Table 4. Results-1.

1) Patient profile	1-a). Sex	Male	34.0%
		Female	66.0%
	1-b). Age	Av. 81.0 yrs (S.D.7.1)	
	1-c). Medical institution visited	Clinic or physician's office	55.4%
		Private hospital	21.5%
		Public hospital	18.0%
		University hospital	5.1%
2) Regimen prescribed	2-a). Donepezil strength & 2-b). Dosage form	Tab 3 mg	3.1%
		Tab 5 mg	24.2%
		Tab 10 mg	0.2%
		OD tab 3 mg	9.0%
		OD tab 5 mg	54.9%
		OD tab 10 mg	8.4%
		Fine granule	0.2%
	2-c). Dosage	Before Breakfast	0.9%
		After Breakfast	88.9%
		After Lunch	0.6%
		After Dinner	7.9%
		Before Bed	0.9%
		Other	0.9%
	2-d). Supply dispensed per prescription	Av. 33.5 days (S.D., 20.5)	
	2-e). How dispensed	Alone in a blister package	56.3%
		One-dose packages with other drugs	39.1%
		One-dose packages with donepezil alone (without other drugs)	4.7%
	2-f). Concomitant drugs	Av. 3.1 medicines (S.D., 2.9)	
3) Physician consultation status		Patient himself/herself sees physician	77.5%
		Someone besides the patient sees the physician	10.0%
		Unknown	12.5%
4) Donepezil adherence		Take all as instructed (4)	81.2%
		Forget once or twice a week (3)	10.2%
		Only take once or twice a week (2)	0.9%
		Never take (1)	0.2%
		Information unavailable (0)	7.5%
5) "Key person" who has the central role in overseeing the donepezil adherence		A family member other than spouse such as a daughter	38.6%
		Spouse	22.6%
		Patient	22.3%
		Professional caretaker	16.5%

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Table 5. Results-2.

6) Key person's understanding of donepezil	6-a). Understanding of donepezil administration and dosage	Understands well (4)	31.30%
		Mostly understands (3)	40.30%
		Does not understand very well (2)	7.50%
		Does not understand at all (1)	1.50%
		Unknown (0)	19.40%
	6-b). Understanding of effect	Understands well (4)	22.30%
		Mostly understands (3)	46.80%
		Does not understand very well (2)	9.20%
		Does not understand at all (1)	1.50%
		Unknown (0)	20.30%
	6-c). Understanding of general side effect	Understands well (4)	13.40%
		Mostly understands (3)	39.50%
		Does not understand very well (2)	17.70%
		Does not understand at all (1)	2.90%
		Unknown (0)	26.50%
7) Key person's understanding of cognitive impairment	7-a). Understanding of the characteristic symptoms of cognitive impairment	Understands well (4)	16.3%
		Mostly understands (3)	42.8%
		Does not understand very well (2)	13.2%
		Does not understand at all (1)	1.5%
		Unknown (0)	26.3%
	7-b). Understanding of the treating Physician's treatment plan	Understands well (4)	19.2%
		Mostly understands (3)	37.2%
		Does not understand very well (2)	12.7%
		Does not understand at all (1)	1.3%
		Unknown (0)	29.6%
8) Key person's awareness of own cognitive impairment		Well aware (4)	26.5%
		Mostly aware (3)	37.8%
		Not very aware (2)	10.2%
		Completely unaware (1)	1.7%
		Unknown (0)	23.8%
9) Key person's awareness of therapeutic effect		Has a thorough awareness (4)	7.1%
		Has a general awareness (3)	20.7%
		Does not have a very good awareness (2)	26.5%
		Has no awareness (1)	2.9%
		Unknown (0)	42.8%
10) Key person's attitude toward treatment (positive/negative)		Positive (4)	15.4%
		Somewhat positive (3)	39.5%
		Somewhat negative (2)	7.9%
		Negative (1)	1.3%
		Unknown (0)	35.9%

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Table 6. Factors related to adherence.

