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Original Paper

A Factorial Analysis of Residual Medicine Using Protocol-Based Pharmacotherapy Management with Basic Patient Information and Residual Medicine Reports Derived from Community Pharmacies

Toshiyuki Hirai[1], Fumiyuki Watanabe[2], Yuusuke Terakado[1], Miwako Kamei[2] and Toshiichi Seki[1]

[1]Hitachi, Ltd., Hitachinaka General Hospital,
[2]School of Pharmacy, Nihon University

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Abstract

Aim: The previous studies on factors of the residual medicines were conducted only through the patients with residual medicines. The aim of this study is to clarify the factors that lead to residual medicine by comparing between groups of patients with and without residual medicines.

Methods: Patients for this study were supported, during study period between April 2016 and March 2018, with a residual medicine protocol, which allowed pharmacists at health insurance pharmacies to decide whether to change the number of prescription days based on the amount of residual medicines. Group of patients without residual medicines (full medicine use group) and group of patients with residual medicines (residual medicine group) were compared. Comparison items were sex, age, hospital department, number of prescribed drugs, number of days per prescription, and classification of drugs by efficacy.

Results: The number of the patients of the full medicine use group was 19,746, and that of the residual medicine group was 1,851. Average ages of two groups were 61.0 and 70.0. Median numbers of prescribed medicines were 2.0 and 4.3, median numbers of days per prescription were 28.0 and 56.0. Percentage of hospital departments visited by patients was high in the rheumatology and the endocrinology in the residual medicine group, and lower in pediatrics. Antidiabetic agents tended to be prescribed more in the residual medicine group.

Conclusion: It might be concluded that old age, having many prescribed drugs, longer prescription durations, and prescriptions for chronic diseases were important factors of residual medicine.

Key words : adherence, residual medicine, pharmacy, prescription, protocol

Introduction

Japanese medical expenses in the 2016 fiscal year reached 42,018.1 billion yen[1]. In this situation, regulations of recount and adjustment of residual medicine at health insurance pharmacies in medical fee were revised[2~4], showing an importance of active involvement of pharmacists. In the United States, based on the contract between pharmacists and physicians, pharmacists are allowed to conduct specialized duties in accordance with protocols, as Collaborative Drug Therapy Management (CDTM)[5]. In Japan, based on protocol-based pharmacotherapy management (PBPM), pharmacists can administer pharmacotherapy, collaborating with doctors, in accordance with a drafted/agreed upon protocol[6]. At Hitachi, Ltd., Hitachinaka General Hospital, according to the prescription format was changed due to the revision of medical fees in fiscal 2016[4] , we started checking “Information provision to insurance medical institutions” for all external prescriptions in April 2016. At the same time, in April 2016, our hospital implemented PBPM, allowing pharmacists at health insurance pharmacies to decide whether to change the number of prescription days based on the amount of residual medicine (a residual medicine adjustment protocol). In the residual medicine adjustment protocol, a pharmacist describe the status of residual medicines in the specific format (the residual medicine status report sheet) as “information provision to insurance

