



## Survey on the management of physical risks induced by psychotropic agents in Japan

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### ABSTRACT

**Purpose:** Several treatment guidelines recommend periodic monitoring (i.e., once per year) of side-effects in patients taking psychotropic agents. However, the actual frequency of side-effects monitoring is unclear. Accordingly, we investigated the frequency of side-effects monitoring in Japanese patients.

**Methods:** We used the national insurance claim database to identify patients prescribed with psychotropic agents for more than 3 years. Among these patients, we identified those who had undergone electrocardiogram, liver or kidney function, serum lipid level, blood glucose level, and serum prolactin level assessment at least once per year for 3 years of treatment. We classified these patients into adults and children and compared the frequency of each examination between the two groups.

**Results:** A total of 8822 patients were included in the analysis. The frequencies of electrocardiogram, blood glucose level, serum lipid level, liver or kidney function, and serum prolactin level monitoring were <0.1%, 16.4%, 16.5%, 20.6%, and 1.1%, respectively. In patients taking antipsychotic agents, children were significantly less frequently screened for blood glucose level, serum lipid level, and liver or kidney function compared with adults ( $p < 0.01$ ).

**Conclusion:** Our data suggest that the frequency of side-effects monitoring in persistent users of psychotropic agents in Japan was lower than that recommended by several guidelines.

**Keywords:** *monitoring, pharmacotherapy, psychotropic agents, retrospective study, side-effect*

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### INTRODUCTION

New concerns regarding the physical risks of second-generation antipsychotics (SGAs) such as electrocardiogram QT prolongation [1], weight gain, hyperglycemia, hyperlipidemia, and hyperprolactinemia [2] have surfaced in recent years. Similarly, a number of first-generation antipsychotics and antidepressants have been associated with

electrocardiogram abnormalities [3-5], weight gain, and/or hyperglycemia [6]. The rate of antipsychotic polypharmacy, which has been associated with an increased risk of side-effects, is known to be high in Japan [7].

Previously, we reported that atomoxetine produced a prolonged QT interval in a dose-dependent manner in female patients [8]. Some treatment guide-

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lines [9, 10] recommend that when initiating or prescribing psychotropic agents, patients should be screened periodically (i.e., once per year) for abnormalities in electrocardiograms, blood glucose levels, and serum lipid levels, in consideration of the various physical risks. Some studies conducted in the United States [11, 12] have reported that metabolic screening rates in patients taking SGAs were lower than recommended. In addition, children are likely to reject painful examination, and then it is possible that periodical blood sampling can be difficult. Therefore, potential risk such as electrocardiogram or metabolic abnormalities in children may be overlooked. The actual frequency of side-effects monitoring in patients taking psychotropic agents and side-effects induced by psychotropic agents in children in the developmental stage remain unclear.

We postulated that side-effects monitoring in Japan was less frequent than the recommendation, and therefore investigated the actual frequency of side-effects monitoring and compared the frequency between children and adults using Japanese national insurance claim data.

## METHODS

### *Database*

In this study, we utilized the health insurance claims database from the Japan Medical Data Center (JMDC), which contains medical data for patients with Employee Health Insurance. This database includes information on approximately 1.5 million employees and their family members aged <75 years who were enrolled between January and May, 2014. The database is composed of inpatient, outpatient, and pharmacy claims, and includes basic demographics (age and gender), International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) [13], diagnosis codes, prescribed drugs, and medical examinations. Drugs were classified according to the Anatomical Therapeutic Chemical Classification System codes (ATC codes).

### *Sample selection*

We identified 33270 patients who were prescribed psychotropic agents including antipsychotics (ATC codes; N05A-), antidepressants (ATC codes; N06A-), or the attention-deficit/hyperactivity disorder (ADHD) medications: methylphenidate hydrochloride (ATC codes; N06B-) and atomoxetine hydrochloride (ATC codes; N07X-), between January 1

and May 31, 2014.

We excluded patients aged <6 years (N = 100); patients with diabetes mellitus (ICD code: E10-E14), dyslipidemia (ICD codes: E78), or arrhythmia (ICD codes: I44) at that time (N = 7396); and patients who had been prescribed psychotropic agents fewer than four times per year for the previous 3 years (N = 16952). This study was approved by the Ethics Committee of Niigata University.

### *Monitoring parameters*

We identified patients who had undergone the following examinations at least once per year for the previous 3 years: (1) electrocardiogram, (2) liver or kidney function, (3) serum lipid level, (4) blood glucose level, and (5) serum prolactin level. The examination of liver or kidney function included lactate dehydrogenase, alanine transaminase, aspartate transaminase, gamma-glutamyl transpeptidase, blood urea nitrogen, and creatinine. The lipid test included free cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride. Serum prolactin level data were identified only in patients prescribed antipsychotics.

### *Comparison of monitoring rates*

We classified patients into two age groups (6-17 years and 18-74 years) for each category of drug (antipsychotics, antidepressants, and ADHD medications). We defined patients aged 6-17 years and 18-74 years as children and adults, respectively.

### *Statistical analysis*

We used a chi-square test to compare the rates of electrocardiogram, liver or kidney function, serum lipid level, blood glucose level, and serum prolactin level assessment between the two age groups. Analyses were performed using SPSS version 21.0 software (IBM SPSS Statistics, Armonk, NY, USA). Values of  $p < 0.05$  were considered statistically significant.

