Note

Investigation of the Real-World Situation and Risk Factors Associated with Olanzapine Prescribed to Diabetes Patients by Using a Japanese Claims Database

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Olanzapine is effective for schizophrenia management; however, it is contraindicated in diabetes patients. In addition, olanzapine is useful for treating nausea and vomiting, such as in the case of chemotherapy-induced nausea and vomiting (CINV). Therefore, we hypothesized that the contraindicated prescription of olanzapine likely occurs among cancer patients with diabetes, especially by non-psychiatric physicians. Hence, we conducted a nationwide survey to elucidate the situation of such contraindicated prescriptions and the associated risk factors. We extracted the data of patients who were newly prescribed olanzapine between April 2015 and March 2017 from the health insurance claims database developed by JMDC, Inc., Tokyo. The patients who were prescribed contraindicated olanzapine were defined as those who were prescribed olanzapine after a diagnosis of diabetes and diabetes drug prescription. In all, the data of 7181 patients were analyzed. We evaluated the proportion of diabetes patients who were prescribed contraindicated olanzapine from among those who were prescribed olanzapine. Furthermore, we investigated the background of patients who were prescribed olanzapine for information such as olanzapine prescribers and history of cancer chemotherapy. In all, 100 diabetes patients (1.39%) were prescribed olanzapine. In these patients, the frequency of olanzapine prescription was higher by non-psychiatry/neurology physicians than by psychiatry/neurology physicians (3.25 and 0.85%, respectively). Additionally, all olanzapine prescriptions in cancer chemotherapy-treated diabetes patients were issued by non-psychiatry/neurology physicians. Thus, our study revealed there were diabetes patients who were prescribed olanzapine. Additionally, olanzapine for CINV management was more likely to be a contraindicated prescription.

Key words contraindication; diabetes; olanzapine; insurance claim

INTRODUCTION

In 2017, the number of diabetes patients in Japan was approximately 3.3 million.¹⁾ Several drugs increase blood sugar levels and cause diabetes,^{2–4)} which is indicated on their package inserts in Japan.^{5–7)} Olanzapine is effective for managing schizophrenia and bipolar disorder.⁵⁾ However, its use leads to hyperglycemia and diabetes and even weight gain by inhibiting 5-hydroxytryptamine 2C receptors.^{5,8)} It induces proinsulin misfolding that subsequently results in decreased normal proinsulin levels.⁹⁾ Olanzapine induced diabetic coma, hyperglycemia, and diabetic ketoacidosis in nine patients in Japan, of whom two died.¹⁰⁾ Therefore, it is contraindicated for diabetes patients, even for those who previously had diabetes, in Japan; furthermore, its package insert in Japan contains this information.⁵⁾ Olanzapine-induced hyperglycemia and diabetic ketoacidosis have also been reported in other countries.^{11,12)}

Olanzapine is useful for treating nausea and vomiting.^{13,14)} As such, it is also used for managing chemotherapy-induced nausea and vomiting (CINV)¹³⁾ and was indicated for treating CINV in Japan in 2017. Given this background, we hypothesized that compared to psychiatric physicians, more non-psychiatric

physicians prescribe olanzapine as an antiemetic agent. The prevalence of diabetes and cancer is higher among older adults than among younger individuals. The prevalence of these conditions is high in Japan, being an aging society.^{15,16)} Therefore, a countermeasure is necessary to avoid drug-disease interactions because prescription of contraindicated olanzapine to diabetes patients will likely increase. However, the real-world olanzapine use in diabetes patients in Japan remains unclear. Medical costs are lower in Japan than in other countries,^{17,18)} because of the country's public health insurance system. Therefore, the use of over-the-counter medications is low in Japan.¹⁹⁾ Considering this scenario, investigation of drug prescription status using insurance claims data could reveal the actual drug use situation. Hence, this study aimed to elucidate the current situation of olanzapine use in diabetes patients, including the clinical departments that prescribed the drug, using a Japanese health insurance claims database. Furthermore, we investigated the factors for olanzapine's contraindicated prescription.

MATERIALS AND METHODS

Data Sources Patient data were extracted from a nation-

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wide health insurance claims database developed by JMDC Inc., Tokyo, Japan.²⁰⁾ It contains completely anonymized records of approximately 5.6 million insured persons from January 2005 to June 2017 (as of June 2018) who were primarily employed individuals and their family members under the age of 75 years, accounting for approximately 5% of Japan's population. The records comprise information such as patient age and sex and prescribed and/or dispensed drug names, doses, and prescription duration.