連絡先：平井利幸　〒312-0057　茨城県ひたちなか市石川町 20-1

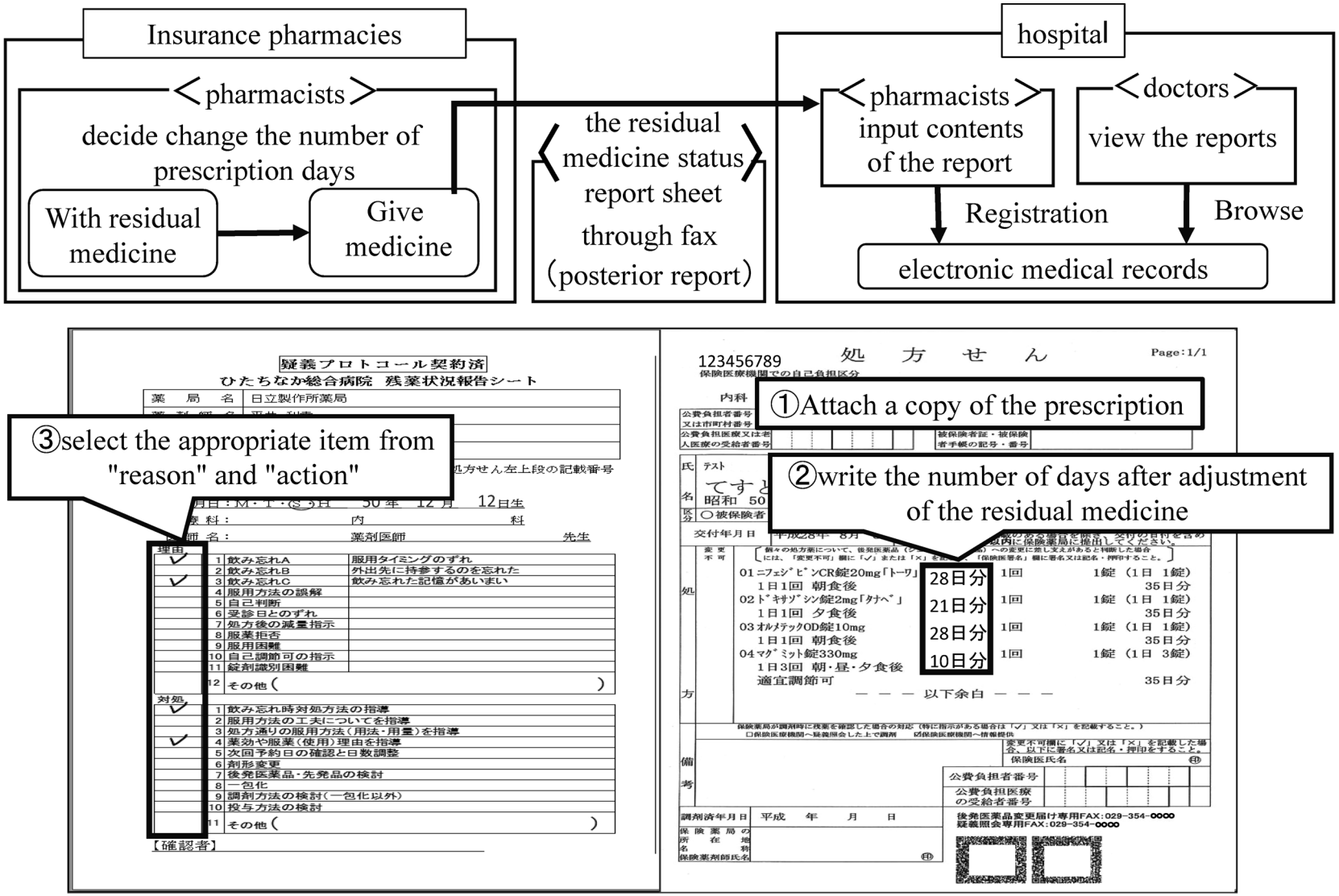

Fig. 1 Flow of a residual medicine adjustment protocol and the residual medicine status report sheet.

