Development and pharmacist-mediated use of tools for monitoring atypical antipsychotic-induced side effects related to blood glucose levels

Running title: Development of monitoring tool by pharmacists

Shunsuke Ishida[1], Kenshi Takechi[2*], Hiroshi Bando[1], Masaki Imanishi[1], Yoshito Zamami[1,3], Masayuki Chuma[2], Hiroaki Yanagawa[2], Yasushi Kirino[1], Toshimi Nakamura[1], Kazuhiko Teraoka[1], and Keisuke Ishizawa[1,3]

[1]Department of Pharmacy, Tokushima University Hospital, Tokushima 770-8503, Japan

[2]Clinical Trial Center for Developmental Therapeutics, Tokushima University Hospital, Kuramoto, Tokushima 770-8503, Japan

[3]Department of Clinical Pharmacology and Therapeutics, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima 770-8503, Japan

*Corresponding author: Kenshi Takechi

Address correspondence and reprint requests to K Takechi at the Clinical Trial Center for Developmental Therapeutics, Tokushima University Hospital, Kuramoto, Tokushima

770-8503, Japan; Tel: +81-88-633-9294; Fax: +81-88-633-9295

E-mail address: dph20010@s.okadai.jp (K. Takechi)

Keywords: atypical antipsychotics, clinical intervention, clinical value, monitoring, side effects

Key points

Drug side effects often cause serious outcomes. Hence, pharmacists need to monitor clinical parameters and side effects of drugs and collect information on clinical laboratory values, determine the appropriate test timing, and coordinate with doctors for further tests. Hence, we developed a side effect-monitoring tool and aimed to clarify the effect and efficiency of monitoring side effects by using the tool in patients taking atypical antipsychotics. The tool lessened the pharmacists' effort in performing the previously mentioned tasks. It enabled patients to undergo tests at appropriate times, allowed for easy monitoring of side effects, and shortened the pharmacist's work hours.

Abstract

Purpose: Drug side effects often lead to serious outcomes. Administration of second-generation antipsychotics has resulted in diabetic ketoacidosis and diabetic coma leading to death. Therefore, pharmacists are required to collect information on clinical test values, determine the appropriate test timing, and coordinate with doctors for further clinical laboratory orders, all of which are labor- and time-intensive tasks. In this study, we developed a side effect-monitoring tool and aimed to clarify the influence and efficiency of monitoring side effects by using the tool in patients taking atypical antipsychotics in whom it is necessary to check clinical test values such as blood sugar levels.

Methods: We extracted clinical test values for patients treated with second-generation antipsychotics from electronic medical records. The test values are automatically displayed in the side effect grade classification specified by CTCAE ver. 4.0. A database was constructed using scripts to provide alerts for the timing of clinical testing. The pharmacist used this tool to confirm clinical test values for patients taking medication and requested the physician to inspect orders based on the appropriate test timings.

Results: The management tool reduced the pharmacists' effort in collecting information on patients' prescription status and test values. It enabled patients to undergo tests at the appropriate time according to the progression of glucose metabolism and allowed for easy

monitoring of side effects.

Conclusion: The results suggested that regardless of pharmacists' experience or skill, the introduction of this tool enables centralization of side-effect monitoring and can contribute to proper drug use.

Introduction

Package inserts of ethical drugs recommend regular clinical laboratory tests such as liver function tests or renal function analyses. Furthermore, the Ministry of Health, Labour and Welfare (MHLW), Pharmaceuticals and Medical Devices Agency (PMDA), and pharmaceutical companies report very important drug safety information. These institutions provide this information to alert healthcare professionals because drugs with package inserts recommending clinical tests can have serious side effects. To avoid serious adverse reactions, it is important for pharmacists to inform physicians about the appropriate timings for clinical laboratory testing, and monitor patients receiving drug treatment. However, pharmacists face difficulties while performing these tasks. First, pharmacists need to spend a lot of time and effort in checking the drugs prescribed to patients and confirming patients' clinical laboratory test results. Because the number of clinical tests differs depending on the type of the drug and because inpatient pharmaceutical service has diversified along with an extension of its scope, pharmacists should cooperate with the physicians and respond to individualized medical care. Therefore, if pharmacists can develop management tools for monitoring side effects, they can determine the appropriate time for clinical laboratory tests and monitor patients effectively. In addition, we considered that the tool would lead to a reduction in labor and