Study Population and Data Collection Patients who were newly prescribed olanzapine from April 2015 to March 2017 (observation period) were selected. To detect new olanzapine prescriptions, data were screened from 2 years before the study period, *i.e.*, April 2013–March 2015 (screening period). Olanzapine was identified using the Anatomical Therapeutic Chemical (ATC) system, code N05AH03. Diabetes patients were defined as those diagnosed with diabetes and prescribed diabetes drugs during April 2013–March 2017. A diagnosis of diabetes was made using the International Classification of Diseases, 10th Revision (ICD-10), code E10–E14. Diabetes drugs were identified using the following ATC system codes: insulin preparation, A10C; sulfonylurea, A10H; biguanide, A10J; glitazone, A10K; α -glucosidase inhibitor, A10L; glinide, A10M; dipeptidyl peptidase-4 (DPP-4) inhibitor, A10N; sodium glucose cotransporter 2 inhibitor, A10P; glucagon-like peptide-1 agonist, A10S; and other diabetes drugs, A10X. Patients who were prescribed contraindicated olanzapine were defined as those who were prescribed olanzapine after a diabetes diagnosis and diabetes drug prescription. Patients were divided into those with past and current diabetes drug use according to the following criteria: (1) current diabetes drug use, overlap of olanzapine and diabetes drug use and (2) past diabetes drug use, olanzapine started after the use of diabetes drugs ended (even if it was started 1 d after terminating diabetes treatment).

Clinical departments and institutions that prescribed olanzapine were identified based on text codes and institution IDs. We divided clinical departments into psychiatry/neurology and non-psychiatry/neurology because we thought that olanzapine prescribed by non-psychiatry/neurology was likely contraindicated. Data on anticancer agents and opioid analgesics (ATC codes: L01–L03 and N02A, respectively) and radiation treatment were extracted from January 2015 to the day until olanzapine treatment started. Radiation treatment was detected according to the text code from procedure data. Moreover, data regarding patient's age at the time of olanzapine prescription and sex (male/female) and prescription period were collected. The prescription period was calculated as the total number of prescription days. If the period from the prescription end date to the next prescription start date exceeded 1 week, the treatment was considered terminated. Patients who were prescribed olanzapine within 28 or 56 d of cancer chemotherapy initiation were defined as cancer chemotherapy-treated patients. Additionally, patients treated with opioid analgesics and/or radiation treatment referred to those who were prescribed olanzapine within 28 d of the initiation of opioid analgesics and/or radiation treatment.

Outcomes As an endpoint, the proportion of diabetes patients who were prescribed olanzapine was determined. The procedure for detecting contraindicated olanzapine prescription to diabetes patients was as follows: (1) detection of the first olanzapine prescription between April 2015 and March 2017 (used as the denominator), (2) extraction of diabetes drugs between April 2013 and March 2017, and (3) detection of olanzapine prescription after the use of diabetes drugs (used as the numerator). Moreover, we evaluated the background of diabetes patients with olanzapine prescription. We determined the number of patients with past and current diabetes drug use and evaluated the factors associated with contraindicated prescriptions such as olanzapine prescribers and history of cancer

Fig. 1. Flowchart of Patients Included in the Study

Diabetes patients were defined as those who were diagnosed with diabetes and prescribed diabetes drugs between April 2013 and March 2017. Diabetes patients who were prescribed contraindicated olanzapine were defined as those who were diagnosed with diabetes and prescribed olanzapine after receiving diabetes drugs.

chemotherapy.

Data Analyses The Mann–Whitney *U* test was used to compare continuous variables (all continuous variables had non-normal distributions). Pearson's chi-square or Fisher's exact test was used to compare categorical variables. Fisher's exact test was used when more than 20% of cells had an expected frequency of 5; *p*-values ≤ 0.05 were considered statistically significant.²¹⁾ JMP 14® (SAS Institute Inc., Cary, NC, U.S.A.) was used for all statistical analyses.

Ethics Approval This study was approved by the institutional review committee of the Faculty of Pharmaceutical Sciences, Hokkaido University. The requirement of informed consent was waived because the data were anonymized.

RESULTS

Number and Proportion of Contraindicated Prescriptions and Patient Characteristics Of the 11296 patients prescribed olanzapine between April 2013 and March 2017, 7181 had not been prescribed olanzapine between April 2013 and March 2015 (screening period) (Fig. 1). In total, 100 (1.39%) diabetes patients received contraindicated olanzapine. Among these, 10 were diagnosed with type 1 diabetes (ICD code: E10). Age and the olanzapine prescription period significantly differed between the two groups (Table 1). Sex distribution was balanced between the groups. Insulin preparations accounted for the highest proportion of diabetes drugs among those with contraindicated prescription, followed by DPP-4 inhibitors and biguanides. The proportion of other diabetes drugs was small ($<10\%$) (Table 2).