medical institutions", when he recognizes residual medicines of patients. Then, he attaches a copy of the prescription to the right side of the sheet. The number of days after adjustment of the residual medicine is written next to the drug name on the copy. Then, he selects the appropriate items in "reason" and "action" areas. Finishing all the procedures, the sheet is facsimiled to the hospital pharmacy as subsequent reports. At the hospital pharmacy, hospital pharmacists input contents of the report into electronic medical records, using the same templates, enabling doctors to view and make a new prescription when they see patients next time (Fig.1). As a result of preparation of systems to report contents of adjustment on residual medicine and amount of the adjustment based on PBPM, this protocol was applied to 92.4% of cases of residual medicine adjustment in our hospital[7] , and 12 million yen of expense of medicine are reduced within one year. In the United States, 'Brown bag' medication reviews (i.e., the act whereby patients bring a bag containing their currently-used drugs to the pharmacy) are practiced, to grasp the all drugs that patients are currently taking[8]. In Japan, 'Setsuyaku medicine bag' has been practiced. As a result, reduction of residual medicine, poor adherence drugs, and medication guidance tools have been reported[9,10]. Countries such as the UK have reported the reasons for residual medicine and the types of remaining drugs[11]. The yearly amount of residual medicine in the UK is reported to be worth 300 million pounds[12]. These types of studies on response to the residual medicine, background of patients with residual medicine, and details of residual medicine have been conducted. However, to our knowledge, studies revealing the factors that lead to residual medicine through a comparison of patients with and without residual medicine have not been published. Therefore, since the procedure to check residual medicine at the insurance pharmacy at the time of dispensing[2,3] and the system to utilize residual drug adjustment protocol as a method of "providing information to insurance medical institutions" with local insurance pharmacies have been established[7], in this study, patients without PBPM were considered as patients without residual drug to be checked, and by comparing the group of patients applied to PBPM and the group of patients not applied to PBPM, the factors that caused residual medicine should be clarified. Patients were divided into two groups: 1) patients with residual medicine adjustments based on the residual medicine adjustment protocol and 2) patients without residual adjustments. An electronic medical record data were utilized to complete this study.

Methods

Study period and subjects

The study period was between April 1, 2016 (i.e., the date when the residual medicine adjustment protocol was implemented) and March 31, 2018. Subjects were patients issued external prescriptions at our hospital during the study period. Patients were divided into two groups: patients who were not applied to any residual medicine adjustment as per the adjustment protocol (full medicine use group), and patients with residual medicine adjustment as per residual medicine adjustment protocol (residual medicine group). The data included all prescribed medicines that were not objects of medicine adjustment protocol.

Study items

The study items were sex, age, number of prescriptions, administration classification, hospital department, number of prescribed drugs, number of days per prescription, and classification of drugs by efficacy. Age means the one at the first follow up session within the trial period. As for the number of drugs prescribed and days of prescriptions were only examined for medicines for internal use.

The number of prescribed drugs was median of the average numbers of prescribed drugs of each patient of each group. To calculate the average of the numbers of prescribed drugs of each patient, the total number of prescribed drugs of each patient was divided by the total number of hospital visits of each patient during the study period. The number of days per prescription was median of the average numbers of day per prescription of each patient of each group. To calculate the average of the numbers of days per prescription of each patient, the total number of the highest numbers of days of prescription of each prescribed drugs of each patient was divided by the total number of hospital visits of each patient during the study period. The number of hospital department was counted as one, when a prescription was issued, excluding the number of patient visit without prescription. In the case that a patient visited two hospital departments in a day, it was counted as two. The ratio of hospital

department issuing prescription was calculated by dividing the number of hospital department of each group by the number of total amount of each group. The number of classification of drugs by efficacy was the number of prescribed drugs classified in accordance with classification of drugs by efficacy. Also, the ratio of classification of drugs by efficacy was calculated by dividing the number of each classification of drugs by efficacy of each group by the total number of classification of drugs by efficacy of each group. To determine classification of drugs by efficacy, the lower classifications of the Standard Commodity Classification for Japan were used[13].

Ethical considerations

This study was carried out in accordance with the "Ethical policy for medical research involving human subjects" and was approved by our hospital's ethics committee (approval number: 16-010) and the Nihon University School of Pharmacy ethics committee (approval number: 16-013). Since this study was retrospective observational using electronic health records, it did not harm any individual person.

Statistical processing

A chi-squared test were used to compare the two groups, in terms of sexes, prescribed hospital department, and classification of drugs by efficacy. Mann-Whitney *U*-tests were used to compare in terms of age, number of prescribed drugs, and number of days per prescription. The level of significance for these tests was a risk ratio of 5% or less. Statistical analysis was conducted using the statistical analysis software, IBM SPSS Statistics 23.

