1.9%). At the start of the study, 194 participants (30.7%) were treated with antipsychotic monotherapy, 218 participants (34.5%) were treated with dual antipsychotic therapy, and 219 participants (34.7%) were treated with a concomitant therapy of 3 or more antipsychotics. The cohort included 238 participants (37.7%) treated with antipsychotics at a mean daily dose (as CPZ) of 300 mg or less, 159 participants (25.2%)

253 treated with antipsychotics at a mean daily dose of 300 to 600 mg, and 234 participants
254 (37.1%) treated with antipsychotics at a mean daily dose of 600 mg or more. The mean daily
255 dose of antipsychotic medication taken by all participants in the study was 589 mg.
256

257 **Table 1. Participant characteristics, baseline monitoring, and medication**

	Values		
	Total	Hyperglycemic progression	
	(*n* = 631)	No (*n* = 537)	Yes (*n* = 94)
Baseline characteristics			
Men/women, n (%)	265 (42.0) / 366 (58.0)	227 (42.3) / 310 (57.8)	38 (40.4) / 56 (59.6)
Age, n (%)			
<40 years	274 (43.4)	239 (44.5)	20 (21.3)
40–60 years	276 (43.7)	234 (43.6)	42 (44.7)
>60 years	81 (12.8)	64 (11.9)	17 (18.1)
Duration of illness, n (%)			
<1.5 years	116 (18.4)	96 (17.9)	35 (37.2)
1.5–10 years	165 (26.1)	145 (27.0)	20 (21.3)
11–20 years	173 (27.4)	148 (27.6)	25 (26.6)
>20 years	177 (28.1)	148 (27.6)	29 (30.9)
Diagnosis, n (%)			
Schizophrenia	454 (72.0)	386 (71.9)	68 (72.3)
Schizoaffective disorder	69 (10.9)	58 (10.8)	11 (11.7)
Bipolar disorder	108 (17.1)	93 (17.3)	15 (16.0)
Out-patient/in-patient, n (%)	328 (52.0) / 303 (48.0)	277 (51.6) / 260 (48.4)	51 (54.3) / 43 (45.7)
Smoking, n (%)	200 (31.7)	169 (31.5)	31 (33.0)
Drinking, n (%)	118 (18.7)	100 (18.6)	18 (19.1)
Familial history, n (%)			
Schizophrenia	84 (13.3)	75 (14.0)	9 (9.6)

Bipolar disorder	19	(3.0)	18	(3.4)	1	(1.1)
Major depression	63	(10.0)	51	(9.5)	12	(12.8)
Diabetes	129	(20.4)	109	(20.3)	20	(21.3)
Dyslipidemia	72	(11.4)	62	(11.5)	10	(10.6)
Coexisting medical diagnoses, n (%)						
Dyslipidemia	77	(12.2)	58	(10.8)	19	(20.2)
Hypertension	58	(9.2)	41	(7.6)	17	(18.1)
Heart disease	23	(3.6)	18	(3.4)	5	(5.3)
Therapeutic interventions, n (%)						
Dietary therapy	24	(3.8)	19	(3.5)	5	(5.3)
Exercise therapy	16	(2.5)	11	(2.0)	5	(5.3)
Medical therapy	22	(3.5)	19	(3.5)	3	(3.2)
Monitoring at baseline						
Body weight, kg: mean (s.d.)	62	(14.5)	62	(14.2)	64	(15.9)
Body mass index, kg/m^2: mean (s.d.)	24	(4.7)	23	(4.6)	25	(5.4)
Body mass index: ≥25, n (%)	209	(33.1)	168	(31.3)	41	(43.6)
Fasting blood glucose, mg/dL: mean (s.d)	88	(9.4)	88	(9.4)	91	(9.6)
Postprandial blood glucose, mg/dL: mean (s.d.)	99	(15.5)	98	(15.4)	104	(15.1)
HbA1c, %: mean (s.d.)	5	(0.3)	5	(0.3)	5	(0.4)
Total cholesterol, mg/dL: mean (s.d.)	187	(38.3)	186	(38.9)	192	(34.7)
Total cholesterol: ≥220, n (%)	121	(19.2)	103	(19.2)	18	(19.1)
HDL cholesterol, mg/dL: mean (s.d.)	58	(17.5)	59	(17.9)	56	(14.8)
HDL cholesterol: <40, n (%)	71	(11.3)	59	(11.0)	12	(12.8)
Triglyceride, mg/dL: mean (s.d.)	117	(81.3)	115	(83.9)	128	(63.8)
Triglyceride: ≥150, n (%)	27	(4.3)	23	(4.3)	4	(4.3)
Baseline medications						
Newly initiated antipsychotics, n (%)						
Aripiprazole	188	(29.8)	164	(30.5)	24	(25.5)
Olanzapine	91	(14.4)	75	(14.0)	16	(17.0)
Quetiapine	72	(11.4)	66	(12.3)	6	(6.4)
Risperidone	52	(8.2)	44	(8.2)	8	(8.5)
Blonanserin	47	(7.4)	40	(7.4)	7	(7.4)
Perospirone	45	(7.1)	35	(6.5)	10	(10.6)
Levomepromazine	43	(6.8)	37	(6.9)	6	(6.4)