| Items (n)		Adherence (%)		P
		Good	Poor	
Key person (407)	Patient	87.5	12.5	0.004
	Spouse	92.3	7.7	
	Family member other than spouse	81.4	18.6	
	Professional caretaker	97.0	3.0	
Understanding of usage and dosage about Donepezil (365)	Understands	88.7	11.3	<0.001
	Does not understand	65.8	34.2	
Understanding of Donepezil's effects (363)	Understands	88.6	11.4	0.002
	Does not understand	72.3	27.7	
Understanding of Donepezil's side effects (334)	Understands	91.3	8.7	<0.001
	Does not understand	72.3	27.7	
Understanding of characteristic symptoms of cognitive impairment (339)	Understands	89.8	10.2	<0.001
	Does not understand	70.8	29.2	
Understanding of physician's therapeutic plan (322)	Understands	90.4	9.6	<0.001
	Does not understand	67.7	32.3	
Awareness of own cognitive impairment (349)	Aware	89.2	10.8	0.001
	Not aware	71.7	28.3	
Awareness of therapeutic effect (270)	Has awareness	92.4	7.6	0.001
	Does not have awareness	77.5	22.5	
Attitude toward cognitive impairment treatment (296)	Positive	89.1	10.9	<0.001
	Negative	67.5	32.5	
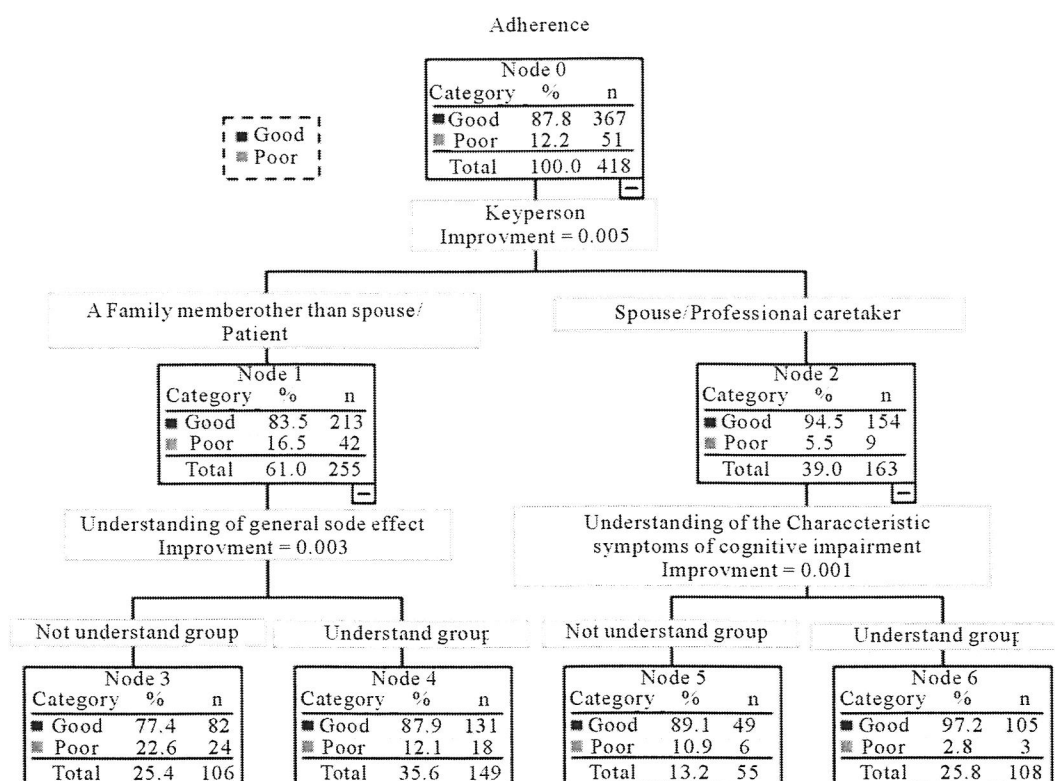
Figure 3. The result of decision tree analysis.

were terminal nodes (where splitting stopped). The deepest splitting in the decision tree model was to the 2nd level.

