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

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25 **Abbreviations**[1]

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[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

61 1. **INTRODUCTION**

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

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

77 Although the effect of a variety of different factors of antipsychotics, such as “type”,
78 “daily dose”, and “number”, on glucose metabolism have been examined in patients treated
79 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

99 decided to examine the affect of "type", "daily dose", and "number" of antipsychotics on the
100 incidence of hyperglycemic progression. When examining the association between
101 antipsychotics and incidence of hyperglycemic progression, it is necessary to consider both
102 antipsychotic-related factors and the effects of glucose metabolism-related background
103 factors, such as age, sex, exercise, diet, and coadministration of non-antipsychotics (Guo et
104 al., 2006; Kusumi et al., 2018; Padwal et al., 2004; Preiss et al., 2011; Steardo et al., 2019;
105 Sugai et al., 2018; Vancampfort et al., 2016). Therefore, the present study examined the affect
106 of antipsychotic treatment-associated factors, such as type, daily dose, and number of drugs
107 on the incidence of hyperglycemic progression after adjusting for the affect of background
108 factors suggested to be associated with glucose metabolism using data from a nationwide,
109 multisite, prospective cohort study.
110

111 **2. METHODS**

112 ***2.1. Study design and population***

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

117 antipsychotics, were recruited from 44 sites in Japan (24 general hospitals, 17 psychiatric
118 hospitals, and 3 psychiatric clinics) as the study cohort between May 2013 and March 2015.
119

120 ***2.2. Definitions and criteria***

121 Study participants were diagnosed with schizophrenia, schizoaffective disorder, or
122 bipolar disorder by their physicians based on ICD-10 criteria (World Health Organization,
123 2013). Inclusion criteria were (i) initiation of a first- or second-generation antipsychotic
124 medication, (ii) a 12 mo history of medication prior to enrollment, and (iii) no diagnosis of
125 diabetes before baseline screening. Exclusion criteria were (i) patients with probable diabetes
126 or prediabetes at baseline screening. This study was conducted according to the guidelines of
127 the Declaration of Helsinki. All participants were fully briefed on study procedures and
128 provided written informed consent.
129

130 ***2.3. Measurements***

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

136 therapy), and 12 mo medication history prior to enrollment and during the study period.
137 Baseline measurements, which included blood glucose (fasting or postprandial) or glycated
138 hemoglobin (HbA1c), serum lipids (total cholesterol, high-density lipoprotein (HDL)
139 cholesterol, and triglycerides), body weight, body mass index (BMI), were obtained prior to
140 the initiation of treatment with new antipsychotics. Baseline medication included the
141 administration of new antipsychotics, number of coadministered antipsychotics, daily dose of
142 antipsychotics, and coadministration of mood stabilizers, antidepressants, antilipidemic
143 agents, and antihypertensives.
144 The Japanese monitoring guidance in patients with schizophrenia (Kusumi et al.,
145 2011) classifies blood glucose levels as follows: (i) normal (fasting blood glucose <110
146 mg/dL, postprandial blood glucose <140 mg/dL, or HbA1c <6.0%), (ii) prediabetes (fasting
147 blood glucose of 110–125 mg/dL, postprandial blood glucose of 140–179 mg/dL, or HbA1c
148 of 6.0–6.4%), and (iii) probable diabetes (fasting blood glucose > 125 mg/dL, postprandial
149 blood glucose > 179 mg/dL, or HbA1c > 6.4%). Blood tests were scheduled in accordance
150 with the Japanese guidelines for blood glucose monitoring in patients with schizophrenia and
151 were conducted at 3, 6, and 12 mo for patients with normal blood glucose levels (Kusumi et
152 al., 2011).
153
154

155 ***2.4. Statistical analyses***

156 The primary endpoint was hyperglycemic progression during 12 mo after new
157 initiation of antipsychotic medication. The incidence of hyperglycemic progression was
158 defined as progression from normal to prediabetes or probable diabetes according to the blood
159 glucose criteria described in the "Measurements" section of the methods. Time-to-event was
160 defined as the time interval between the date of new initiation of antipsychotic medication and
161 the date of hyperglycemic progression or the censor date of the last follow-up period. We
162 used Cox proportional hazard regression models (Cox, 1972) to assess whether the affect on
163 hyperglycemic progression differed between each factor associated with antipsychotic
164 medication (type, daily dose, and number of antipsychotics) in multivariable analysis adjusted
165 for available background factors reported to have an affect on hyperglycemic progression
166 (Kusumi et al., 2018; Koller and Doraiswamy, 2002; Mukherjee et al., 1996; Sweileh et al.,
167 2013).