Paliperidone	22	(3.5)	21	(3.9)	1	(1.1)
Haloperidol	21	(3.3)	20	(3.7)	1	(1.1)
Clozapine	20	(3.2)	14	(2.6)	6	(6.4)
Sulpiride	18	(2.9)	15	(2.8)	3	(3.2)
Zotepine	12	(1.9)	6	(1.1)	6	(6.4)
Number of coadministered antipsychotics, n (%)						
0	194	(30.7)	169	(31.5)	25	(26.6)
1	218	(34.5)	188	(35.0)	30	(31.9)
≥2	219	(34.7)	180	(33.5)	39	(41.5)
Daily dose of antipsychotics (CPZ), n (%)						
<300 mg	238	(37.7)	207	(38.5)	31	(33.0)
300−600 mg	159	(25.2)	133	(24.8)	26	(27.7)
>600 mg	234	(37.1)	197	(36.7)	37	(39.4)
Daily dose of antipsychotics (CPZ), mg: mean (s.d.)	589	(576.5)	579	(566.7)	648	(629.6)
Coadministered non-antipsychotics, n (%)						
Mood stabilizers	141	(22.3)	123	(22.9)	18	(19.1)
Antidepressants	104	(16.5)	85	(15.8)	19	(20.2)
Antilipidemic agents	43	(6.8)	34	(6.3)	9	(9.6)
Antihypertensives	52	(8.2)	38	(7.1)	14	(14.9)

Footnote: A total of 631 participants for all factors shown in Table 1 except fasting (n = 161), postprandial blood glucose (n = 466), and HbA1c (n = 619). In the non-hyperglycemic group, there were a total of 537 participants for all factors shown in Table 1 except fasting (n = 148), postprandial blood glucose (n = 385), and HbA1c (n = 526). In the hyperglycemic group, there were a total of 94 participants for all factors shown in Table 1 except fasting (n = 13), postprandial blood glucose (n = 81), and HbA1c (n = 93).

3.2. Affect of baseline medication on the incidence of hyperglycemic progression

Examination of the affect of each antipsychotic on the risk of hyperglycemic progression using multivariate Cox regression analysis, including adjustment for baseline factors and measurements, showed that initiation of treatment with clozapine (HR = 3.08, 95% CI = 1.05–9.02, *P* = 0.04) and zotepine (HR = 4.95, 95% CI = 1.72–14.26, *P* = 0.003) was associated with a significantly higher incidence of hyperglycemic progression than that with initiation of treatment with aripiprazole (Table 2). To confirm the affect of the duration of newly initiated antipsychotic medication on the incidence of hyperglycemic progression, additional analyses were conducted by stratifying the duration of these treatments into 3, 6, and 12 mo. In both subgroups, zotepine showed a significantly higher incidence of hyperglycemic progression than that with initiation of treatment with aripiprazole. In contrast, there was a trend toward a higher rate of progression of hyperglycemia with clozapine in the subgroup, although this was not statistically significant (Supplemental Table S1-3).