Results

Number of patients and patient backgrounds

Of the patients studied, 19,746 belonged to the full medicine use group, and 1,851 belonged to the residual medicine group. Out of former group 18,199 were prescribed medicines for internal use, and Out of latter group 1,836 were prescribed medicines for internal use. The former group had 10,563 males (53.5%) and 9,183 females (46.5%) while the latter had 1,008 males (54.5%) and 843 females (45.5%). There were no significant differences between males and females (P = 0.43). Median age was 61.0 years in the full medicine use group (males: 62.0, females: 61.0) and 70.0 years in the residual medicine group (males: 70.0, females: 69.0) $P <$ 0.001, Fig.2.

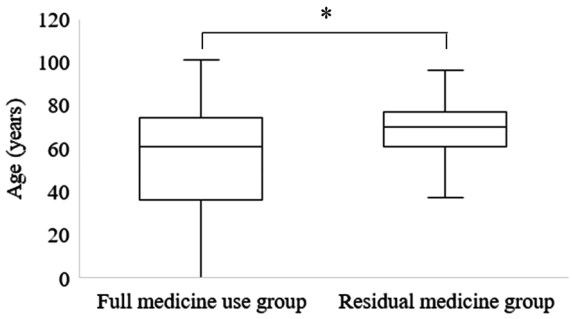

Fig. 2　Age comparison between the full medicine group and residual medicine group. *P < 0.001, Mann-Whitney *U*-test.

Number of prescriptions and administration classification

Numbers of prescriptions were 136,702 in the full medicine use group and 30,622 in the residual medicine group. The administration classifications of prescriptions were 416,791 medicines for internal use, 70,953 medicines for external use, and 7,012 injectable medicines in the full medicine use group; and 133,383 medicines for internal use, 15,156 medicines for external use, and 4,304 injectable medicines in the residual medicine group.

Prescribed hospital department

Table 1 shows, in descending order, the ranking of prescription numbers of 24 hospital departments of each group. There were 136,702 cases in the full medicine use group and 30,622 cases in the residual medicine group. The top 5 hospital departments, in descending order of prescription frequency, were cardiovascular medicine, dermatology, pediatrics, rheumatology, and gastrointestinal medicine for the full medicine use group, and for the residual medicine group they were cardiovascular medicine, rheumatology, endocrinology, dermatology, and gastrointestinal medicine. The total number of prescription at cardiovascular medicine was the highest in both group, and the ratio of prescription at cardiovascular medicine was the highest in the residual medicine group. In the residual medicine group, also, the ratio of prescription at rheumatology and endocrinology was higher in the residual medicine group. On the other hand, the ratio of prescription at pediatrics was low in the residual medicine group and pediatrics was ranked lower in the same group（P<0.001）.

Number of drugs prescribed and number of days per prescription

The Median of the number of drugs prescribed

Table 1　Hospital departments visited by patients in the full medicine group and the residual medicine group.