## RESULTS

A total of 8822 patients were included in the analysis. Table 1 shows the rates of the five types of examination in the two age groups for the three categories of drugs. A total of 2925, 6426, and 306 patients were receiving antipsychotics, antidepressants, and ADHD medications, respectively. Among these, 835 patients were prescribed multiple types of medicine, and were therefore included in multi-

**Table 1.** Number of patients who received monitoring examinations

	Antipsychotics			Antidepressants			ADHD medications		
	Children N=272	Adults N=2653	P	Children N=75	Adults N=6351	P	Children N=264	Adults N=42	P
Monitoring parameters									
Electrocardiogram	0 (0.0)	1 (<0.1)	n.s.	0 (0.0)	1 (<0.1)	n.s.	0 (0.0)	0 (0.0)	n.s.
Blood glucose level	19 (7.0)	433 (16.3)	<0.01	3 (4.0)	547 (8.6)	n.s.	4 (1.5)	1 (2.4)	n.s.
Serum lipid level	14 (5.1)	436 (16.4)	<0.01	3 (4.0)	575 (9.1)	n.s.	2 (0.8)	1 (2.4)	n.s.
Liver/Kidney function test	27 (9.9)	545 (20.5)	<0.01	5 (6.7)	741 (11.7)	n.s.	16 (6.1)	3 (7.1)	n.s.
Serum prolactin level	1 (0.4)	28 (1.1)	n.s.	-	-		-	-	

$\chi^2$  tests were conducted to compare the rate of each examination in the two age groups.

Data represents the number of patients who received monitoring (%).

Children, patients aged 6 to 17 years; Adults, patients aged 18 to 74 years, n.s., not significant.

ple groups simultaneously.

In the antipsychotics group, children were significantly less frequently screened for blood glucose level, serum lipid level, and liver or kidney function compared with adults ( $p < 0.01$ ). We found no significant differences in the rates of each type of examination for the two age groups, regardless of whether they were taking antidepressants or ADHD medications.

## DISCUSSION

In this study, most of the patients taking psychotropic agents received less than one electrocardiogram per year. Additionally, the rates of once-yearly examinations of blood glucose level, serum lipid level, liver or kidney function, and serum prolactin level in patients taking psychotropic agents were less than a quarter. Children received fewer examinations compared with adults. Furthermore, inpatients, who are likely to be screened more frequently than outpatients, were included in this study. The ratio of outpatients to inpatients was unclear, but the frequency of side-effects monitoring in outpatients might be much lower the overall frequency described in our study.

The Japanese Society of Psychiatry and Neurology recommends electrocardiogram monitoring at baseline and upon dosage change in patients taking psychotropic agents which may affect the QT interval [10]. However, the findings of the present study indicate that electrocardiogram monitoring of these patients is not sufficiently frequent.

The use of SGAs is associated with metabolic side-effects. Therefore, the Maudsley Prescribing Guide-

lines in Psychiatry, 12th Edition [9] recommends monitoring blood glucose and serum lipid levels at periodic intervals in patients taking antipsychotics. An American study [11] of metabolic screening reported annual testing rates of 38% for blood glucose level and 23% for serum lipid level among 3140 adult outpatients treated with SGAs. However, a study in Japan showed that blood glucose screening and serum lipid assessment rates were 6.4% and 8.0% per month, respectively, among 499 psychiatric outpatients treated with SGAs [14]. In the present study, glucose screening and lipid testing rates were lower than in previous studies. However, previous studies included only patients taking SGAs, which are associated with metabolic side-effects. Additionally, the sample size in the Japanese study was smaller than that in the present study, which may have affected the results.

To our knowledge, no study to date has evaluated whether the monitoring of liver or kidney function in patients taking psychotropic agents is appropriate. In Japan, once-yearly examinations of liver and kidney function are recommended in patients taking psychotropic agents. However, the results of the present study indicate that appropriate liver or kidney function monitoring was not performed in the patient population evaluated.

The Maudsley Guidelines recommend that serum prolactin level is monitored once a year in patients taking antipsychotic agents. However, our findings indicate that appropriate serum prolactin monitoring has not been performed.

Our data also indicate that children tend to undergo fewer monitoring examinations than adults. The monitoring of blood glucose and serum lipid levels

is recommended once every 6 months in children taking SGAs [2]. However, the screening rates of blood glucose and serum lipid levels in the present study were lower than recommended. This may be explained by the following reasons: (a) in general, children tend to be less likely to voluntarily undergo painful examinations, meaning that periodical blood sampling can be difficult in this population; and (b) metabolic parameters might be monitored less frequently in children because complications are less frequent than in adults. However, because of potential risks such as congenital long QT interval syndrome [15], obesity [16], or diabetes mellitus [17], appropriate screening and periodic monitoring are necessary in children taking SGAs.

There are several limitations to this study. First, we did not have access to data on the ratio of outpatients to inpatients in our sample. Second, significantly fewer children than adults were included. Third, we used national insurance claim data, which do not include information on polypharmacy, high-dose medications, detailed dosage of each drug or anticholinergic drug combinations, accurate treatment compliance, detailed age distribution, body weight, height, waist circumference, total treatment period, accurate diagnoses, socioeconomics or family history. The lack of these data may have impacted the results of the present study.

## CONCLUSION

Our data suggest that the frequency of side-effects monitoring in persistent users of psychotropic agents in Japan is lower than recommended in several guidelines. To perform appropriate monitoring of side-effects, it is necessary to establish and adhere to unified detailed guidelines regarding side-effects monitoring.

## CONFLICT OF INTEREST

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