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Scientific Research

Factors Related to Medication Adherence of Cognitively Impaired Patients in Community Pharmacies

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ABSTRACT

Objective: The objective of the study was to identify factors related to donepezil medication adherence ("adherence") of cognitively impaired patients in community pharmacies. **Methods:** One hundred and twenty community pharmacies in 28 regions in Japan were randomly selected. Questionnaires were mailed to these pharmacies. The pharmacists answered based on the medication profiles ("YAKUREKI") of the patients given donepezil at their pharmacies. The survey items were "adherence", "who is the key person" and the key person's understanding and awareness of donepazil and its symptoms. The χ^2 test and decision tree modeling analysis were performed to examine factors affecting adherence. A 5% level of statistical significance was used in the χ^2 test. **Results:** Questionnaires with data on 479 patients were returned. The most common level of adherence was "take as instructed" (81.2%), followed by "forget once or twice a week" (10.2%). The χ^2 test revealed that adherence was good if "key person" was professional caretaker ($P = 0.004$). Also, adherence was better if key person understood medication about dosage, $P < 0.001$; effect, $P = 0.002$; and general side effects, $P < 0.001$. According to decision tree analysis, the key person had the strongest relationship with adherence. **Conclusions:** It was confirmed that the key person's understanding of the medication and symptoms of cognitive impairment are related to adherence. In particular, it was suggested that there is a strong relationship between the key person and adherence and that factors related to adherence differ according to who the key person is. It is essential in the treatment of cognitive impairment to accurately identify the "key person", in order to provide better pharmaceutical care in community pharmacies.

Keywords: Japan; Pharmacist; Community Pharmacy; Medication; Adherence; Cognitive Impairment

1. Introduction

It is estimated that over 25% of the Japanese population will be 65 years of age or older by 2015. The Japanese Ministry of Health, Labor and Welfare estimated that the number of people 75 years of age and older would be about 14 million in 2009 [1]. About 120,000 out of these people will have cognitive impairment [2].

We know that it is essential for medication to be taken continually in the treatment of cognitive impairment and that maintaining treatment adherence is the key to improving the quality of treatment and the quality of life [3]. There is an abundance of research on factors related to medication adherence ("adherence") worldwide. It has been suggested that such factors include age [4,5], sex [6], economic status [5], disease severity [5], degree of cognitive dysfunction [7], complications [5,8], drug regimen prescribed [6,9], cooperation from family [10], physician-patient relationship [7,11], patient satisfaction [12], and generic substitution [13]. Inadequate awareness of the necessity to follow the treatment regimen has been identified as a reason for the patient's decision to discontinue treatment of their own accord [4].

Research on adherence in patients with cognitive impairment includes studies on factors such as persistence (refill adherence) and duration for multiple cholinesterase inhibitors [14-16]. These studies suggest that the type of drug and ease of use affect continuation or discontinuation of treatment [18], and that the sex, age, and degree of economic burden from medication costs affect adherence to treatment regimens for cognitive impairment [17]. A study compared treatment adherence in outpatients for multiple medications for cognitive impairment (multiple cholinesterase inhibitors) [18,19]. Belle SH *et al.* inspected the influence of medication for cognitive enhancement on family care-givers, and suggested that there is substantial geographic variability and effects de-

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pending on the physician's education [20], Sevilla C *et al.* compared satisfaction of the care-givers on cognitive impairment medications prescribed for the patient [21].

There are no studies on adherence of cognitively impaired patients, but several studies examined the adherence on medication for some diagnoses in Japan. Hayashi *et al.* identified irregularity of meals as a factor related to adherence in a survey of inpatients with ischemic heart disease, by checking whether or not patients forgot to take their medication on a 2-grade yes/no scale [22]. Ishida *et al.* demonstrated the beneficial effect of one dose packaging in an evaluation of adherence to an oral antidiabetic drug regime based on whether diabetics could take their medication per physician's instructions (evaluated on a three-grade scale of "I am taking medication," "sometimes forget," and "often forget") [23]. Yamaoka *et al.* evaluated adherence to a α-glucosidase inhibitor on a four-grade scale ("take all as instructed," "usually take," "sometimes take," and "don't take") and demonstrated that adherence was lower than with other oral antidiabetic agents [24]. Tatemichi *et al.* demonstrated that adherence improved according to the instructtions given by physician in an evaluation of long-term adherence in male Japanese workers using a four-grade scale (always took the drug according to the prescription (complete), occasionally forgot to take the drug (good), frequently forgot to take the drug (poor), always forgot to take the drug (very poor)) [25]. Evaluating adherence on a four-grade scale for forgetting to take medication or having left-over medication ("happens a lot," "sometimes happens," "doesn't happen very often," "almost never happens"), Kamei *et al.* identified occupation and having diabetes as factors affecting adherence [26].