	Full medicine group				Residual medicine group			
Ranking	Hospital department	Number of cases	Proportion (%)	Ranking	Hospital department	Number of cases	Proportion (%)	*P*
1	cardiovascular medicine	22,015	16.1	1	cardiovascular medicine	6,352	20.7	<0.001
2	dermatology	12,596	9.2	2	rheumatology	5,202	17.0	
3	pediatrics	12,299	9.0	3	endocrinology	3,322	10.8	
4	rheumatology	11,164	8.2	4	dermatology	2,530	8.3	
5	gastrointestinal medicine	10,890	8.0	5	gastrointestinal medicine	2,440	8.0	
6	surgery	8,544	6.3	6	pulmonary medicine	2,081	6.8	
7	orthopedic surgery	8,363	6.1	7	neurology	1,965	6.4	
8	urology	7,410	5.4	8	orthopedic surgery	1,247	4.1	
9	endocrinology	7,360	5.4	9	surgery	1,159	3.8	
10	neurology	6,374	4.7	10	nephrology	935	3.1	
11	pulmonary medicine	5,627	4.1	11	urology	876	2.9	
12	otolaryngology	4,172	3.1	12	hematology	723	2.4	
13	dental surgery	3,742	2.7	13	otolaryngology	405	1.3	
14	hematology	3,661	2.7	14	psychiatry	236	0.8	
15	obstetrics and gynecology	1,986	1.5	15	pediatrics	225	0.7	
16	ophthalmology	1,811	1.3	16	ophthalmology	224	0.7	
17	psychiatry	1,675	1.2	17	internal medicine	160	0.5	
18	nephrology	1,590	1.2	18	neurosurgery	142	0.5	
19	plastic surgery	1,458	1.1	19	dental surgery	120	0.4	
20	internal medicine	1,415	1.0	20	obstetrics and gynecology	115	0.4	
21	neurosurgery	1,263	0.9	21	plastic surgery	77	0.3	
22	radiology	986	0.7	22	radiology	67	0.2	
23	anesthesiology	296	0.2	23	anesthesiology	19	0.1	
24	rehabilitation	5	0.0	24	rehabilitation	0	0.0	
	Total	136,702	100.0		Total	30,622	100.0	

Table 1 shows the numbers of hospital departments issuing prescriptions arranged in descending order in both groups. Compared to the full use medicine group, the ratio was high in cardiovascular medicine department, rheumatology department, and endocrinology department, and it was low in pediatrics department. A difference was also found between the two groups in terms of the ratio of hospital department issuing prescriptions.
$P < 0.001$, Chi-squared test.

(minimum-maximum) was 2.0 (1.0–24.0) in the full medicine use group, and 4.3 (1.0–14.8; $P < 0.001$, Fig.3) in the residual medicine group. The median of the number of days per prescription (minimum-maximum) was 28.0 (1.0–222.5) in the full medicine use group, and 56.0 (4.0–203.0; $P < 0.001$, Fig.4) in the other group.

Classification of drugs by efficacy

To compare classification of drugs by efficacy between the two groups, 25 classifications of drugs by efficacy, which were the top 25 of them in the full medicine use group, occupying more than 80% of all classifications, were picked up. These 25 classifications were not equal to those of 25 of the residual medicine group. Table 2 shows, in descending order, the top 25 classifications of drugs by efficacy including the two groups. Number of drugs which belonged to the top 25

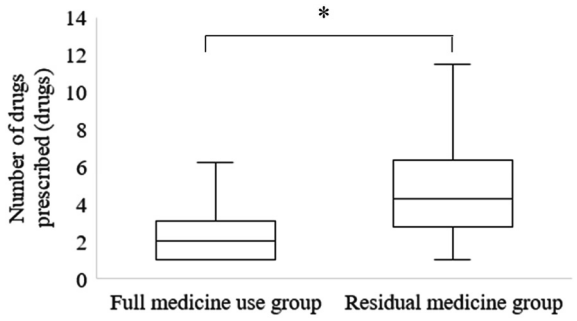

Fig. 3　Comparison of the number of drugs prescribed for the full medicine group and residual medicine group. *P < 0.001, Mann-Whitney U-test.

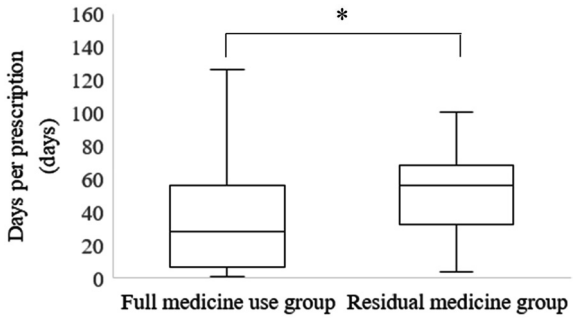

Fig. 4　Comparison of the number of days per prescription between the full medicine group and residual medicine group. *P < 0.001, Mann-Whitney U-test.