enable sharing of information between healthcare professionals. We focused on monitoring side effects in patients who were prescribed second-generation antipsychotics (SGAs). SGAs (e.g., olanzapine, quetiapine, and aripiprazole) are advantageous, in that the likelihood of extrapyramidal symptoms is lesser than that associated with first-generation antipsychotics (FGAs). However, it has been reported that SGAs induce weight gain, hyperlipidemia, and type 2 diabetes. [1] A meta-analysis comparing the risk of diabetes associated with antipsychotic drugs revealed a significantly higher risk of diabetes in SGA-treated patients than in FGA-treated patients. [2] Other studies have reported a higher risk of diabetes in younger people than in older people. [3] Therefore, we need to assess the development of diabetes in light of considering the vital prognosis and quality of life of patients with schizophrenia. Previous literature including that published by the American Diabetes Society, [4] the monitoring protocol to be followed during the administration of antipsychotic drugs described in the 12th edition by the American Psychiatric Society, [5] literature published by the Belgian Consensus Group of the United Kingdom, [6] and a review by Calkin et al., [7] clearly describes the frequency of blood glucose measurement. However, there is no consensus and the frequency of clinical laboratory testing differs worldwide. The guidelines for Pharmacological Therapy of Schizophrenia by the Japanese Society of Neuropsychopharmacology do not specify the

frequency of clinical laboratory tests for monitoring blood glucose levels, despite reports that SGA administration may lead to death. Kusumi et al. proposed guidelines for monitoring blood glucose levels in patients with schizophrenia based on collaboration between diabetes specialists and psychiatrists. [8] This guidance is a rare protocol that recommends changes in the frequency of monitoring in response to the progression of glucose metabolism disorders, and thus may be very useful for preventing glycolipid metabolism disorders.

On the basis of the above-mentioned monitoring protocol, we aimed to develop a management tool that would allow easy determination of the period for which antipsychotic drug administration is necessary and monitoring of patients' clinical laboratory findings. In addition, we aimed to determine the effectiveness of the management tool.

Methods

Ethical approval of the study protocol

This study was performed in accordance with the ethical guidelines of the Japanese government and was approved by the Ethics Committee of Tokushima University Hospital (approval number: 2897).

Research data and tool for monitoring the development of side effects

It has been established that periodic clinical testing is required in cases in which atypical antipsychotic drugs such as olanzapine, quetiapine, and aripiprazole are used. Patients with psychiatric disorders enrolled at Tokushima University Hospital between May 2015 and April 2017 and prescribed antipsychotic drugs were included. Based on the blood glucose monitoring guidance, a protocol that could be used by pharmacists at our hospital to request clinical laboratory orders was established. In this study, the hospital has two pharmacists with a hospital experience of 2 to 5 years in a ward. We have developed a monitoring tool incorporating this protocol using database software. Data Warehouse was used to capture the clinical laboratory values of patients receiving atypical antipsychotic drugs. On the basis of the appropriate timing of inspection determined using the management tool, the pharmacist requested doctors for clinical laboratory orders (Fig. 1). The rate and timing of clinical laboratory tests before and after the introduction of the management tool were compared and evaluated. Blood glucose levels were categorized as fasting blood glucose levels and casual blood glucose levels. Fasting blood glucose levels were determined based on the criteria of the Japan Diabetes Society (normal: less than 110 mg/dL, borderline: 110-125 mg/dL, and strongly suspected diabetes: more than 126 mg/dL). On the other hand, casual blood glucose levels were determined based on

the criteria of the Guideline for the Treatment for Diabetes in Japan 2016 (normal: less than 140 mg/dL, borderline: 140-179 mg/dL, and strongly suspected diabetes: more than 180 mg/dL). Patients who belonged to the "borderline" or "strongly suspected diabetes" categories were those in whom the corresponding blood glucose levels were reached at once during administration. Hemoglobin A1c (HbA1c) was defined as follows by using international standard values (National Glycohemoglobin Standardization Program [NGSP]): normal; less than 6.0%, borderline: 6.0 to 6.5%, strongly suspected diabetes: more than 6.5%.

Analysis

The data are shown as the means and standard deviation. This study was performed at Psychiatric Department of Tokushima University Hospital using data from electronic medical records dated between May 2016 and April 2017. We excluded the medical records of patients who were administered the drugs for fewer than 7 days. A total of 148 patients were included in the study. According to the protocol prepared, the pharmacist asked the doctor to measure fasting blood glucose levels; in cases in which a laboratory order was entered into the system within 10 days after drug administration, the monitoring order was set and monitoring was performed. A p value of <0.05 was considered

significant.

Determination of the rate of clinical laboratory tests before and after the introduction of the management tool

In each case before and after the introduction of the management tool, we calculated that the number of cases in which clinical laboratory tests that the pharmacist asked the doctor for performing the clinical tests, and it performed at the appropriate time divided by the total number of clinical laboratory tests in all patients prescribed atypical antipsychotics.