In contrast, with regard to the number of antipsychotics at the start of the study, we did not detect any significant increase in the incidence of hyperglycemic progression in the dual antipsychotic therapy and concomitant three or more antipsychotic therapy groups compared with that in the antipsychotic monotherapy group (Table 2). Furthermore, with regard to the daily dose calculated as CPZ, no significant increase was observed in the incidence of hyperglycemic progression in the groups with a daily dose between 300 and 600 mg and those with a daily dose greater than 600 mg compared with those with a daily dose

285 less than 300 mg (Table 2). We checked the multicollinearity of independent variables
286 through GVIF. We found that GVIF ranged from 1.02 to 2.50, indicating that
287 multicollinearity was denied in this multiple regression analysis.

288 In a post hoc analysis in which antipsychotics were grouped according to the
289 strength of blockade of H_1, M_1, M_3, and 5-HT_{2C} receptors, which are receptors associated with
290 abnormal glucose metabolism, there was no association between the daily dose of
291 antipsychotics and incidence of hyperglycemic progression in the antipsychotic group with
292 weak blockade of these receptors (Supplemental Table S4). On the contrary, in the group of
293 antipsychotics with strong blockade of these receptors, the incidence of hyperglycemic
294 progression was significantly increased in the groups with a daily dose between 300 and 600
295 mg (HR = 3.44, 95 % CI = 1.07–10.98, $P = 0.037$) and those with a daily dose greater than
296 600 mg (HR = 4.15, 95 % CI = 1.19–14.43, $P = 0.025$) compared with that in the group with a
297 daily dose less than 300 mg (Supplemental Table S4).

298

299 **Table 2. Affect of baseline medication on the incidence of hyperglycemic progression**

			Multivariate analysis (n = 633)		
	n	Events	Hazard ratio (95%CI)		P
Baseline medications					
Newly initiated antipsychotics					
Aripiprazole	188	24	Ref		
Olanzapine	91	16	1.11	(0.56 - 2.19)	0.768
Quetiapine	72	6	0.45	(0.17 - 1.18)	0.103

Risperidone	52	8	1.03	(	0.43	-	2.44	)	0.954
Blonanserin	47	7	0.89	(	0.34	-	2.29	)	0.805
Perospirone	45	10	1.49	(	0.65	-	3.45	)	0.348
Levomepromazine	43	6	0.95	(	0.37	-	2.47	)	0.921
Paliperidone	22	1	0.33	(	0.04	-	2.63	)	0.297
Haloperidol	21	1	0.43	(	0.06	-	3.40	)	0.427
Clozapine	20	6	3.08	(	1.05	-	9.02	)	0.040
Sulpiride	18	3	1.61	(	0.43	-	5.97	)	0.476
Zotepine	12	6	4.95	(	1.72	-	14.26	)	0.003
Number of coadministered antipsychotics									
0	194	25	Ref						
1	218	30	1.02	(	0.53	-	1.96	)	0.960
≥2	219	39	1.15	(	0.53	-	2.49	)	0.718
Daily dose of antipsychotics (CPZ)									
<300	238	31	Ref						
300−600	159	26	1.43	(	0.71	-	2.87	)	0.311
>600	234	37	1.48	(	0.70	-	3.10	)	0.303

Footnote: All factors shown in Table 1 except body weight, body mass index, fasting and postprandial blood glucose, HbA1c, total cholesterol, HDL cholesterol, and triglycerides were adjusted.