classifications are 416,791 in the full medicine use group, and 133,383 in the residual medicine group. Among them, the top 5 classifications in descending order were peptic ulcer healing drugs, antihypertensive agents, antidiabetic agents, antihyperlipidemic agents, and other blood/body fluid drugs, in the full medicine use group, and in the residual medicine group those of top 5 were antidiabetic agents, peptic ulcer healing drugs, antihypertensive agents, antihyperlipidemic agents, and other blood/body fluid drugs. Thus, the top 5 items of classifications of drugs by efficacy were the same in both groups. On the other hand, antidiabetic agents were ranked third in the full medicine use group, the ratio of the number of prescribed drugs of antidiabetic agents was higher, and the number of the prescribed drugs of antidiabetic agents was the highest in the residual medicine group（P<0.001）.

Discussion

In this study, comparing the group whose residual medicine was adjusted and the group whose residual medicine was not adjusted, we determined the factors leading to residual medicine for patients to who external prescriptions. As a result, patients in old age, more kinds of prescribed medicine, and longer term prescription, were the important factors that lead to residual medicine. For example, prescribed drugs at rheumatology and endocrinology, and a drug such as antidiabetic agents had higher possibility to be residual medicine.

In this result, age of patients was older in the residual medicine group. Also, in the residual group, number of prescribed medicine per time was more, and duration of prescription per time was longer. As a previous study reports that an increase in age was associated with an increase in the number of drugs taken by patients[14], the older age in the residual medicine group may be linked to the more number of drugs prescribed and longer duration per prescription. Other studies also have indicated that elderly people had reduced medication compliance due to factors such as an increase in the number of drugs prescribed[15,16]. For the elderly, both complicacy of pharmaceutical management and reduction of precise understanding of drug were the factors of residual medicine which could be caused by more number of the prescribed drugs and longer duration of the prescription per time. As one report said that creating individualized pharmaceutical compounds for patients that took many drugs at once increased medication compliance[17], utilization of pharmaceutical compounds could be one option to reduce the number of drugs prescribed to patients. Currently, there are some attempts that pharmacists at health insurance pharmacies make decisions on specific matters regarding prescriptions, such as changing specifications and one dose packaging, based on PBPM between health insurance pharmacies and medical institutions[18,19]. In addition to these matters, if pharmacists at health insurance pharmacies are allowed to decide on utilization of pharmaceutical compounds, it would be easier for them to work on residual medicine.

The difference was found between the residual medicine group and the full medicine use group in term of the ratio of hospital department issuing prescriptions. Among the number of hospital departments issuing prescriptions, that of cardiovascular medicine department was the highest in both groups, and also, that of rheumatology department, dermatology department, and gastrointestinal medicine department were ranked higher in both groups. This fact had possibility of misleading to the conclusion that this was the tendency

Table 2　Drug classification by efficacy in the full medicine group and residual medicine group.

		Full medicine group		
Ranking	Drug classification by efficacy	Number of cases	Proportion (%)	
1	232: peptic ulcer healing drugs	36,368	8.7	
2	214: antihypertensive agents	31,280	7.5	
3	396: antidiabetic agents	24,655	5.9	
4	218: antihyperlipidemic agents	23,426	5.6	
5	339: other blood/body fluid drugs	20,939	5.0	
6	399: other metabolic drugs	18,891	4.5	
7	114: antipyretic analgesics	18,367	4.4	
8	217: vasodilators	16,331	3.9	
9	449: other allergy medications	15,715	3.8	
10	112: sedatives, anxiolytics	11,129	2.7	
11	245: adrenal hormone preparations	10,438	2.5	
12	213: diuretics	10,288	2.5	
13	212: antiarrhythmic drugs	10,054	2.4	
14	333: anticoagulants	9,862	2.4	
15	117: psychotropic drugs	9,422	2.3	
16	223: expectorants	8,674	2.1	
17	113: antiepileptic drugs	8,244	2.0	
18	234: antacids	8,236	2.0	
19	394: gout treatments	7,770	1.9	
20	313: vitamin B (excluding vitamin B_1)	7,651	1.8	
21	231: antidiarrheals, intestinal regulators	6,602	1.6	
22	259: miscellaneous of urogenital and anal organ agents	6,424	1.5	
23	520: traditional Chinese medicines	6,371	1.5	
24	119: miscellaneous of agents affecting central nervous system	5,679	1.4	
25	239: miscellaneous of digestive organ agents	5,464	1.3	
	other	78,511	18.8	
	Total	416,791	100.0	