The statistical significance of the differences resulting from comparisons was evaluated using the $\chi 2$ test. The survey period extended from May 2015 to April 2016 before the introduction of the management tool. The management tool was used from May 2016 to April 2017.

Determination of side effect-monitoring time

The time for monitoring side effects was defined as the time required to identify patients receiving atypical antipsychotics and to extract clinical laboratory values for patients identified both before and after the introduction of the management tool, and in

individual patients, the evaluation of the drug administration or the appropriate timing of the clinical examination using Welch t-test. The survey period extended from August 2015 to October 2015 before the introduction of the management tool. The management tool was used from May 2016 to July 2016.

Results

3-1. Administrative tools

The developed management tool could be used to identify patients according to the time when antipsychotic drug treatment was started for the patients. To confirm if the patients who need medication, the tool alerted appropriately in cases of patients aged over 65 years and for whom caution was needed. Whether careful administration was required was determined based on the information in package inserts and alerts were set accordingly. The number of days of administration from the start date of drug administration to the present was determined for each patient. In the evaluation of test values, the most recent glucose and HbA1c levels, date of measurement, and classification by values were indicated. If the classification of diabetes was normal "blue character", the borderline was "yellow character", and if diabetes was strongly suspected, it was colored by "red character". When viewing detailed data, if the test value is higher than

the standard value specified in the hospital "red", if the value is lower than the standard value "blue character", and normal values were indicated in black words. In addition, the tool allowed identification of the grade of clinical laboratory values based on CTCAEv 4.0. The tool automatically displayed data alerts by incorporating prescription data and laboratory values in the database software. As a result, it was possible to easily extract the necessary information, and the tool enabled monitoring of side effects uniformly regardless of the pharmacist’s experience or skill.

3-2. Clinical effects of seamless interventions by pharmacists.

During monitoring using the management tool, there were 10 prescriptions. The pharmacist was able to monitor side effects of 25 patients on average every month. The total number of requests for inspection was 35. The pharmacist asked the doctor to request the test order, and the examination was performed in 81.3% of cases (Fig. 2). There were two main reasons why an inspection was not performed in approximately 19% of the cases: a patient’s sudden discharge after receiving treatment, leading to a cancellation of the examination; and examination deemed unnecessary by the doctor after being consulted by the pharmacist. Before administration of antipsychotic drugs, two patients were diagnosed as "borderline" or "suspected diabetes mellitus". However, both patients

showed a slight improvement in the test values and were not diagnosed with diabetes. During the administration of antipsychotic drugs, one patient was diagnosed as "borderline" or "Be suspected of diabetes mellitus." However, the patient showed an improvement in the test values without any further worsening of the condition.

Further, the execution rate of clinical test before and after the introduction of the administration tool was examined. In the unintroduced group, the rate of test execution was 80% (106/132); in contrast, the test execution rate in the introduction group was 91% (130/143) ($P < 0.05$; Fig. 3). The execution rate before and after the introduction of the management tool for each atypical antipsychotic drug was compared. The results showed an increase in the rate of tests performed in quetiapine- and aripiprazole-treated patients; however, the increase was not significant. For olanzapine, the rate of testing significantly increased from 75.0% (27/36) to 92% (45/49) ($P < 0.05$; Fig. 4). In addition, the time required for interventions such as checking of the test value and contraindication before and after the introduction of the management tool was determined in order to analyze the efficiency of the side effect-monitoring operation by the pharmacist’s intervention. Before the introduction of the management tool, the business hours were 16.9 (minutes/day) while the duration was 2.8 minutes/day after the tool was introduced, indicating a significant shortening of work hours ($P < 0.05$; Fig. 5).

Discussion

Thus far, few studies have been conducted by pharmacists for the purpose of improving the effectiveness of side effect-monitoring operations in anticipation of personalized medical care. [9, 10] Many medical workers are concerned about drug package insert that do not describe the frequency of clinical testing. In this study, cooperation between ward pharmacists and pharmacists in charge of drug information could prevent serious adverse reactions and facilitate more efficient operations. The tool displayed the latest blood glucose and HbA1c levels simultaneously. The most recent test date, risk classification by blood glucose levels (normal, borderline, or diabetes mellitus), and appropriate timing for testing for each patient were determined using the management tool. As an intervention method, a management tool was developed using a protocol that considers the dosing days and clinical parameter values associated with the drug.[4)] Before the prescription of antipsychotic drugs, the pharmacist started the intervention using this tool. After administration, the pharmacist asked doctors to test the blood glucose level according to the previous test values and days of administration and continued to intervene continuously until the patient was discharged. By adopting this new approach, the pharmacist and doctor have a better understanding of the appropriate timing for antipsychotic drug administration. As a result of comparing before and after introducing