3.3. Affect of baseline factors and measurements on the incidence of hyperglycemic progression

Regarding the affect of baseline factors and measurements on incidence of hyperglycemic progression, we noticed that being overweight (BMI greater than or equal to

309 25) (HR =1.70, 95% CI = 1.07–2.71, P = 0.026) was significantly associated with the
310 incidence of hyperglycemic progression (Supplemental Table S5).
311
312 ***3.4. Changes in markers related to glycolipid metabolism after initiation of antipsychotic***
313 ***medications***
314 To investigate the affect of antipsychotic medications on glycolipid metabolism over
315 time, we examined changes in HbA1c levels at 3, 6, and 12 mo after initiation of each
316 antipsychotic medication. Additionally, we analyzed total cholesterol, triglycerides, HDL
317 cholesterol, and BMI at 12 mo after initiation of the medication. The change in HbA1c levels
318 after 6 mo of zotepine treatment was significantly higher than that after blonanserin and
319 haloperidol treatment. In addition, the change in HbA1c levels after 6 mo of blonanserin
320 treatment was significantly lower than that after aripiprazole treatment (Figure 2 and
321 Supplemental Table S6). In contrast, there was no significant difference in the change in total
322 cholesterol, triglycerides, HDL cholesterol, and BMI between the antipsychotics at any
323 timepoint (Supplemental Table S7).

