Effect of Antipsychotic Polypharmacy On Obesity, Hypertension, Dyslipidemia, and Diabetes

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Research Article

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Abstract

Background

It is no exaggeration to say that, in Japan, the primary treatment approach for patients with schizophrenia continues to be high-dose antipsychotic polypharmacy. However, the supporting evidence for the efficacy of antipsychotic polypharmacy is insufficient. In fact, antipsychotic polypharmacy is more likely to cause side effects, increase mortality, and decrease treatment adherence. Further, on average, mortality in patients with schizophrenia is 20 years earlier than in people without schizophrenia, and the gap is widening. One potential explanation for the increased mortality rates observed in patients with schizophrenia is that they are at higher risk for metabolic syndrome, indicated by increased rates of obesity, hypertension, dyslipidemia, and diabetes.

Results

Therefore, we recruited 7,655 outpatients and 15,461 inpatients with schizophrenia from the facilities of the Japan Psychiatric Hospitals Association and conducted a large-scale investigation of the prevalence of obesity, hypertension, dyslipidemia, and diabetes mellitus using a questionnaire. We also examined the relationship between antipsychotic polypharmacy on the parameters that regulate each lifestyle-related disease. As a result of examining the relationship between parameters that regulate each lifestyle-related disease and antipsychotic polypharmacy, we found that the more antipsychotics a patient was on, the higher their values for body mass index, diastolic blood pressure, low-density lipoprotein cholesterol and fasting blood glucose were.

Conclusion

The present study demonstrates that antipsychotic polypharmacy may actually exacerbate obesity, hypertension, dyslipidemia and diabetes. Therefore, it may be better to utilize alternative treatment strategies other than antipsychotic polypharmacy in order to avoid these metabolic side effects.

Background

In Japan, it is no exaggeration to say that the primary treatment of choice for patients with schizophrenia remains high-dose antipsychotic polypharmacy. Surprisingly, there is little evidence supporting the safe and effective use of antipsychotic polypharmacy [1, 2]. There is also a paucity of clinical studies comparing the efficacy of monotherapy and polypharmacy in the treatment of schizophrenia [3, 4]. Furthermore, the previous clinical trials that did address this problem were limited in sample size, had a short follow-up period, and poor study designs. Moreover, they compared only some of the treatments, and not the various drugs directly [5, 6]. Although most of the currently available studies do not address

the efficacy of antipsychotic polypharmacy, their results are useful in that they provide various explanations of why an individual antipsychotic medication was discontinued in monotherapy [7, 8].

Antipsychotic polypharmacy is also thought to be more likely to cause side effects, increase mortality, and decrease treatment adherence in patients [9]. According to prescription surveys in Japan, about 30% of patients with schizophrenia are treated with a single agent, while about 40% of patients are treated with two or more agents [10]. Importantly, mortality in patients with schizophrenia is on average 20 years earlier than in people without schizophrenia, and this gap is widening [11]. This increased mortality rate in schizophrenia patients may be driven by the fact that they are at higher risk of metabolic syndrome, as evidenced by increased rates of obesity, hypertension (HT), hyperlipidemia, and diabetes [12]. Therefore, it is important to consider the effects of antipsychotic polypharmacy treatment on patients with schizophrenia, as this may lead to metabolic side effects and thus a shortened lifespan.

Schizophrenia is a disease that requires long-term antipsychotic treatment. However, the side effects caused by antipsychotics are known to accumulate over time, and may increase the risk of diabetes, HT, and hyperlipidemia in the long run [13]. The condition of metabolic change that leads to an increased risk of cardiovascular and metabolic disorders is known as metabolic syndrome (MetS). Importantly, it has been previously reported that Japanese outpatients with schizophrenia have a higher prevalence of MetS compared to the general population [14].

Additionally, antipsychotic polypharmacy is still controversial due to a lack of clear evidence of efficacy and the increased risk of side effects compared to monotherapy [15]. In fact, previous studies have reported conflicting results, suggesting either an increased or decreased risk associated with antipsychotic polypharmacy and metabolic syndrome [16, 17].

In the present study, we collected various data points concerning the physical risks of patients with schizophrenia using a nationwide survey. Previous studies have already revealed that the prevalence of each lifestyle-related disease in patients with schizophrenia was higher than that of the general population, and that outpatients were at higher risk than inpatients [18]. Therefore, the aim of this study was to clarify the relationship between factors that compose each lifestyle-related disease and multiple drug combination treatment using large-scale epidemiological data.