the management tool, the implementation rate after introduction was high. By providing information to physicians to allow feedback to doctors and to avoid the occurrence of diabetes, it is considered that medical workers have been able to have a high awareness of proper use with drug treatment. By using this intervention method, patients who were suspected to have diabetes before and after the administration of antipsychotic drugs achieved remission, and no diabetes mellitus was observed. Conducting clinical tests at appropriate times determined using the tool, allowed the identification of patients with hyperglycemia during drug administration. It has been suggested that the use of the intervention with the tool contributes to early prevention of serious adverse reactions by leading to measures such as preparation of a report to help avoid adverse drug reactions. Continued intervention led to an increase in the rate of inspection orders.

Pharmacists actively intervene in the monitoring of side effects, and early avoidance of serious adverse reactions may shorten hospital stay. [11, 12] However, in this study, the intervention did not shorten hospital stay. The monitoring of adverse reactions with clinical values is performed for long periods during drug administration. It is difficult to confirm whether the duration of hospitalization in patients with psychiatric disorders has been shortened because the time to adapt to the environment gradually increases. For this reason, antipsychotic drugs were used properly, but the duration of hospitalization for

schizophrenia and depressed patients was not shortened. With regard to interventions by pharmacists before and after the administration of antipsychotic drugs, the number of cases which the pharmacist requested was high after the administration of aripiprazole and quetiapine. In these cases, the doctor voluntarily inputs the test order before drug administration and confirms whether drug administration should be started. However, because it was difficult to determine the proper timing of individual examination of the patients after drug administration, it was indicated that the number of cases requested by pharmacists was high. The introduction of the management tool significantly shortened the time required for monitoring side effects by checking clinical values. Prior to the introduction of the tool, pharmacists searched the electronic record of each patient and spent time checking clinical values. However, after the introduction of the tool, pharmacists were able to easily determine patients' prescriptions and clinical test values to be careful, and the next test date, regardless of the number of patients. In this analysis, we evaluated a new pharmacist-mediated intervention method, but there are several limitations. First, it is necessary to refer to both the guidelines and data from clinical trials to determine the appropriate timing of clinical tests for drugs whose package inserts do not specify this information. Second, in the case of interstitial pneumonia, which is described under "Warnings" in the package insert, it is necessary to perform chest x-rays.

In our hospital, interstitial pneumonia with deterioration of respiratory symptoms is often primarily diagnosed using images. Furthermore, in the case of diagnostic imaging, we can understand the facts measured, but it is difficult to judge with this management tool whether the patient has interstitial pneumonia without clinical test values. Therefore, the examination value is used as a preliminary means for confirming it, the monitoring of side effects is difficult for such drugs. Thirdly, the hospitalization period is 2 to 3 months in cases of psychiatric disorders; therefore, if the test values are normal, the test frequency is once every 3 months. Therefore, monitoring is difficult if the next test period is after discharge from a hospital. If a pocketbook with such examination history is available, it would be possible to monitor side effects in each medical institution even after hospital transfers.

In this study, a pharmacist in the section of drug information cooperated with a pharmacist in the hospital ward about a new intervention method for pharmacists, and this tool was developed. This tool is a highly useful system that enables monitoring of the side effects and layouts that correspond to the needs of pharmacists in wards. Using this method, pharmacists were able to contact physicians easily to determine patients' blood glucose levels at the appropriate times and conduct tests for patients. Thus, it was possible to collect cases in which test values were abnormal before and after drug administration,

because of which severe diabetes mellitus did not develop. In addition, pharmacists were able to significantly reduce the time required for monitoring side effects by using the tool. Because the start date and the number of days of antipsychotic treatment vary across individuals, pharmacists spend a lot of time in checking the timing of a blood test and the appropriate scheduled date of the next test by using medical records. Therefore, we have a problem that the examination timing was delayed before using this tool. With the development of this tool, pharmacists will be able to easily get information about different blood tests for each patient, and sharing of this information with doctors may contribute to proper drug use. The findings of this study suggest that this management tool enables more secure medical care for patients. By utilizing the tool developed, all pharmacists would be able to provide the same quality of medical care for patients regardless of experience.

Conflicts of interest: The authors have no conflicts of interest to declare.

References

1. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009;373(9657):31-41.

2. Smith M, Hopkins D, Peveler RC, Holt RI, Woodward M, Ismail K. First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry* 2008;192(6):406-411. doi: 10.1192/bjp.bp.107.037184.