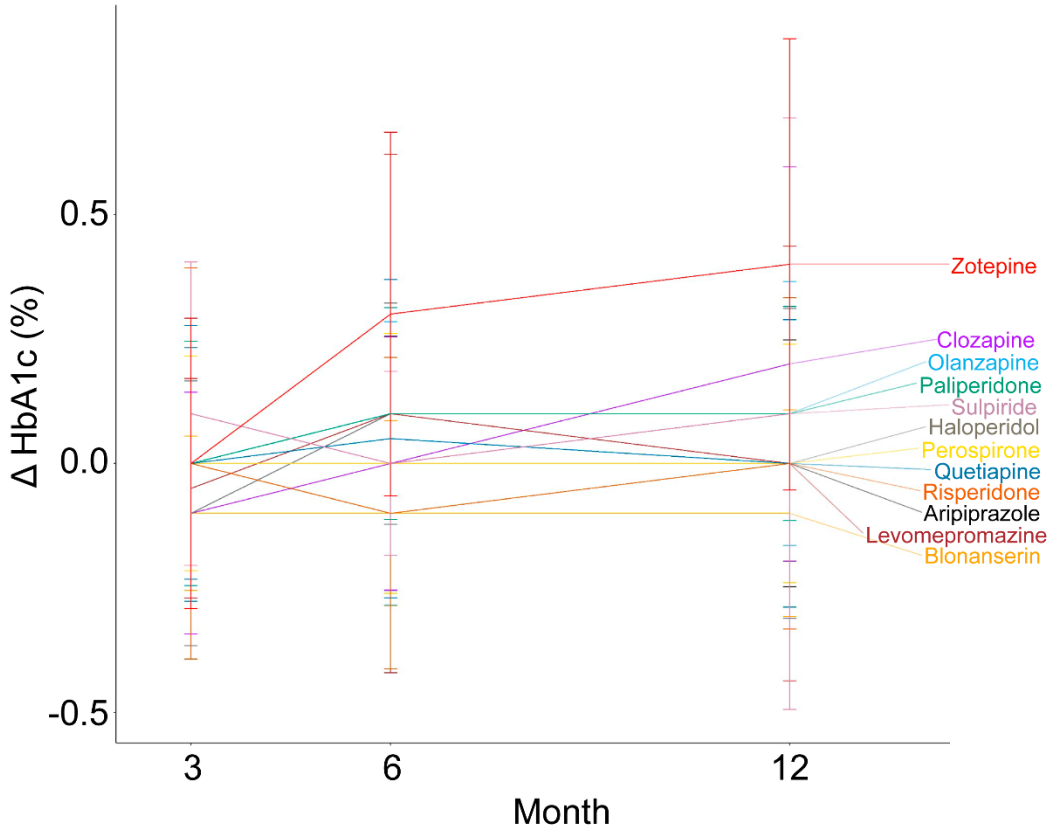

Figure 2. Changes in HbA1c levels after initiation of antipsychotic medications. Changes from baseline in markers related to glycolipid metabolism (HbA1c, total cholesterol, HDL cholesterol, triglycerides, and BMI) after initiation of each antipsychotic medication were expressed as median ± standard deviation. The difference in the change in HbA1c levels from baseline at each time point was compared between the antipsychotics. Statistical analysis was performed by Kruskal-Wallis test followed by Steel-Dwass test for post-hoc comparison. $^{*}P <$ 0.05 versus blonanserin, and haloperidol; $^{\#}P < 0.05$ versus aripiprazole.

4. DISCUSSION

335 Our current study examined the affect of antipsychotic treatment-associated factors
336 ("type", "daily dose", and "number" of antipsychotics) on incidence hyperglycemic
337 progression in the real-world clinical setting. Our results showed that initiation of treatment
338 with zotepine and clozapine led to significantly higher incidence of hyperglycemic
339 progression than that with aripiprazole treatment. In contrast, the "daily dose" and "number"
340 of antipsychotics were not associated with the risk of hyperglycemic progression in this study.
341 However, in a post hoc analysis of only participants who had initiated treatment with
342 antipsychotics that strongly blocked H_1, M_1, M_3, and 5-HT_{2C} receptors, the incidence of
343 hyperglycemic progression was significantly higher in medium- and high-daily dose groups
344 than in the low-daily dose group. Furthermore, the change in HbA1c levels after 6 mo of
345 initiation of zotepine treatment was significantly higher than that after blonanserin or
346 haloperidol treatment. In contrast, there were no significant differences in total cholesterol,
347 triglycerides, HDL cholesterol, and BMI between the antipsychotics at any timepoint.
348 Treatment with both zotepine and clozapine was associated with a higher incidence
349 of hyperglycemic progression compared with that in placebo, as recently reported in a
350 network meta-analysis of controlled studies (Pillinger et al. 2020). Our current study showed
351 that these two antipsychotics were associated with a higher incidence of hyperglycemic
352 progression even in real-world clinical settings. It has been reported that blockade of central
353 5-HT_{2C} and H_1 receptors leads to the development of insulin resistance and direct blockade of

354 M_3 receptors in pancreatic β-cells leads to reduction of insulin secretion (Holt, 2019;
355 Kowalchuk et al., 2019; Starrenburg and Bogers, 2009). As zotepine and clozapine are known
356 to exhibit these pharmacological properties (Holt, 2019; Yonemura et al., 1998; Gardner et
357 al., 2005; Starrenburg and Bogers, 2009; Kroeze et al., 2003; Philibin et al., 2009), the results
358 of our study were further supported from this aspect. Among them, zotepine has consistently
359 been shown to increase the risk of hyperglycemic progression in our study. Furthermore,
360 participants who initiated zotepine treatment had an increased incidence of hyperglycemic
361 progression without lipid abnormalities or weight gain. These findings suggest that zotepine
362 may cause hyperglycemic progression in a short term by reducing insulin secretion via
363 blockade of M_3 receptor. In contrast, olanzapine, quetiapine, and levomepromazine, which
364 were included in this study and have these pharmacological properties (Holt, 2019; Yonemura
365 et al., 1998; Gardner et al., 2005; Starrenburg and Bogers, 2009; Kroeze et al., 2003; Philibin
366 et al., 2009), were shown to not significantly increase the incidence of hyperglycemic
367 progression. Levomepromazine was prescribed at lower doses than other antipsychotics
368 (Supplemental Table S8); therefore, it might not have had sufficient pharmacological action
369 to induce the hyperglycemic progression in the study. Although olanzapine and quetiapine
370 have been reported in various studies to have an increased the incidence of hyperglycemic
371 progression, the results of a recently reported network meta-analysis showed that the risk for
372 elevated blood glucose levels in patients treated with these antipsychotics was not significant

compared with those treated with placebo (Pillinger et al. 2020). In addition, olanzapine and quetiapine are contraindicated in patients with a history of diabetes in Japan. Therefore, physicians tend to avoid prescribing them to patients at risk for hyperglycemic progression. As a result, the incidence of hyperglycemic progression following treatment with olanzapine and quetiapine observed in our study might be lower than the inherent risk.