Materials And Methods

The number of Japanese patients with schizophrenia is about 80,000 [19], most of whom are treated at affiliated facilities of the Japan Mental Hospital Association. A joint project between the Japanese Society of Clinical Neuropsychiatry and the Japan Psychiatric Hospital Association has been implemented in Japan with the aim of protecting patients with schizophrenia [14, 18]. The results of this study are based on a secondary analysis of the data obtained from the project [14, 18]. The survey was approved by the Institutional Review Board of the Japan Psychiatric Hospital Association, and all participants received written informed consent.

Subjects

We conducted a questionnaire survey between January 2012 and July 2014. We obtained responses from 7655 outpatients across 520 facilities, and 15,461 inpatients across 247 facilities belonging to the Japan Psychiatric Hospitals Association [14, 18]. All patients were diagnosed with schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision, or the International Statistical Classification of Diseases and Related Health Problems, version 10 [14, 18]. We excluded individuals younger than 20 years of age and those whose sex and body mass index (BMI) data were not assessed (n = 3,438). We analyzed a final total of 19,678 individuals (5,441 outpatients, 14,237 inpatients; Figure 1) [14, 18].

Measurements

We compiled a brief questionnaire covering demographic data (age and gender), body height and weight, waist circumference (WC), blood pressure (BP), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and fasting plasma glucose (FPG) levels after reviewing the relevant literature and guidelines [14, 18], BP was measured twice using a standard mercury sphygmomanometer while the individual was seated, after at least a 5-minute rest period [14, 18]. BMI was determined as the ratio of body weight to height (kg / m2). Height, weight, waist circumference, and blood pressure were measured by skilled medical staff [14, 18]. We used a standardized health questionnaire to determine behaviors, including current smoking status [14, 18]. Medical staff also compared TC, TG, LDL, HDL, and FPG data with the most indignant medical records within three months. TC, TG, LDL, HDL, LDL / HDL ratios, and FPG were also measured using standard analytical techniques [14, 18].

Definitions

Obesity was classified using the definition of obesity in the Asia-Pacific region (BMI ≥ 25 kg / m2). DM was defined based on FPG ≥ 126 mg / dl. An individual was diagnosed with HT if systolic blood pressure was 130 mmHg or higher, or diastolic blood pressure was 85 mmHg or higher. Hypertriglyceridemia was defined as TG ≥ 150 mg / dl. High LDL cholesterolemia was defined as LDL ≥ 140 mg / dl. Low HDL cholesterolemia was defined as HDL <40 mg / dl in males and <50 mg / dl in females [14, 18].

Statistical analysis

To compare the main demographic and clinical characteristics between the groups, we performed an unpaired Student's *t* test to analyze continuous variables and a chi-square test to analyze categorical variables. A multivariate regression analysis was performed to assess the effect of age, gender, type of care (outpatients or inpatients), number of antipsychotics as a risk factor for BMI, blood pressure, TG, LDL, HDL and FBS. The threshold for significance was set at $p<0.05$. SPSS for Windows, version 19.0 (IBM Japan, Tokyo, Japan) was used for all statistical calculations.

Results

Clinical characteristics between the outpatients and inpatients

Table1 shows the clinical characteristics between the outpatients and inpatients.

These results were reported in our previous study [18]. Compared with inpatients, outpatients had significantly higher BMI, WC, systolic BP, diastolic BP, LDL, LDL/HDL ratio, TC, TG, and FPG levels. Inpatients were also significantly older and had lower BMI and WC than the outpatients. There was a significant difference in antipsychotic therapy status between the outpatients and inpatients; that is, total antipsychotics (chlorpromazine equivalents) administered were greater in the inpatients than in outpatients.