"Key person" was selected as the factor that would be split at node 0. On the process of the decision tree modeling, the key person was split on the group having "the patient" or "a family member other than the spouse" as the key person (node 1) and the group having "the spouse" or "a professional caretaker" as the key person (node 2), and there was a higher percentage of "good" adherence in node 2 than node 1. Nodes 1 and 2 were also split at the next level. "The key person's understanding of donepezil's side effects" was selected as the factor on which node 1 would be split. There was a higher rate of "good" adherence in the group that gave the response of "4. Understands well" and "3. Mostly understands" (node 4) for "key person's understanding of donepezil's side effects" than in the group that responded "2. Does not understand very well" to "0. Unknown" (node 3). Node 2 was split on the factor "the key person's understanding of the characteristic symptoms of cognitive impairment". There was a higher rate of "good" adherence in the group that gave the response of "4. Understands well" or "3. Mostly understands" (node 6) for "the key person's understanding of the characteristic symptoms of cognitive impairment" than in the group that responded "2. Does not understand very well" or "0. Unknown" (node 5).

Decision trees are generally "pruned" to limit the number of levels so that the results will not be overly complex. However, since the analysis stopped after generating only 2 levels, we did not do any pruning and used the results here as is.

4. Discussion

In our study, 81.2% of the patient data showed "take all as instructed". The results indicated that general adherence to donepezil treatment regimens was good in outpatients with cognitive impairment. This trend is consistent with previous studies [18,19]. The χ^2 test results also suggested that all types of key persons contributed to adherence, that not only a professional caretaker but also a family member involved contributed to the adherence to donepezile, and that it was possible that adherence could improve with education by pharmacist to the key person.

Our result suggested that the relationship of the key person with adherence is such that adherence is comparatively low when the key person is the patient himself/herself or a family member other than the spouse, and that adherence is good when the key person is "a professional caretaker". This may be because it is highly likely that a patient with a professional caretaker as the

key person lives in a care facility and adherence is maintained because the facility staff manages the patient's medication.

This issue is correspondent with the issue written by Kemuyama, which said care workers in care facilities of cognitively imparied patients are required to stay compliant by recognizing the symptoms [31].

Furthermore, our results implied that maintaining adherence has a linkage with improving knowledge about the medication (knowledge of donepezil administration and dosage, effects, and general side effects) and with improving the key person's understanding of the symptoms of cognitive impairment and the physician's treatment plan. The relationship with adherence of the key person's awareness of his own cognitive impairment may be such that if the key person is aware that he has cognitive impairment, the significance of the drug treatment regimen will become clear and adherence will be maintained. It was also confirmed that the key person's awareness of the effectiveness of the therapy and attitude toward the treatment (positive/negative) are related to maintaining adherence. Donepezil does not promise to improve symptoms markedly; rather, the objective of the therapy is to "maintain the status quo" by slowing down the progression of symptoms. Given the nature of donepezil therapy for cognitive impairment, the present results suggested that the ability to increase the key person's understanding of the significance of taking donepezil or his or her awareness of its effectiveness holds the key to improved attitude toward the treatment (positive/negative) and, in turn, maintaining adherence.

The results of the decision tree modeling showed that the key person has the strongest relationship with adherence. On the process of the decision tree analysis, key person was split on the group having "the patient" or "a family member other than the spouse" as the key person (node 1) and the group having "the spouse" or "a professional care taker" as the key person (node 2). Node 1 was then split on "the key person's understanding of donepezil's side effects," and node 2 was split on "the key person's understanding of the characteristic symptoms of cognitive impairment." This suggests that the first step in maintaining and improving adherence is to know who the "key person" is.

The extent of the key person's involvement in care giving may be the reason why the factors related to adherence differed according to who the key person is. Since "the spouse" or "a professional caretaker " at node 2 is frequently in a position to directly support the patient's activities of daily life, there was a tendency for adherence to be higher when the key person's understanding of the patient's symptoms was good. Conversely, with "a family member other than the spouse or patient" at node 1, adherence tended to be higher when

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there was a good understanding of side effects because 1) there is a tendency to deny the presence of cognitive impairment and 2) a good understanding of the side effects eliminates resistance to and anxiety about taking the medication.