168 Participant data associated with antipsychotic medication included newly initiated
169 antipsychotic medication (type of antipsychotics), number of antipsychotics, and daily dose of
170 antipsychotics in chlorpromazine equivalent (CPZ) (Inada et al., 2015). Participant data
171 related to hyperglycemic progression included sex, age, diagnosis (schizophrenia and
172 schizoaffective disorder or bipolar disorder), duration of illness, treatment status (out-patient
173 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

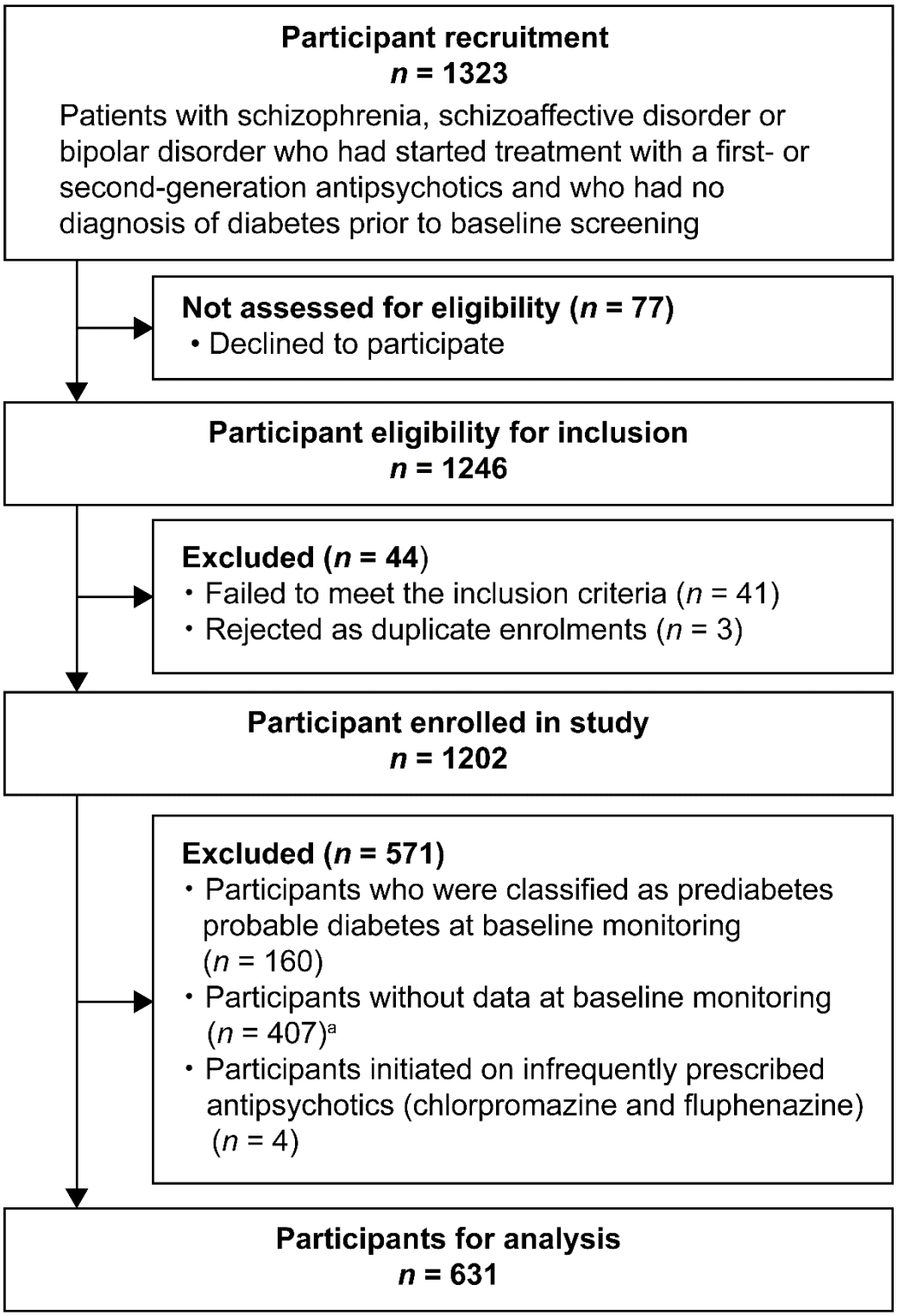
192 further confirm the robustness of the results, the same tests were conducted in the groups
193 stratified by the duration of newly initiated antipsychotic medication (3, 6, and 12 mo).
194 Furthermore, we conducted two post hoc analyses to further assess the affect of type
195 of antipsychotic on 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