		Residual medicine group		
Ranking	Drug classification by efficacy	Number of cases	Proportion (%)	P
1	396: antidiabetic agents	12,147	9.1	
2	232: peptic ulcer healing drugs	11,641	8.7	
3	214: antihypertensive agents	11,463	8.6	
4	218: antihyperlipidemic agents	9,047	6.8	
5	339: other blood/body fluid drugs	8,177	6.1	
6	399: other metabolic drugs	8,032	6.0	
7	217: vasodilators	5,738	4.3	
8	213: diuretics	3,948	3.0	
9	114: antipyretic analgesics	3,807	2.9	
10	212: antiarrhythmic drugs	3,395	2.5	
11	245: adrenal hormone preparations	3,315	2.5	
12	333: anticoagulants	3,274	2.5	
13	313: vitamin B (excluding vitamin B_1)	2,977	2.2	
14	394: gout treatments	2,898	2.2	<0.001
15	112: sedatives, anxiolytics	2,876	2.2	
16	234: antacids	2,863	2.1	
17	449: other allergy medications	2,624	2.0	
19	117: psychotropic drugs	2,026	1.5	
20	520: traditional Chinese medicines	2,009	1.5	
22	239: miscellaneous of digestive organ agents	1,734	1.3	
24	119: miscellaneous of agents affecting central nervous system	1,690	1.3	
25	231: antidiarrheals, intestinal regulators	1,509	1.1	
27	223: expectorants	1,354	1.0	
28	259: miscellaneous of urogenital and anal organ agents	1,353	1.0	
33	113: antiepileptic drugs	1,060	0.8	
	other	22,426	16.8	
	Total	133,383	100.0	

Table 2 shows the numbers of drug classifications by efficacy in descending order in both groups. Top 25 of drug classifications by efficacy in the full medical use group were used as items to be compared. Although the top 5 ratios of drug classifications by efficacy were the same in both groups, the ratio of antidiabetic agents was the highest in the residual medicine group, which was also higher, compared to the full medicine use group.

$P < 0.001$, Chi-squared test.

of the residual medicine group, in spite of the fact that the number of cases was also high in the full medicine use group in the study of the patients with residual medicine. It was necessary to compare the ratio of both groups. Among hospital departments issuing prescriptions, the ratios of issuing prescriptions were not higher in dermatology department and gastrointestinal medicine department in residual medicine group. The ratio of hospital department issuing prescriptions was higher in cardiovascular medicine department, rheumatology department, and endocrinology department in residual medicine group. Especially, a big difference was found in rheumatology department and endocrinology department in terms of the ratio of hospital department issuing prescriptions. On the other hand, that of pediatrics department was extremely low in residual medicine group. The World Health Organization reported that medication compliance for drugs prescribed for chronic diseases is approximately 50%[20]. These facts indicate that prescriptions issued by medical departments dealing with chronic diseases with long-term treatment have influence on lower medication compliance.