3. Hammerman A, Dreiher J, Klang SH, Munitz H, Cohen AD, Goldfracht M.. Antipsychotics and diabetes: an age-related association. *Ann Pharmacother* 2008;42(9):1316-1322. doi: 10.1345/aph.1L015.

4. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004;27(2):596-601.

5. Taylor DM, Paton C, Kapur S, *The Maudsley Prescribing Guidelines in Psychiatry*. CRC Press; 2015.

6. De Nayer A, De Hert M, Scheen A, Van Gaal L, Peuskens J, On Behalf Of The Consensus Group, De Nayer A, De Hert M, Scheen A, Van Gaal L, Peuskens J. Belgian

consensus on metabolic problems associated with atypical antipsychotics. *Int J Psychiatry Clin Pract* 2005;9(2):130-137. doi: 10.1080/13651500510018310.

7. Calkin CV, Gardner DM, Ransom T, Alda M. The relationship between bipolar disorder and type 2 diabetes: more than just co-morbid disorders. *Ann Med* 2013;45(2):171-181. doi: 10.3109/07853890.2012.687835.

8. Kusumi I, Ito K, Honda M, Hayashishita T, Uemura K, Hashimoto N, Murasaki M, Atsumi Y, Kadowaki T, Koyama T. Screening for diabetes using Japanese monitoring guidance in schizophrenia patients treated with second-generation antipsychotics: a cross-sectional study using baseline data. *Psychiatry Clin Neurosci* 2011;65(4):349-355. doi: 10.1111/j.1440-1819.2011.02218.x.

9. Correll CU, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA, Marcy P, Addington J, Estroff SE, Robinson J, Penn DL, Azrin S, Goldstein A, Severe J, Heinssen R, Kane JM. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry* 2014;71(12):1350-1363. doi: 10.1001/jamapsychiatry.2014.1314.

10. Kwan Y, Fernandes OA, Nagge JJ, Wong GG, Huh JH, Hurn DA, Pond GR, Bajcar JM. Pharmacist medication assessments in a surgical preadmission clinic. *Arch Intern Med* 2007;167(10):1034-1040. doi: 10.1001/archinte.167.10.1034.

11. Okada N, Fushitani S, Azuma M, Nakamura S, Nakamura T, Teraoka K, Watanabe H, Abe M, Kawazoe K, Ishizawa K. Clinical evaluation of pharmacist interventions in patients treated with anti-methicillin-resistant *Staphylococcus aureus* agents in a hematological ward. *Biol Pharm Bull* 2016;39(2):295-300. doi: 10.1248/bpb.b15-00774.

12. Meijvis SC, Hardeman H, Remmelts HH, Heijligenberg R, Rijkers GT, van Velzen-Blad H, Voorn GP, van de Garde EM, Endeman H, Grutters JC, Bos WJ, Biesma DH. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011;377(9782):2023-2030. doi: 10.1016/s0140-6736(11)60607-7.

Figure legends

Fig. 1 Development of management tools and flow of intervention by pharmacy

Fig. 2 Implementation rate of a clinical laboratory test requested by a pharmacist

Number (%): (Number of implementation/total number of cases)

Fig. 3 Implementation rate of clinical laboratory test before and after the introduction of the monitoring tool

Number: Number of implementation/total number of cases *$P < 0.05$

Fig. 4 Implementation rate of the clinical laboratory test for each drug in patients before and after the introduction of monitoring tools

Number: Number of implementation/total number of cases *$P < 0.05$

Fig. 5 Comparison of business hours before and after the introduction of the monitoring tool