Most of the previous research in Japan has been performed at specific medical institutions or in specific communities; none has been performed on patients with cognitive impairment over a wide area in a community pharmacy setting. The purpose of this study is therefore to identify factors related to adherence of cognitively impaired patient.

There are several assessment methods for adherence, mainly consisting of pill counting methods such as the MEMS (Medication-Event-Monitoring System) [27], and self-administered rating scales such as the Morisky Scale, which assesses adherence by scoring the frequency with which patients forget to take medication or discontinue their medication [28]. Hiratsuka *et al.* studied the validity of the 4-grade Drug Compliance Scale (DCS), consisting of 4 items, by using it in combination with pill counting; however, their study suggested that only 2 of the items were valid [29]. Nevertheless, pill counting devices such as the MEMS are not widely available in Japan, nor are Japanese translations of assessment tools such as the Morisky Scale widely accepted. Thus, while several methods for assessing adherence are available in Japan, a unified assessment method has not been established.

We therefore performed a pilot study of assessment scales among pharmacists and selected the most universally used assessment scale for use in the present study. The assessment tool selected is a patient profiling system that is used by pharmacies throughout Japan for collecting data on adherence and related factors across multiple geographic regions.

This profiling system in Japan is called the "YAKUREKI". Regulations concerning the "YAKUREKI" mandate community pharmacists to "record data for monitoring and counseling patients". Information to be recorded is specified by the Japanese Health Insurance Law (**Table 1**). Since Japanese pharmacies do not have technicians or other certified support staff who dispense drugs and provide medicine work, pharmacists are the only ones who deal with patients. As a result, several different pharmacists often work on the same cases. The purpose of the "YAKUREKI" profile is for pharmacists to share information on patients in order to maintain the quality of pharmacists' counseling.

Table 1. Items to be included in "YAKUREKI" under the Rule of Pharmacies Dispensing Fee Schedule.

No.	Items
1	Patient data (name, age, address, gender, health insurance number)
2	Prescription data (hospital name, physician's name, date of issue, contents)
3	Dispensing data (date of dispensing, dispensing method, contents referred to hospital)
4	Patient's general condition (allergy, history of side effects, kidney/liver diseases, severe diseases)
5	Detailed information of patient and/or caregivers' inquiry
6	The status of adherence
7	Changes in health condition or symptoms while under drug treatment
8	OTC and/or dietary supplements currently taken
9	Possibility of disease complication
10	Other medications or hospital/clinic visits
11	Potential side effects
12	Potential food-drug and/or drug-drug interactions
13	Name of counseling pharmacist
14	Change in medications
15	Pharmacist's assessment
16	Problems related to medication
17	Contents of counseling and guidance by pharmacists
YAKUREKI Fee targets = 1 - 13	
Pharmaceutical counseling fee targets = 14 - 17	

Keeping medication records using "YAKUREKI" has been required as standard skill for community pharmacists by Health Insurance Law in Japan.

So, the training for handling "YAKUREKI" is one of the core-requirements in undergraduate program.

A schematic depiction of the research protocol appears in **Figure 1** below.

In general, the target patients with cognitive impairment are identified by checking the disease name on their prescriptions. But in Japan, no prescriptions carry disease names, so the only way to select patients with cognitive impairment is by checking the medication contents. In Japan, donepezil HCl is used in symptomatic treatment that controls the progression of cognitive disorders including dementia of the Alzheimer's type (AD), mild cognitive impairment (MCI), and dementia with Lewy bodies (DLB). This acetylcholinesterase inhibitor was the only drug approved in Japan for the treatment of cognitive impairment when this study was conducted at the end of June 2010.

2. Subjects and Methods

2.1. Subjects and Survey Methods

One hundred and twenty community pharmacies in 28 of the 47 regions throughout Japan were randomly selected using the Domestic Sales Data of Donepezil for the survey. These establishments were selected from among pharmacies that had dispensed donepezil using random number generated by computer.

This number of pharmacies was calculated based on the assumption reached by our pilot study that there would be data from 100 patients (50 in the "good" adherence group and 50 in the "poor" adherence group), with a response rate of 50%, and that data from 2 patients could be obtained per pharmacy. Pharmacies were provided with a general explanation of the survey and pharmacies with no patients taking donepezil were excluded.