Risk Factors Associated with Contraindicated Prescriptions The numbers of patients with current and past diabetes

drug use who were prescribed contraindicated olanzapine were 31 and 69, respectively (Fig. 2A). Non-psychiatry/neurology physicians issued more olanzapine prescriptions to diabe-

Table 1. Characteristic of the Study Patients

Contraindications	Yes (<i>n</i> = 100)	No (<i>n</i> = 7081)	<i>p</i> -Value
Age (years), median (IQR)	53 (43–60)	40 (29–49)	$<0.001^b$ *
Male patients, <i>n</i> (%)	50 (50)	3499 (49.41)	0.9073 ^{a)}
Female patients, <i>n</i> (%)	50 (50)	3582 (50.59)	
Prescription period of olanzapine, median (IQR)	25 (7–73)	64 (20–241)	$<0.001^b$ *

IQR: inter-quartile range, *a)* Chi-squared test, *b)* Mann–Whitney *U* test. **p*-Values ≤ 0.05 were considered statistically significant.

Table 2. Characteristics of Patient Prescribed Diabetes Drugs

Diabetes drugs (ATC code), <i>n</i> (%)	
Insulin preparation (A10C)	54 (31.0)
Sulfonylurea (A10H)	12 (6.90)
Biguanide (A10J)	28 (16.1)
Glitazone (A10K)	15 (8.62)
α -Glucosidase inhibitor (A10L)	17 (9.77)
Glinide (A10M)	2 (1.15)
Dipeptidyl peptidase-4 inhibitor (A10N)	42 (24.1)
Sodium glucose cotransporter inhibitor (A10P)	0 (0)
Glucagon-like peptide-1 agonist (A10S)	4 (2.30)
Other diabetes drugs (A10X)	0 (0)

ATC: Anatomical Therapeutic Chemical. Some patients received multiple diabetes drug prescriptions. This table shows the proportion of each category of diabetes drug prescriptions.

Fig. 2. Risk Factors Associated with Olanzapine Prescription

(A) The number of patients with past and current diabetes drug use who were prescribed contraindicated olanzapine. (B) Proportions of psychiatry/neurology and non-psychiatry/neurology physicians who prescribed olanzapine to diabetes patients and the number and proportion of diabetes patients who were prescribed olanzapine with or without cancer chemotherapy. Past diabetes drug use: olanzapine was started after the end of diabetes drug treatment. Current diabetes drug use: the prescription period of olanzapine and diabetes drugs overlapped. With cancer chemotherapy: olanzapine prescribed within 28 d of initiation of cancer chemotherapy. Without cancer chemotherapy: no history of cancer chemotherapy. **p*-Values ≤ 0.05 were considered significant. Variables were compared using Pearson's chi-square test.

Table 3. Details of the Departments That Prescribed Olanzapine

Departments	Total	Contraindications	
		<i>n</i>	%
Psychiatry/Neurology	5552	47	0.85
Internal medicine	1232	42	3.4
Other departments	274	11	4.0
Pediatrics	54	0	0
Neurosurgery	15	0	0
Surgery	10	0	0
Orthopedics	7	0	0
Otorhinolaryngology	6	0	0
Dermatology	5	0	0
Obstetrics and gynecology	3	0	0
Urology	2	0	0
Ophthalmology	1	0	0
Radiology	1	0	0
Anesthesiology	1	0	0
Unknown	18	0	0

tes patients than did psychiatry/neurology physicians (3.25 and 0.85%, respectively) (Fig. 2B). Barring psychiatry/neurology departments, only internal medicine and other departments prescribed contraindicated olanzapine use for diabetes patients (Table 3). Additionally, 10 diabetes patients were prescribed olanzapine within 28 d of cancer chemotherapy initiation (Fig. 2B). Within 56 d, the number of patients was 16. The numbers of diabetes patients who were prescribed olanzapine within 28 d of the initiation of radiation treatment and opioids analgesics were 7 and 16, respectively. Some patients received multiple treatments. In all cases, contraindicated olanzapine was prescribed by non-psychiatry/neurology physicians.

DISCUSSION

Olanzapine causes decreased insulin secretion and insulin resistance^{8,9}; thus, its use may hinder diabetes treatment, negatively affecting diabetes patients. Hence, it is important to investigate the status of olanzapine prescription to diabetes patients. Here, we elucidated the current situation regarding olanzapine use, diabetes, and the factors associated with contraindicated olanzapine prescriptions for diabetes patients using insurance claims data. We found that 1.39% of the patients who had been prescribed olanzapine had diabetes (Fig. 1). Furthermore, olanzapine is prescribed to diabetes patients although it is contraindicated in these patients in Japan and this information is included in the drug's package insert in the country. Age significantly differed between the two groups because diabetes patients are generally older (Table 1). According to the olanzapine's Japanese package insert, the drug is contraindicated even in past diabetes patients. The number of patients with past diabetes drug use was higher than that of patients with current diabetes drug use (Fig. 2A).