*$P < 0.05$

Fig. 1

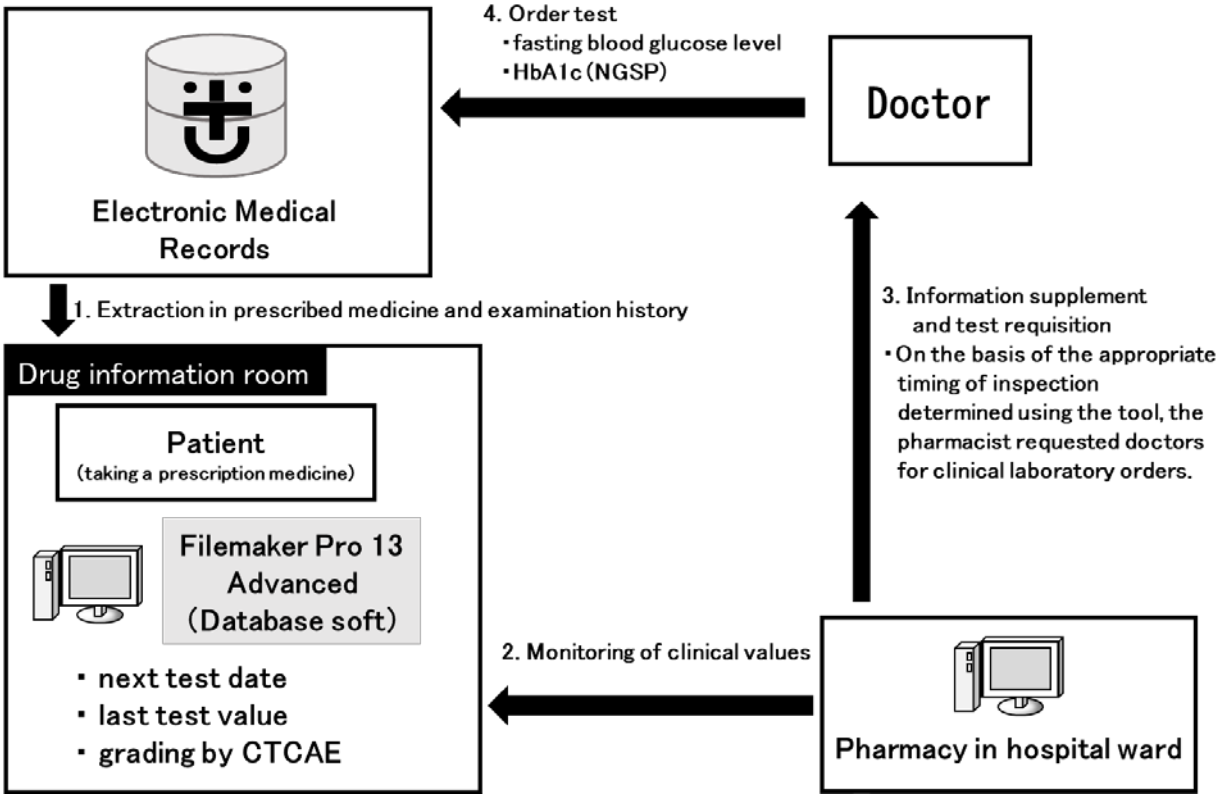

4. Order test
・fasting blood glucose level
・HbA1c (NGSP)
Doctor
Electronic Medical Records
1. Extraction in prescribed medicine and examination history
3. Information supplement and test requisition
・On the basis of the appropriate timing of inspection determined using the tool, the pharmacist requested doctors for clinical laboratory orders.
Drug information room
Patient
(taking a prescription medicine)
Filemaker Pro 13 Advanced (Database soft)
・next test date
・last test value
・grading by CTCAE
2. Monitoring of clinical values
Pharmacy in hospital ward