The questionnaire consisting of 20 items in 10 domains (**Table 2**) was mailed to the supervising pharmacists at the participating pharmacies. Pharmacists who had counseled patients on the use of donepezil were requested to record and evaluate information in these patients' profiling system ("Yakureki") in the questionnaire. The completed questionnaire forms were returned by mail. The questionnaire was based on a review of previous studies, cognitive impairment treatment guidelines, and information gleaned from meetings with academics and pharmacists. The questionnaire was then reworked into its present state after a pilot study using 5 pharmacists. So that care-giver and familial recognition influence it for cognitive impairment medical treatment [30], We should conduct an investigation into recognition of care-giver in an item of this study, We have to describe "key person" because we set this research based on recording of interview at counter in community pharmacy as investigation subject, therefore the degree of care-giver is various by degree of cognitive impairment, it is difficult to make judge who is care-giver at counter in community pharmacy because of various person coming to receive medicine.

2.2. Statistical Methods

The χ^2 test was performed using the level of adherence and other survey items. Adherence was categorized as

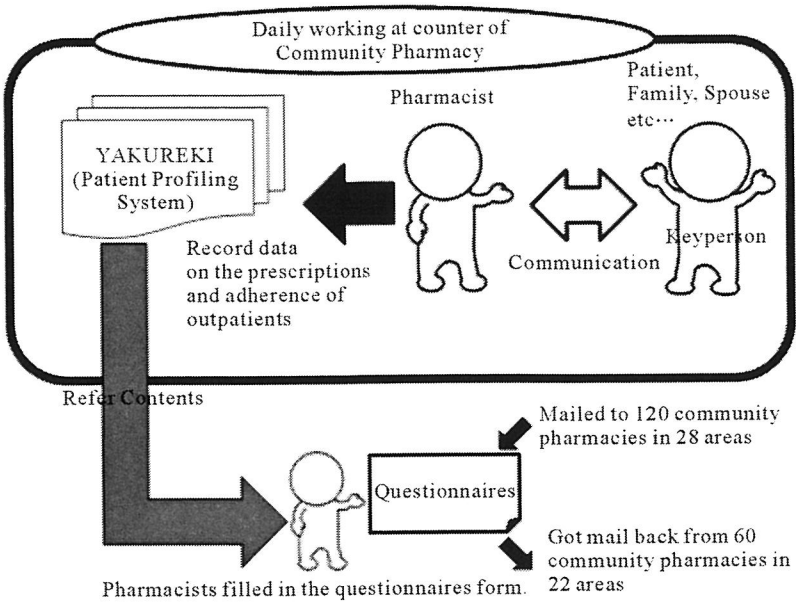

Figure 1. Process of study.

Table 2. Questionnaire items (20 items, 10 domains).

1) Patient profile	1-a). Sex	
	1-b). Age	
	1-c). Medical institution visited	
2) Regimen prescribed	2-a). Donepezil strength	
	2-b). Dosage form	
	2-c). Dosage	
	2-d). Supply dispensed per prescription	
	2-e). How dispensed	
	2-f). Concomitant drugs	
3) Physician's consultation status		
4) Donepezil adherence		scored on a four-grade scale
5) "Key person" who has the central role in overseeing the donepezil adherence		
6) Key person's understanding of donepezil	6-a). Understanding of donepezil administration and dosage	scored on a four-grade scale
	6-b). Understanding of effect	scored on a four-grade scale
	6-c). Understanding of general side effects	scored on a four-grade scale
7) Key person's understanding of cognitive impairment	7-a). Understanding of the characteristic symptoms of cognitive impairment	scored on a four-grade scale
	7-b). Understanding of the treating physician's treatment plan	scored on a four-grade scale
8) Key person's awareness of own cognitive impairment		scored on a four-grade scale
9) Key person's awareness of therapeutic effect		scored on a four-grade scale
10) Key person's attitude toward treatment (positive/negative)		scored on a four-grade scale

"good" ("take all as instructed") or "poor" ("forget once or twice a week," "only take once or twice a week," "never take"). "Information unavailable". "unknown," and "no response" were excluded as missing data. The following factors were each divided into 2 groups: age (≤74 years and ≥75 years), supply dispensed per prescription (in days) (≤29 days and ≥30 days), and number of concomitant drugs (≤4 and ≥5). "Key person" was divided into 4 groups: patient, spouse, family member other than spouse, and professional caretaker (**Table 3**). The decision tree analysis was performed, using adherence level as the target variable and items suggested by the χ^2 test to be related to adherence as independent variables.