Table 1
Clinical characteristics between outpatients and inpatients

	Outpatients	Inpatients	p value
	n = 5441	n =14237	
Age (years)	52.2 ± 13.7	60.0 ± 12.9	<0.001[a]
Body mass index (kg/m^2)	25.3 ± 4.6	22.3 ± 4.0	<0.001[a]
Systolic blood pressure (mmHg)	127.2 ± 18.2	120.4 ± 17.2	<0.001[a]
Dyastolic blood pressure (mmHg)	78.2 ± 12.4	74.5 ± 12.1	<0.001[a]
HDL-cholesterol (mg/dl)	55.9 ± 19.0	55.0 ± 19.9	NS[a]
LDL-cholesterol (mg/dl)	117.6 ± 34.9	106.9 ± 44.8	<0.001[a]
LDL/HDL ratio	2.1 ± 1.0	2.3 ± 1.0	<0.001[a]
Triglycerides (mg/dl)	141.9 ± 99.4	101.0 ± 58.7	<0.001[a]
Fasting plasma glucose (mg/dl)	108.4 ± 40.3	92.6 ± 24.4	<0.001[a]
Status of antipsychotic therapy			
No treated (%)	6.2	7.3	<0.001[b]
Antipsychotic monopharmacy (%)	49.4	40.3	
Antipsychotic polypharmacy (%)	44.4	52.4	
Ratio of SGA therapy (%)	73.3	75.8	<0.001[b]
Total CP equivalence (mg)	532.0 ± 472.6	691.1 ± 622.3	<0.001[a]
[a] Data analyzed using unpaired student's t test between outpatients and inpatients			
[b] Data analyzed using χ2 test between outpatients and inpatients			
Data are expressed as mean ± SD			
CP, chlorpromazine; HbA1c, haemoglobin A1c; SGA, second-generation antipsychotic			
NS.; Not Significant, HDL; High density lipoprotein cholesterol,			
LDL; Low density lipoprotein cholesterol, TC; Total cholesterol, TG; Triglyceride			

The relationship between metabolic parameters and the number of antipsychotics

Table 2 shows each metabolic parameter divided by the number of antipsychotics. The value of BMI, dBP, LDL, and FBS tended to increase as the number of antipsychotics increased in both outpatient and inpatient groups.

Table 2
Metabolic parameters and the number of antipsychotics

The number of antipsychotics	0 (n = 1180)	1 (n = 8425)	2 (n = 6326)	3 and more (n = 3547)
Body mass index (kg/m^2)	23.4 ± 4.5	23.6 ± 4.3	24.1 ± 4.5	24.2 ± 4.5
Systolic blood pressure (mmHg)	124.3 ± 17.3	123.9 ± 18.2	124.5 ± 18.5	121.8 ± 18.0
Dyastolic blood pressure (mmHg)	74.1 ± 11.5	75.7 ± 12.6	76.2 ± 12.0	77.7 ± 12.6
HDL-cholesterol (mg/dl)	54.7 ± 24.8	55.4 ± 18.3	55.0 ± 20.4	55.3 ± 15.2
LDL-cholesterol (mg/dl)	109.7 ± 34.0	112.3 ± 34.2	113.8 ± 35.0	116.6 ± 38.7
Triglycerides (mg/dl)	122.8 ± 90.8	121.2 ± 99.1	121.9 ± 102.0	119.6 ± 98.6
Fasting plasma glucose (mg/dl)	101.0 ± 43.4	101.8 ± 34.1	102.5 ± 41.9	105.1 ± 48.5

The effect of antipsychotic polypharmacy on BMI, BP, TG, HDL, LDL and FBS

To assess the independent effect of antipsychotic polypharmacy for BMI, BP, TG, HDL, LDL and FBS, a multiple regression analysis was performed (Table 3). Antipsychotic polypharmacy was detected as a factor that increases the values of BMI, dBP, LDL and FBS. Similarly, age, gender and type of care (outpatients) were also detected as a factor that increases these values.

Table 3
The effect of antipsychotic polypharmacy on BMI, dBP, LDL and FBS

	Independent variables	β	t	P
BMI	Age	-0.152	-21.000	< 0.001
	Gender	-0.026	-3.741	< 0.001
	type of care	-0.279	-38.702	< 0.001
	antipsychotic polypharmacy	0.035	5.008	< 0.001
sBP	Age	0.176	17.672	< 0.001
	Gender	2.910	11.327	< 0.001
	type of care	7.882	26.069	< 0.001
	antipsychotic polypharmacy	-0.060	-0.003	—
dBP	Age	-0.052	-6.885	< 0.001
	Gender	0.092	12.629	< 0.001
	type of care	0.118	15.725	< 0.001
	antipsychotic polypharmacy	0.033	4.444	< 0.001
TG	Age	-0.357	-7.443	< 0.001
	Gender	-9.798	-7.941	< 0.001
	type of care	-37.644	-26.691	< 0.001
	antipsychotic polypharmacy	-2.157	-2.966	—
HDL	Age	0.011	0.652	—
	Gender	9.236	21.722	< 0.001
	type of care	-1.412	-2.946	< 0.001
	antipsychotic polypharmacy	0.383	1.546	—
LDL	Age	0.063	1.800	—
	Gender	-0.100	-9.499	< 0.001
	type of care	-0.120	-11.367	< 0.001
	antipsychotic polypharmacy	0.028	2.663	0.008
FBS	Age	0.128	11.589	< 0.001
	Gender	0.056	5.339	0.021

Independent variables	β	t	P
type of care	-0.265	-23.937	< 0.001
antipsychotic polypharmacy	0.025	2.308	< 0.001

Discussion

We found that antipsychotic polypharmacy may be an exacerbation factor for obesity, HT, hyper-LDL, and diabetes in the present study.