Fig. 2

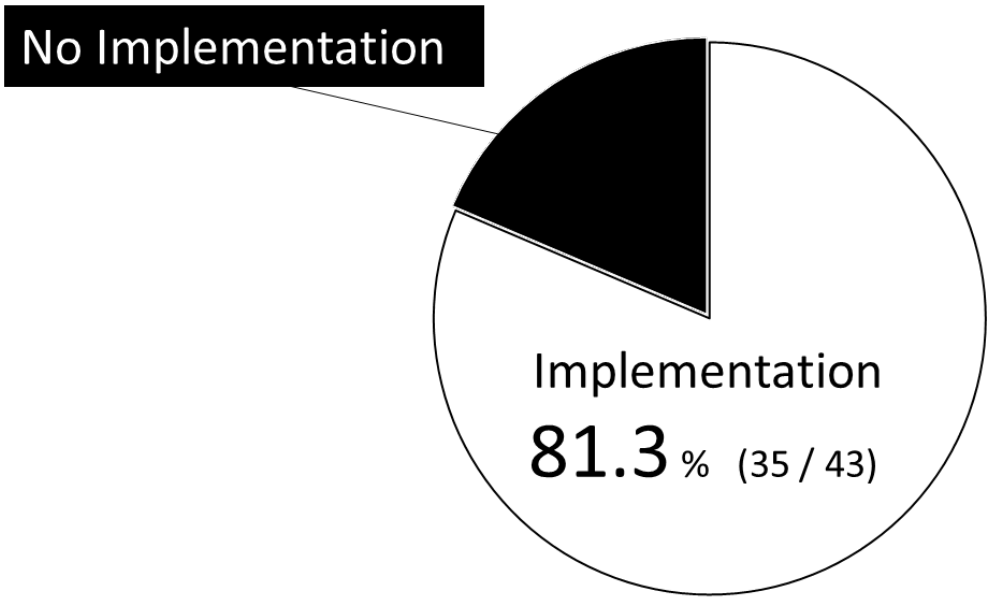


Fig. 3

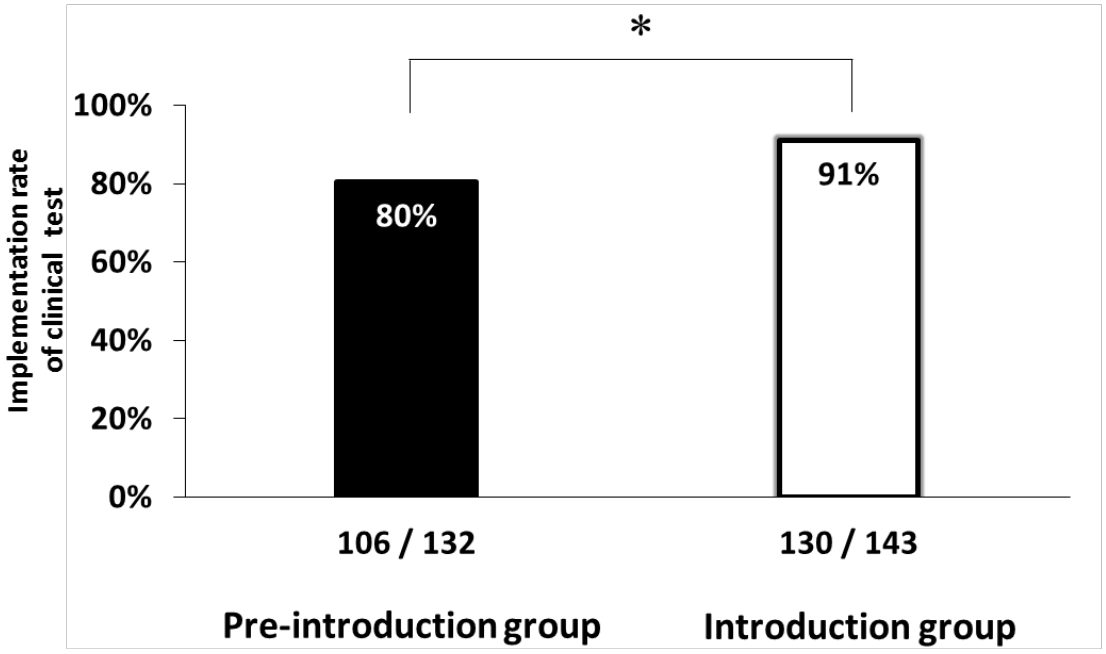

*
100%
80%
60%
40%
20%
0%
Implementation rate of clinical test
80%
91%
106 / 132
130 / 143
Pre-introduction group
Introduction group