The results of this study showed that the “daily dose” and “number” of antipsychotics were not associated with the risk of hyperglycemic progression in this study. However, in a post hoc analysis of only participants who initiated antipsychotics with potent blockade of H_1, M_1, M_3, and $5HT_{2c}$ receptors showed that higher daily doses increased the incidence of hyperglycemic progression, and there may be a dose-dependent increase in the incidence of hyperglycemic progression following treatment with antipsychotics with these pharmacological properties. A previous report has shown that there is a significant correlation between the incidence of diabetes and receptor occupancy of H_1, muscarinic acetylcholine, and 5-HT_{2C}; our results support these findings (Matsui-Sakata et al., 2005).

There were several limitations to this study. First, the independent variables assessed in this study for their affect on hyperglycemic progression were obtained at the time of the initiation of new antipsychotic medications. As such, they do not necessarily reflect the status of treatment, as this might have changed after the initiation of the study. However, many newly initiated antipsychotics were continuously administered for a long period of time

during the study, and their daily doses did not change considerably between the initiation and end of the study (Supplemental Table S8). Moreover, the results were robust in a sensitivity analysis of the group that had been on long-term treatment with newly initiated antipsychotics (Supplemental Table S1-3). Second, the present study did not exclude the effect of drug-drug interactions. Because antipsychotics are metabolized by a variety of drug-metabolizing enzymes, including cytochrome P450 (CYP) 3A4, 1A2, and 2D6, the incidence of hyperglycemic progression might have been altered by the concomitant use of drugs that inhibit or induce metabolism. This study confirmed the affects of mood stabilizers and antidepressants, which may cause drug interactions with antipsychotics, but did not show any affect on the incidence of hyperglycemic progression. Third, a 1-y follow-up period might not have been sufficient to observe the incidence of hyperglycemic progression in participants. However, 1 y might have been long enough compared with the timeline used in many previous studies (Pillinger et al. 2020; Zhang et al., 2017; Ulcickas Yood et al., 2011). Fourth, although race has been reported to be a risk for diabetes, this study included only Japanese subjects. Therefore, further studies should replicate our results with races other than Japanese.

5. CONCLUSION

The study was the first to examine the affect of the type, number, and daily dose of antipsychotics on the incidence of hyperglycemic progression in real world clinical settings,

411 after adjustment for the affect of abnormal glucose metabolism-associated background
412 factors. We found that the type of antipsychotics had a greater affect on the incidence of
413 hyperglycemic progression than the daily dose of antipsychotics or their number.
414 Furthermore, among the antipsychotics, zotepine was found to increase the incidence of
415 hyperglycemic progression. These results suggested that caution should be exercised
416 regarding the incidence of hyperglycemic progression when this antipsychotic is prescribed.
417

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427

428 **DECLARATION OF INTEREST**

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AUTHOR CONTRIBUTIONS

Shuhei Ishikawa: Formal analysis, Investigation, Writing-Original Draft, Funding acquisition

Naoki Hashimoto: Formal analysis, Investigation, Writing-Original Draft

Ryodai Yamamura: Formal analysis, Writing-Original Draft

Ryo Okubo: Project administration, Investigation, Supervision

448 Ryo Sawagashira: Formal analysis, Supervision

449 Yoichi M Ito: Conceptualization, Formal analysis, Methodology, Supervision

450 Norihiro Sato: Conceptualization, Methodology, Supervision

451 Ichiro Kusumi: Conceptualization, Investigation, Methodology, Supervision

452

453 **DATA AVAILABILITY STATEMENT**

454 Data are not available due to the participants of this study not agreeing to have their data be

455 shared publicly.

456

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