211 abnormalities in glycolipid metabolism over time. This analysis examined differences in
212 changes over time in markers related to glycolipid metabolism (HbA1c, total cholesterol,
213 HDL cholesterol, triglycerides, and BMI) at 3, 6, or 12 mo after initiation of each
214 antipsychotic medication. In this analysis, the significance of the differences in changes in
215 markers between antipsychotics at each timepoint was assessed using the Kruskal-Wallis test
216 and Steel-Dwass post-test. All statistical analyses were performed using the dplyr packages
217 run on R statistics 4.0.2. All probability values were two-tailed, and the significance level was
218 set at $P < 0.05$.
219

220 **3. RESULTS AND STATISTICAL ANALYSES**

221 ***3.1. Participants and baseline characteristics***

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



231

232 **Figure 1. Flowchart of study participants.** The number of participants excluded from the

233 study due to missing data for each factor is shown. We noticed the overlap of exclusion

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

242 The characteristics of participants are shown in Table 1. Of the 631 participants, we
243 observed that 94 progressed to hyperglycemia during the study term. Among them, 523
244 (82.9%) participants were diagnosed with schizophrenia or schizoaffective disorder and 108
245 (17.1%) with bipolar disorder. Administered antipsychotics included aripiprazole (29.8%),
246 olanzapine (14.4%), quetiapine (11.4%), risperidone (8.2%), blonanserin (7.4%), perospirone
247 (7.1%), levomepromazine (6.8%), paliperidone (3.5%), haloperidol (3.3%), clozapine (3.2%),
248 sulpiride (2.9%), and zotepine (1.9%). At the start of the study, 194 participants (30.7%) were
249 treated with antipsychotic monotherapy, 218 participants (34.5%) were treated with dual
250 antipsychotic therapy, and 219 participants (34.7%) were treated with a concomitant therapy
251 of 3 or more antipsychotics. The cohort included 238 participants (37.7%) treated with
252 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

266 Examination of the affect of each antipsychotic on the risk of hyperglycemic
267 progression using multivariate Cox regression analysis, including adjustment for baseline
268 factors and measurements, showed that initiation of treatment with clozapine (HR = 3.08,
269 95% CI = 1.05–9.02, *P* = 0.04) and zotepine (HR = 4.95, 95% CI = 1.72–14.26, *P* = 0.003)
270 was associated with a significantly higher incidence of hyperglycemic progression than that
271 with initiation of treatment with aripiprazole (Table 2). To confirm the affect of the duration
272 of newly initiated antipsychotic medication on the incidence of hyperglycemic progression,
273 additional analyses were conducted by stratifying the duration of these treatments into 3, 6,
274 and 12 mo. In both subgroups, zotepine showed a significantly higher incidence of
275 hyperglycemic progression than that with initiation of treatment with aripiprazole. In contrast,
276 there was a trend toward a higher rate of progression of hyperglycemia with clozapine in the
277 subgroup, although this was not statistically significant (Supplemental Table S1-3).
278 In contrast, with regard to the number of antipsychotics at the start of the study, we
279 did not detect any significant increase in the incidence of hyperglycemic progression in the
280 dual antipsychotic therapy and concomitant three or more antipsychotic therapy groups
281 compared with that in the antipsychotic monotherapy group (Table 2). Furthermore, with
282 regard to the daily dose calculated as CPZ, no significant increase was observed in the
283 incidence of hyperglycemic progression in the groups with a daily dose between 300 and 600
284 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).