Patients with past diabetes drug use were likely to be prescribed olanzapine by physicians and pharmacists because of lack of patients' complete background data. In Europe and the United States, electronic health records (EHRs) and personal health records are used to centralize patient information.^{22,23} However, in Japan, the introduction of medical information technology has been delayed. A retrospective analysis based

on EHR-based alerts to deter concurrent prescription of opioids and benzodiazepines was conducted in the United States, which showed that benzodiazepine prescription decreased after EHR-based alerts were introduced.²⁴ Therefore, the introduction of medical information technology systems is necessary in Japan.

Olanzapine is used in patients with schizophrenia and bipolar disorder and for managing CINV.⁵ Thus, the drug may be prescribed more by non-psychiatry/neurology physicians who are unaware about the risk of hyperglycemia. Therefore, we investigated the clinical departments that prescribed olanzapine and whether the patients were treated with cancer chemotherapy. Non-psychiatry/neurology physicians were more likely to prescribe olanzapine to diabetes patients than psychiatry/neurology physicians (Fig. 2B). Additionally, all olanzapine prescriptions for diabetes patients and those who had undergone cancer chemotherapy were issued by non-psychiatry/neurology physicians. We also investigated whether a history of radiation treatment or opioid analgesic use was a factor because they generally cause nausea and vomiting.^{25,26} We obtained similar results for radiation treatment and opioid analgesic use. Therefore, contraindicated olanzapine was likely to be prescribed for nausea and vomiting to diabetes patients. This hypothesis is also supported by the olanzapine prescription period being shorter in patients with contraindications (Table 1); this may be because olanzapine was prescribed as an anti-nausea drug. A previous study²⁷ on drug–drug interactions (DDIs) revealed that inappropriate prescriptions were caused by differences in clinical departments. However, we newly discovered that contraindicated olanzapine prescription was attributable to differences in the prescription purpose. Additionally, the period of olanzapine use for CINV is 4–6 d. However, the drug increased blood sugar levels in a few minutes in schizophrenia patients²⁸ and caused glucose intolerance for 10 d in healthy volunteers.²⁹ Thus, olanzapine prescription to diabetes patients is avoided regardless of the prescription period. Hence, we believe our study is meaningful.

Our study has several limitations. We used the JMDC claims database, which includes data limited to patients aged less than 75 years; thus, we could not evaluate elderly people who generally have multiple diseases.³⁰ However, our findings, such as patients with past diabetes drug use were more likely to be prescribed olanzapine than those with current diabetes drug use, is worth examining in the elderly in the future. Second, we could obtain patient data only from January 2005 to June 2017; therefore, we could not study the period after olanzapine was indicated for treating CINV. We need to study this using other databases to expand patient age and the period of research. Third, the codes of clinical departments and institutions are determined by the representative department of the hospital or clinic where the patient was treated and may not be the department where the patient was treated according to the JMDC claims database. Thus, the codes of clinical departments and institutions could not be validated. Fourth, diabetes was detected based on the diagnosis of diabetes and prescriptions of diabetes drugs, *i.e.*, we could not assess prediabetes and mild diabetes. To perform diabetes-related blood tests, doctors need to give the diagnosis of diabetes to calculate the medical fee; therefore, we excluded patients who were diagnosed only with diabetes. However, we

elucidated contraindicated prescriptions were observed even with this stringent definition. Finally, olanzapine prescription to diabetes patients might not be inappropriate. This means that there may be physicians who prescribe olanzapine to diabetes patients after discussing the risks and benefits of the prescription with pharmacists and diabetologists.

In summary, we elucidated the current situation regarding olanzapine prescription to diabetes patients and the associated risk factors. Contraindicated prescription may occur in Japan. Patients with past diabetes drug use were more likely to be prescribed olanzapine than those with current diabetes drug use. Non-psychiatrist physicians issue more contraindicated prescriptions; olanzapine use for CINV management results in more contraindicated prescriptions. We believe our findings are important to the medical field. Physicians who prescribe olanzapine must check patients' medical history, and pharmacists must pay attention to medical history and drugs used, especially when olanzapine is prescribed to cancer patients by non-psychiatrists.

Conflict of Interest The authors declare no conflict of interest.

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