The present study is not the first to report such findings, as several other studies have investigated the relationship between antipsychotic polypharmacy and metabolic parameters. In a previous study, subjects who received polypharmacy with antipsychotics were more likely to show abdominal obesity and elevated blood sugar levels, and could show elevated blood pressure, compared to subjects who received monotherapy. [20]. Although direct comparisons are difficult, other previous studies have reported an association between antipsychotic polypharmacy and the prevalence of metabolic syndrome[21]. These findings are partly consistent with our results in that they suggest antipsychotic polypharmacy may affect different types of metabolic parameters. In contrast, Softic et al. found that schizophrenic subjects receiving antipsychotic monotherapy had significantly higher rates of metabolic syndrome and serum triglyceride levels than those receiving antipsychotic polypharmacy [22]. While the explanation for these opposite findings is unclear, it could possibly be due to differences in study design (cross-sectional vs longitudinal studies), or the number of subjects as well as types of antipsychotic drugs examined. Therefore, to better understand this, future studies aimed at tracking changes in metabolic parameters over time using a longitudinal study design in drug naive subjects are necessary.

In Japan, high-dose antipsychotic polypharmacy is still the mainstream treatment strategy for patients with schizophrenia. There are several valid clinical grounds for using antipsychotic polypharmacy. For one, the identification of certain non-dopaminergic receptors, such as serotonergic, glutamatergic, and adrenergic receptors, in the etiology of psychotic symptoms provides justification for the use of combinations of antipsychotic drugs to target multiple systems [23]. However, there is little clinical evidence to support these concepts [24]. On the other hand, there are several clinical situations that may lead to patients receiving concomitant antipsychotics. For example, a clinician may add a second antipsychotic to manage difficult psychotic symptoms, including persistent attacks. Further, in some cases a patient may be concerned about the risk of a side effect stemming from a particular antipsychotic drug. Thus, a clinician may choose to lower the dose of the first antipsychotic and add another low-dose antipsychotic in an attempt to reduce the unwanted side effect and achieve a greater therapeutic response. However, the consequent attempt to prescribe multiple antipsychotics at low doses and avoid high dose prescriptions often results in a sustained resistance to antipsychotic polypharmacy. A second antipsychotic can also be added to counteract certain side effects produced by the first antipsychotic. Examples include the addition of aripiprazole to reduce plasma prolactin levels by other

antipsychotics, which are potent D2 receptor blockers [25]. Nevertheless, antipsychotic polypharmacy treatment should be carefully discussed in the future.

Why are Japanese outpatients with schizophrenia more prevalent in obesity, HT, hypertriglyceridemia, hyper-LDL cholesterolemia, and DM than those of inpatients? One possible explanation is that long-term hospitalization may result in a protective effect on the physical health of patients with schizophrenia, as the inpatients in Japan are subject to constant lifestyle management [14, 18]. On the other hand, considering that Japan has the largest number of psychiatric beds per person in the world, long-term hospitalization is a severe problem leading to greater medical costs [14, 18].

Our study does have some of the limitations found in the other cross-sectional surveys of patients with schizophrenia and metabolic syndrome. For example, because we were unable to obtain information about the duration of illness and medication, we unable to consider the influence of antipsychotics. We also did not assess several potential confounding factors, including antipsychotic medications, duration of illness, treatment, and the severity of schizophrenia. Further, although the severity of schizophrenia may also affect the onset of MetS, we did not evaluate the severity of each patient, so we were unable to examine this association in the current study.

In the present study, we found that antipsychotic polypharmacy treatment may actually be an exacerbation factor that increases the values of BMI, dBP, LDL and FBS. Therefore, it is possible that factors other than the treatment environment, especially antipsychotic polypharmacy, have an effect on the risk of lifestyle-related diseases, such as obesity, hypertension, dyslipidemia and diabetes. The type of care had the greatest effect on BMI, dBP, LDL, and FBS, and the effect was greater than that of polypharmacy. When treating with consideration of the physical risk of patient with schizphrenia, it is necessary to give sufficient consideration to the effect of polypharmacy and the type of care. Our findings provide further evidence of antipsychotic polypharmacy treatment leading to increased physical risk and therefore highlights the need for more studies examining this relationship. Furthermore, patients with schizophrenia exposed to antipsychotic polypharmacy treatment strategies may need to be monitored and blood tested regularly with the management of physical risk in mind.