Fig. 4

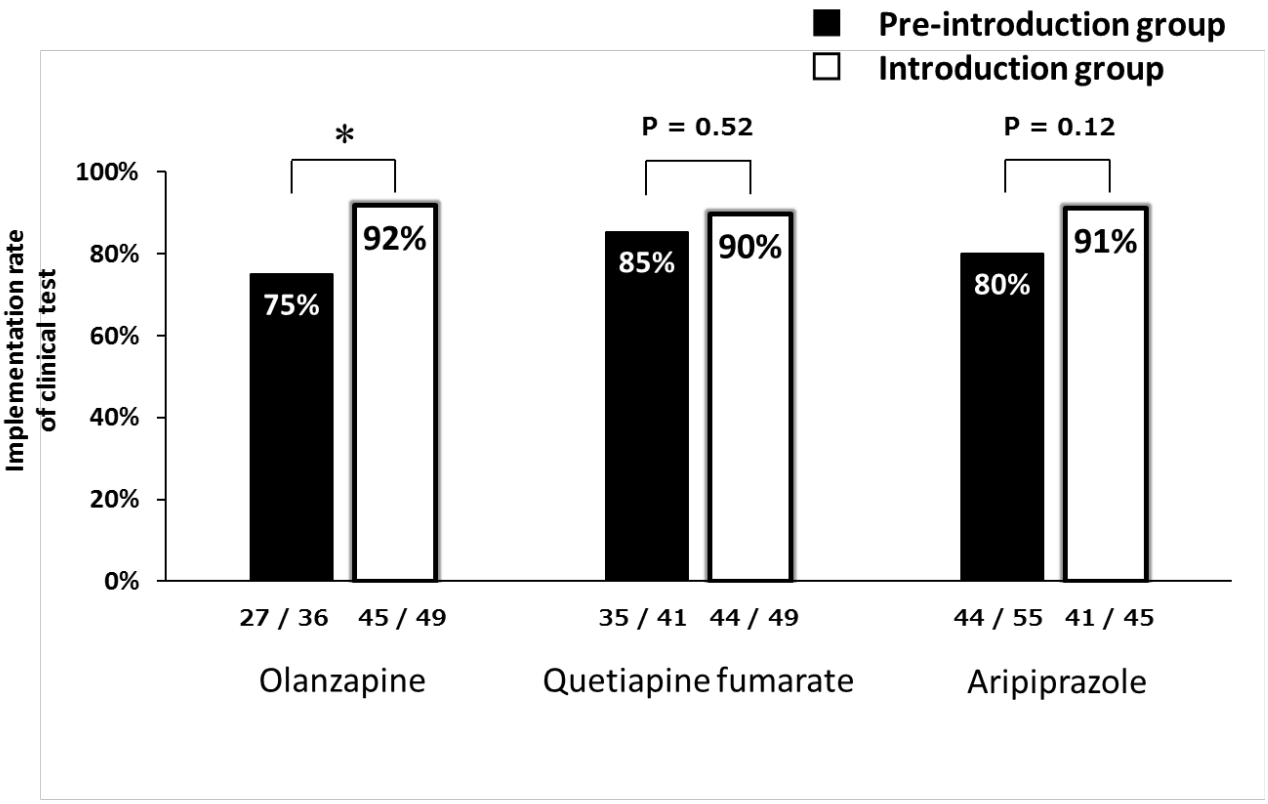
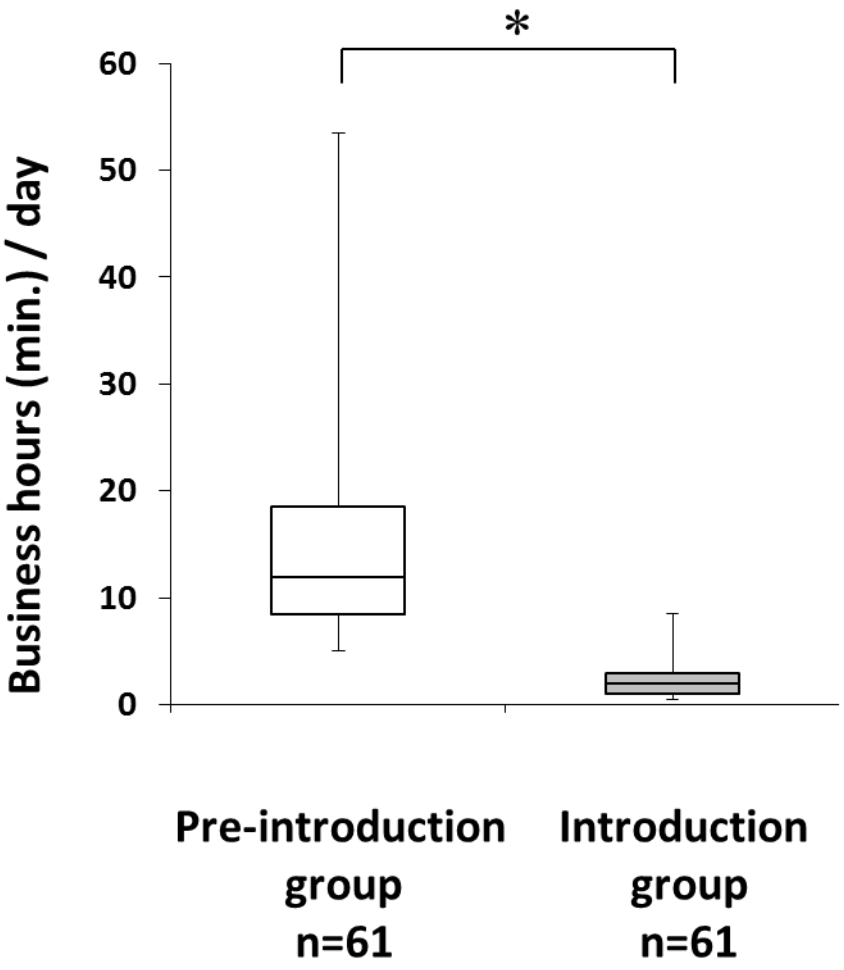

Pre-introduction group
Introduction group
Implementation rate of clinical test
100%
80%
60%
40%
20%
0%
*
P = 0.52
P = 0.12
75%
92%
85%
90%
80%
91%
27 / 36
45 / 49
35 / 41
44 / 49
44 / 55
41 / 45
Olanzapine
Quetiapine fumarate
Aripiprazole

Fig. 5


*
60
50
40
30
20
10
0
Business hours (min.) / day
Pre-introduction group n=61
Introduction group n=61