Of the various methods of decision tree analysis, we used CRT (classification and regression trees). In the CRT analysis, a branch splits in two at the cutoff point showing the largest change in impurity found by Gini measurement among a combination of cutoff points for all independent variables used ("Impurity" refers to the extent to which responses are concentrated in a single target category in a node). This process then repeats itself. The "good" adherence group was selected as the target category. The minimum number of cases per group before running the analysis (the parent nodes) was set at 100 and the minimum per group after running the analysis (the child nodes) was set at 50. The analysis was considered completed when a minimum of 100 cases in the parent node and 50 cases in the child node was reached. The Windows versions of SPSS (18.0J) and SPSS Decision Tree software packages were used in the analysis. A level of significance of less than 5% was used.

3. Results

3.1. Questionnaire Return Rate

Four-hundred-and-seventy-nine patient data responses were collected from 60 community pharmacies in 22 regions throughout Japan (**Figure 2**).

3.2. Results

The results of each of the questionnaire items are shown in **Table 4** and **Table 5**.

More than half of the patients visited a "clinic or physician's office" for treatment. 79.1% of the patients were prescribed a 5 mg tablet once daily, with treatment

Table 3. Items and groups used in the x^2 test.

Questionnaire item	Response	Group
Medical facilities patient visited	University hospitals	Hospital
	Public hospitals	
	Private hospitals	
	Clinics or physician's offices	physician's office
Physcian's consultation status	Patient sees physician	Patient sees physician
	Patient only gets medication w/o seeing physician	Patient only gets medication w/o seeing physician
Dispensing methods of Donepezil	Alone in a heat-sealed packet	Donepezil alone
	One-dose packages alone	One dose packaging
	One-dose packages with other drugs	
Key person's understanding (dosage, effect, general side effect)	Understands well	Understands
	Mostly understands	
	Does not understand very well	Does notunderstand
	Does not understand at all	
Key person's awareness of own cognitive impairment	Well aware	Aware
	Generally aware	
	Not very well aware	Not aware
	Completely unaware	
Key person's awareness of therapeutic effect	Has a thorough awareness	Has awareness
	Has a general awareness	
	Does not have a very good awareness	Does not have awareness
	Has no awareness	
Key person's attitude toward cognitive impairment treatment	Positive	Positive
	Somewhat positive	
	Somewhat negative	Negative
	Negative	

regimen stating "to be taken after breakfast". There was an average of 3.1 concomitant medications.

77% of the patients were accompanied by someone when visiting their physicians. 10% visited their physicians for treatment alone. This information was not clear for 12% of the patients.

81.2% of the patients were found to be adherent. A family member other than the spouse was the most common "key person", followed by the spouse, the patient himself/herself, and a professional caretaker, in that order.

There were common tendencies in the key person's understanding of donepezil and cognitive impairment, as well as the awareness of own cognitive impairment. The most common degree of understanding was "mostly understand", followed by "well", "not very well", and "not at all", in that order.

As for the therapeutic effect, the most common response was "do not have a very good understanding" followed by "have no understanding".

Concerning the attitude toward treatment, there was a common tendency on the understanding and awareness on the part of the key person: "unknown" was the highest at 35.9%.

3.3. Factors Affecting Adherence to the Donepezil Regimen

The χ^2 analysis of the key person's relationship to adherence to the donepezil regimen revealed that a higher per-