Jane R. *et al.* said it is important that a pharmacist educates the care-giver of the cognitively impaired patient [32], and this research suggested the possibility that "education to have you understand the symptoms of cognitive impairment" was effective.

The results also suggested that "to educate about symptom of cognitive impairment" is more effective for persons who are directly involved in the care such as the spouse or caretakers.

In addition, Sen-Roy states that a pharmacist should tell the patient and his or her family that the drug used in the treatment of cognitive impairment is for the purpose of maintaining the status quo [29], but our study suggested that it is important that the pharmacist informs about the "side effects and cognitive impairment symptoms". Furthermore, it was suggested that points of reporting were different by key person.

A study about classification of care-givers of cognitive impairment patients, report on a male spouse [34] and an unpleasant female spouse [35], but our study suggests the possibility that education for a family except the spouse influenced adherence to medication.

Jane R. mentions the education that pharmacist provides to the care-giver should be done based on the observation of the behavioral disorder of the cognitive impairment patients living in the local area, because pharmacists are able to contact them on a regular basis [28].

We believe that we were able to clearly state "what kind of education is effective for what kind of caregiver" by this study.

Mort and Tasler wrote that pharmacists must educate caregivers of cognitive impairment patients [28], and our present study also suggested that educating caregivers on the symptoms of cognitive impairment is potentially effective. Sen-Roy wrote that the patient and his or her family should be told that medications for cognitive impairment simply maintain the status quo [29]. However, our results confirmed that it is important to provide information about the side effects of cognitive impairment medications and the symptoms of the disease, as well as the "effects" of the medication. In addition, our results suggested that the information to be provided to key persons differs according to who the key person is.

In the present study, we performed a statistical analysis of data based on the information that pharmacists record in the patients' profiling system called "YAKU-REKI", but there were many responses of "Unknown" for certain items on the survey, reflecting the fact that a sufficient amount of information is not being obtained

and/or the pharmacist may have transcribing errors. This is because it is difficult for the pharmacist to directly confirm the patient's condition and the pharmacist can only hear indirectly from caregivers, family members, and the like, since there are many cases in which the person who visits the pharmacy is not the patient himself/herself, given the nature of cognitive impairment. Consequently, pharmacists must make a greater effort to collect information from the people who go to pharmacies to receive medicines and from other healthcare professionals, and to record more information in the profiling system.

5. Limitations of the Study

The objective of the present study was to identify factors related to treatment adherence in outpatients with cognitive impairment by examining the regimens prescribed and treatment adherence at community pharmacies in Japan. However, we became aware of 2 limitations to the study due to its special circumstances.

The first limitation is that it is difficult to identify patients with cognitive impairment because pharmacists at Japanese community pharmacies cannot view the medical records kept by physicians and diagnoses are not written on prescriptions. We therefore considered patients prescribed donepezil to be "patients with cognitive impairment" because the acetylcholinesterase inhibitor was the only drug approved for cognitive impairment in Japan at the time of the survey. As a result, one cannot rule out the possibility that patients with cognitive impairment not taking donepezil were excluded from the study.

The second limitation concerns the method of assessing adherence. The authors developed their own measures of adherence since a standardized assessment tool does not exist in Japan. In the present study, we did not question patients directly about adherence, but rather selected a protocol under which pharmacists performed an objective assessment using data in the profiling system. Therefore, we concluded that an evaluation using pill counts and multiple choices would not be valid as an adherence assessment scale for the present study, and we adopted an assessment scale in which "information unavailable" was added to a 4-grade scale for frequency of forgetting to take medication per week. The pharmacists who participated in the pilot study said that this assessment scale afforded easy communication with the key person, enabling them to make an assessment reflecting the actual situation. It was therefore concluded that the present assessment method would not present major problems in the interpretation of the results.

6. Conclusion

It was confirmed that the key person's understanding of

the medication and symptoms of cognitive impairment are related to adherence in outpatients with cognitive impairment. 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 therefore essential in the treatment of cognitive impairment to accurately identify the key person, collect suitable information on the patient, provide the counseling desired, and provide instructions on taking the medication.

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