Declarations

Ethics approval and consent to participate

This survey was approved by the Ethics Committee at the Japan Psychiatric Hospitals Association in accord with the principles of the Declaration of Helsinki. All participants provided written informed consent.

Consent for publication

The participants were informed during the consent process of the prospect of the personal information and pertinent findings of this study being published in an international peer reviewed journal at an

appropriate time. Participants were reassured of optimal levels of confidentiality being adhered to with regards to handling and dissemination of any potentially identifying information.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests and Funding

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"Author's Contributions"

All authors read and approved the final manuscript.

Conceptualization: TS1, YS, TS2

Methodology: TS1, MY, TM, HM, KO, TS

Software: TS1

Validation: TS1, YS KS, YO, NS, NYF

Formal analysis: TS1, YS

Investigation: TS1, YS, YW, TS2

Resources: TS1, YS, KS, NS, NYF, TS2

Data curation: TS1, YS

Writing – original draft: TS1, YS, YW, TS2

Writing – review & editing: TS1, YS, YW, MT, KS, YO, HM, NS, NYF, KO, TS3, TS2

Visualization: TS1

Supervision: YS, TS

Project administration: TS1, YS, TS2

Funding acquisition: KS, MY, TM

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Figures

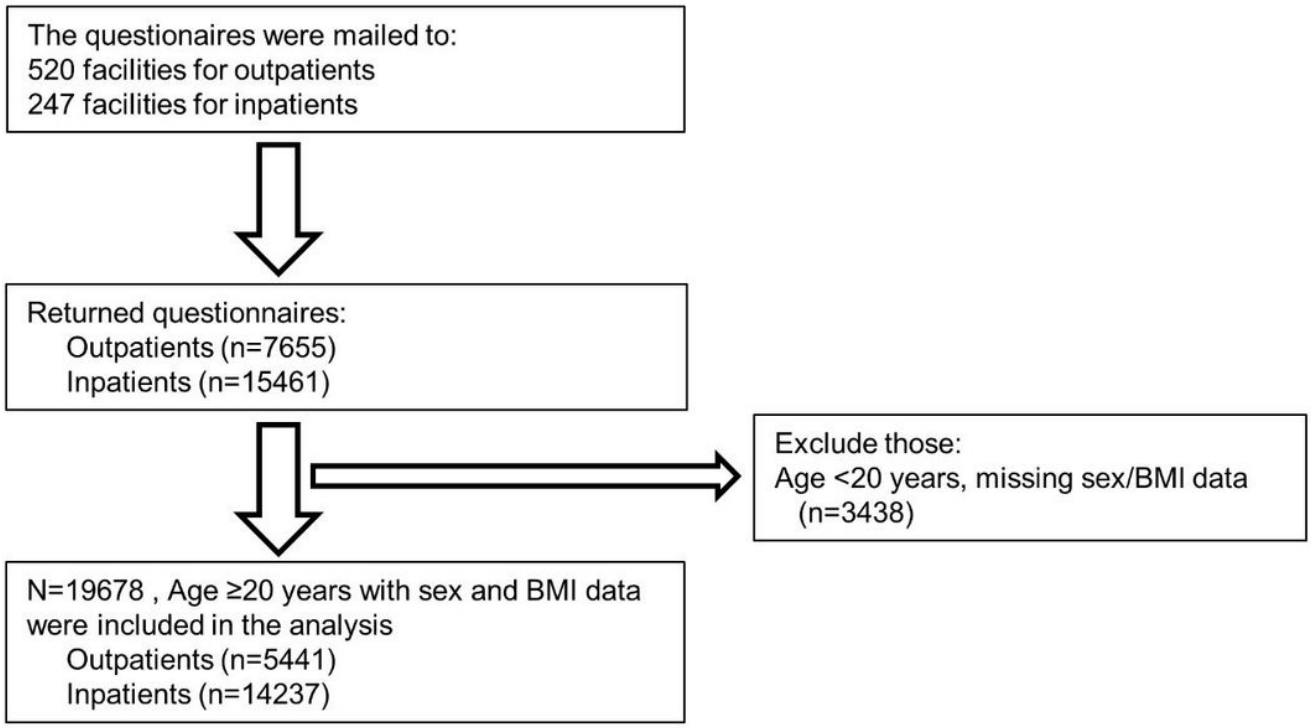

Figure 1

Flow diagram of participant inclusion and exclusion