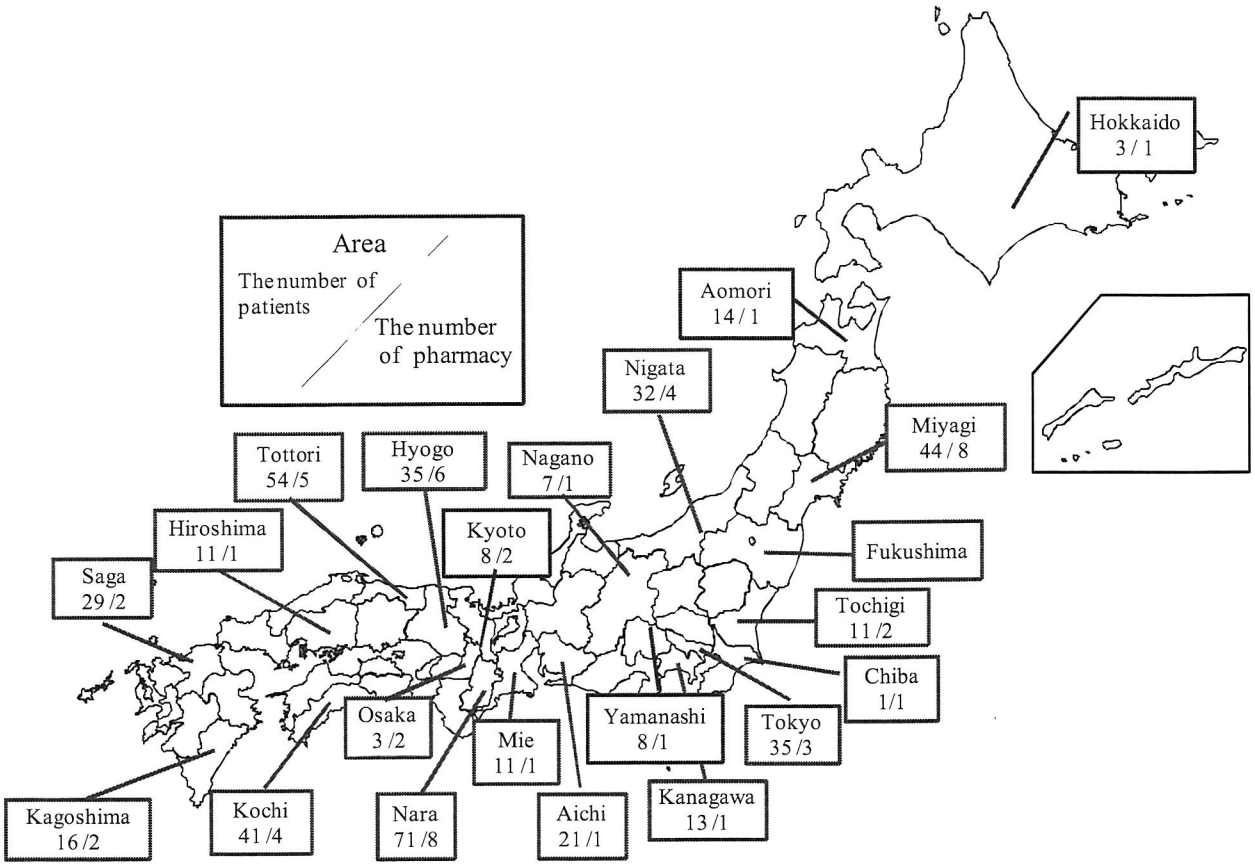

Figure 2. Distribution of responses.

centage of patients with "a professional caretaker" had "good" adherence than patients with the other three key person types, whereas a lower percentage of patients with "a family member other than the spouse" as the key person showed "good" adherence than patients in the three other key person types (P = 0.004) (**Table 6**). The χ^2 test was also used to compare patients with themselves ("patients") as the key person with those with "a professional caretaker" as the key person, revealing a higher rate of "good" adherence when "a professional caretaker" was the key person (P = 0.034).

The χ^2 analysis of the relationship between adherence and the key person's understanding of donepezil revealed that a higher percentage of "good" adherence was seen when the key person "understands," compared to when the key person "does not understand" all donepezil-related items (administration and dosage, P < 0.001; effects, P = 0.002; general side effects, P < 0.001).

The results for the χ^2 analysis of other factors related to donepezil adherence are discussed below. The key person's understanding of cognitive impairment: There were significant differences for understanding of both "characteristic symptoms" and "physician's treatment plan." A higher percentage of "good" adherence was seen when the key person "understands" than when the key person "does not understand" (P < 0.001). The key person's awareness of patient's illness: There was a higher percentage of "good" adherence when the key-person was "aware" than when he/she was "not aware" of patient's illness (P = 0.001). Keyperson's awareness of therapeutic effect: There was a higher percentage of "good" adherence when the key person "is aware" than when the key person "is not aware" of the therapeutic effect (P = 0.001). Key person's attitude toward cognitive impairment treatment (positive/negative): There was a higher percentage of "good" adherence when the key person was "positive" than when the key person was "negative" about treatment (P < 0.001). The factors sex, age, medical institution visited, regimen prescribed, and whether patient personally sees physician to get prescription did not show a relationship with adherence.

3.4. Building the Decision Tree Model

There were 418 subjects in the analysis, after excluding patients for whom the "information was unavailable" or there was "no response." **Figure 3** shows the results of the decision tree analysis conducted at the first parent node (node 0). A total of 6 child nodes (nodes 1 to 6) were obtained in this analysis. Four of these (nodes 3 to 6)