Although the top 5 classifications of drugs by efficacy were the same in both groups, the order was different in both groups. The difference was also found in terms of comparison of ratio of classifications of drugs by efficacy. When the two groups were compared, the ratio of classifications of drugs of antidiabetic agents, antihypertensive agents, antihyperlipidemic agents, and other blood/body fluid drugs was higher in the residual medicine group. This indicated that medications for chronic diseases were tend to be residual medicine. Among them, especially, antidiabetic agents had higher rate in the number of prescription in residual medicine group than in the full medicine use group. In the residual medicine group, the number of prescription of antidiabetic agents was the most highest. Since the endocrine medicine department is the one which prescribes antidiabetic agents, there seems to have relationships between high ratio of prescription of antidiabetic agents and high ratio of hospital visit for the endocrine medicine department in the residual medicine group. The reason that antidiabetic agents were a lot in the residual medicine group is that antidiabetic agents were drugs for chronic disease, and also that dosage schedules of antidiabetic agents, such as before meals or right before meals, which are different from other medicines, both of which are likely to be factors of failure to take medicines. In addition to patient's failure to take medicines, cessation of taking antidiabetic agents on sick days[21] and cessation of taking biguanide antidiabetic drugs while using an iodine contrast agent[22] are possible factors to cause more residual medicine in the residual medicine group. Compared to the full medicine use group, the ratio of hospital visit to rheumatology department was high, and in terms of efficacy classifications, Other metabolic drugs and vitamin B (excluding vitamin B_1) were high in the residual medicine group. These efficacy classifications were those which include methotrexate and folic acid prescribed in rheumatology, and they should be taken on a weekly basis, not on a daily basis. Therefore, not only dosage schedules in a day, but also the difference of dosing interval from other drugs seemed to be one of the factors of the residual medicine caused by decrease in compliance. In 2013, targeting patients, a study on the check of residual medicine in Japan was conducted, whose result was that approximately 30% of patients indicated that they shared residual medicine information with the pharmacist during their visit to the pharmacy[23]. Since 2014, when the check of residual medicine prior to dosing was clarified[3], the performance of residual medicine check has possibly been increasing. However, the fact that the check of residual medicine was located as one of the calculation requirements for the medication history management and guidance fee in 2012 Revision of Medical Fee[2] should be remembered. Since the check for residual medicine was one of the requirements, the higher rate should have been estimated. In fact, the executing rate was about 30%, which should be concluded as low. By checking the residual medicine every time when patients come to pharmacies, pharmacist can find the patients with the high risk of having residual medicine. Moreover, if patients bring all the medicines they have to health insurance pharmacies, as done in the setsuyaku bag initiative[9], it could be one approach for patients and pharmacists to share residual condition of medicine. Furthermore, there is a report that when pharmacists interact regularly with patients with chronic diseases, they contribute to an increase in medication compliance[24], and there also is another report that when pharmacists interact with patients who have repeatedly the same drugs prescribed, they contribute

to a decrease of the number of drugs[25]. These reports indicate that it is important for pharmacists to check deliberately the residual medicine and the change of physical condition especially of the patients with chronic diseases under the treatment when they conduct medication management. By doing so, they can share the information with doctors to prescribe, and contribute to not only the reduction of drugs through the residual medicine, but also the reduction prescribed drugs through medication condition and physical condition.

This study had several limitations. First of all, because it was a retrospective study conducted at a single medical facility, we could not mention anything about the influence on the medication prescribed by other medical institutes. Secondly, since the group of patients to whom residual medicine adjustment was conducted was the one with the adjustment based on the residual medicine adjustment protocol, we could not refer to patients who did not inform of their residual medicine at insurance pharmacies even if they have it, and could not refer to patients who had residual medication adjusted at the time of prescription. Thirdly, the group of the patients with residual medicine adjustment was the one who had had residual medicine adjusted at least once. This means that we could not avoid the influence by the implementation rate of the residual medicine adjustment.

We revealed that older age, increase in the number of prescribed drugs, and the increase in the number of prescription days are all connected to the residual medicine, by comparing the backgrounds and prescription details of patients with report about residual medicine to those of patients without that report. Also, we found that drugs prescribed from rheumatology and endocrinology as well as antidiabetic agents are both likely to become residual medicine. In the future, we may be able to contribute to the reduction of medical fees and improve patient adherence to medication intake, by investigating factors leading to residual medicine through combining actual residual medicine with patient background, and by investigating influence of having residual medicine on the treatment effect of patients.

Disclosure Statement

The authors declare no conflicts of interest.

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