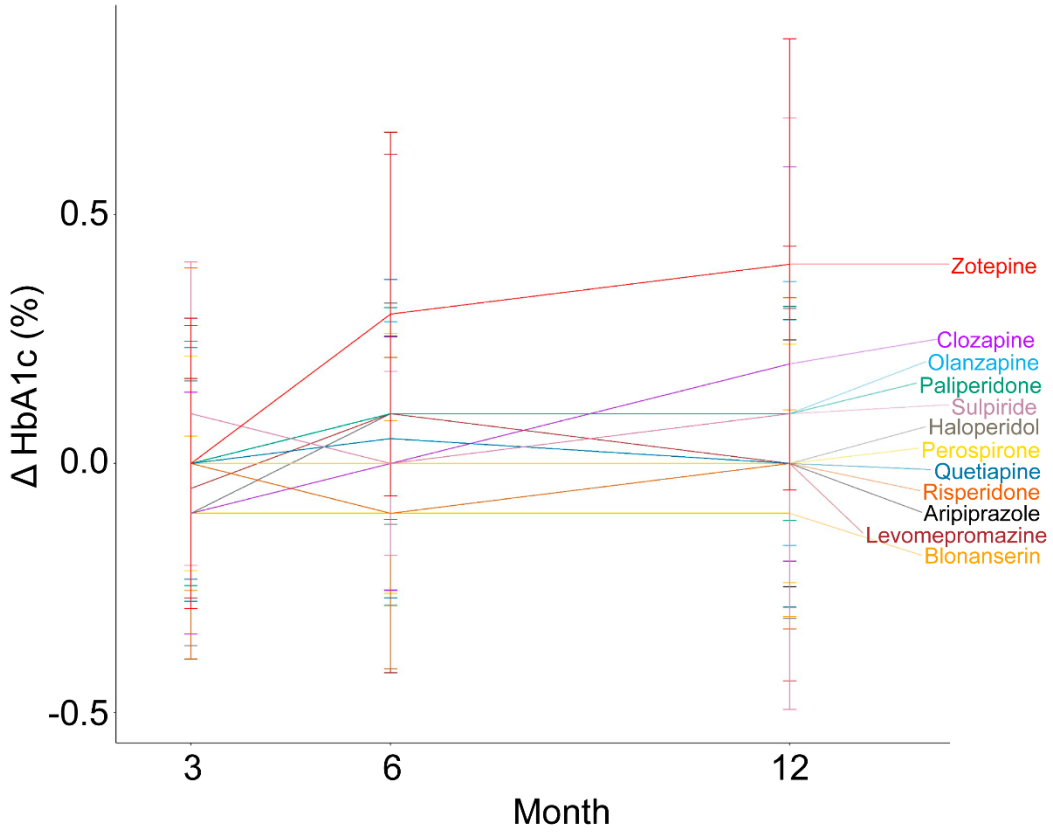


Figure 2. Changes in HbA1c levels after initiation of antipsychotic medications. Changes from baseline in markers related to glycolipid metabolism (HbA1c, total cholesterol, HDL cholesterol, triglycerides, and BMI) after initiation of each antipsychotic medication were expressed as median ± standard 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

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

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

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

392 during the study, and their daily doses did not change considerably between the initiation and
393 end of the study (Supplemental Table S8). Moreover, the results were robust in a sensitivity
394 analysis of the group that had been on long-term treatment with newly initiated antipsychotics
395 (Supplemental Table S1-3). Second, the present study did not exclude the effect of drug-drug
396 interactions. Because antipsychotics are metabolized by a variety of drug-metabolizing
397 enzymes, including cytochrome P450 (CYP) 3A4, 1A2, and 2D6, the incidence of
398 hyperglycemic progression might have been altered by the concomitant use of drugs that
399 inhibit or induce metabolism. This study confirmed the affects of mood stabilizers and
400 antidepressants, which may cause drug interactions with antipsychotics, but did not show any
401 affect on the incidence of hyperglycemic progression. Third, a 1-y follow-up period might not
402 have been sufficient to observe the incidence of hyperglycemic progression in participants.
403 However, 1 y might have been long enough compared with the timeline used in many
404 previous studies (Pillinger et al. 2020; Zhang et al., 2017; Ulcickas Yood et al., 2011). Fourth,
405 although race has been reported to be a risk for diabetes, this study included only Japanese
406 subjects. Therefore, further studies should replicate our results with races other than Japanese.
407

408 **5. CONCLUSION**

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

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

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440 Pharmaceutical and Tanabe Mitsubishi Pharma. R.S., R.Y., R.O., Y.I. and N.S. declare that
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442

443 **AUTHOR CONTRIBUTIONS**

444 Shuhei Ishikawa: Formal analysis, Investigation, Writing-Original Draft, Funding acquisition
445 Naoki Hashimoto: Formal analysis, Investigation, Writing-Original Draft
446 Ryodai Yamamura: Formal analysis, Writing-Original Draft
447 Ryo Okubo: Project administration, Investigation, Supervision

Ryo Sawagashira: Formal analysis, Supervision

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

Norihiro Sato: Conceptualization, Methodology, Supervision

Ichiro Kusumi: Conceptualization, Investigation, Methodology, Supervision

DATA AVAILABILITY STATEMENT

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

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