

Original Article
Neuroscience



Adherence of Anti-Dementia Medications in Alzheimer's Disease and Related Dementia: A Nationwide Cohort Study in Korea

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Received: Nov 14, 2024

Accepted: Feb 19, 2025

Published online: Aug 5, 2025

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ABSTRACT

Background: Readily available treatments for Alzheimer's disease and related dementia (ADRD) include acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists. Non-adherence and early discontinuation of anti-dementia medications are prevalent issues. We aimed to investigate factors associated with suboptimal usage of anti-dementia medications in ADRD.

Methods: Based on data extracted from a claim database in South Korea, 508,958 patients with ADRD who began taking anti-dementia medication between 2018 and 2020 were included. The mean possession ratio is the ratio of the sum of prescribed medication supply over one year and non-adherence is defined as mean possession ratio < 80%. Discontinuation is defined as no prescription of anti-dementia medications, or no switch to other anti-dementia medications, within 45 days after the run-out date. The cumulative incidence of discontinuation of anti-dementia medication was estimated using the Kaplan-Meier method. Factors associated with non-adherence were evaluated using logistic regression analyses.

Results: Within the first year, the non-adherence ratio was 40.8%, while the discontinuation ratio was 43.6%, and approximately 30% of patients discontinued medication within 90 days after initiation. Younger age at diagnosis, female sex, and prescription at non-tertiary hospitals or clinics other than neurology/psychiatry were associated with increased risk of non-adherence. Compared with Seoul, a prescription issued by neurology/psychiatry departments at a tertiary hospital in other provinces was associated with a 75% higher risk of non-adherence.

Conclusion: Strategies targeting non-adherence are warranted to minimize disparities in the management of patients with dementia.

Keywords: Alzheimer's Disease; Anti-Dementia Medication; Adherence; Discontinuation; Disparity

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of neurodegenerative dementia, and the number of patients is increasing rapidly as the population ages. Readily

Funding

This research was supported by the research grant funded by the Korean Dementia Association and by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare and Ministry of Science and ICT, Republic of Korea (grant number: HI22C0977).

Disclosure

The authors have no potential conflicts of interest to disclose.

Data Availability Statement

The data of this study can be made available from the NHIS of Korea upon reasonable request. Restrictions may be imposed on the availability of these data due to privacy or ethical concerns.

Author Contributions

Conceptualization: Lee E, Kang S, Ye BS, Lee YG. Data curation: Lee E, Lee YG. Formal analysis: Lee E, Lee YG. Investigation: Lee E, Lee YG. Methodology: Lee E, Lee YG. Writing - original draft: Lee E. Writing - review & editing: Kang S, Ye BS, Lee YG.

available treatments for Alzheimer's disease and related dementia (ADRD) include acetylcholinesterase inhibitors (AChEi) and an N-methyl-D-aspartate (NMDA) receptor antagonists; these drugs are recognized by the US Food and Drug Administration for their efficacy in cases of mild and moderate AD,^{1,2} and are used as official treatments worldwide.^{3,4} The effects of these drugs are also proven in cases of Lewy body dementia and vascular dementia⁵⁻⁷; therefore, they are frequently prescribed "off-label" for other types of non-AD dementia.

Although there is strong evidence that symptoms worsen after discontinuation of the drugs,^{8,9} suboptimal adherence and early discontinuation of anti-dementia medications are prevalent issues. Studies based on claims from countries in Europe reveal that 10–30% of patients discontinue the medication within a year.¹⁰⁻¹² Analysis of Medicare data from the United States shows a discontinuation rate of 21.7–24%, and 44% suboptimal adherence.^{13,14} Hospital-based data from Asia also shows persistence rate of anti-dementia medication within a year ranging from 50–70%.^{15,16}

Although patient-related factors such as age, sex, and co-morbidities are associated with compliance with anti-dementia medications,^{10,11,17,18} there is ample evidence that healthcare system-related factors influencing patient compliance. Some studies reveal that ethnicity and socioeconomic factors are associated with suboptimal adherence.¹⁴ Healthcare system-related factors such as hospital class, reimbursement for medications, and the specialty of the prescriber are also associated with medication usage patterns.^{10,15,19,20} Furthermore, health disparities play a role in the diagnosis and management of dementia.^{21,22} Evaluation of clinical and socioeconomic factors associated with suboptimal adherence or discontinuation of anti-dementia medications will also impact adherence to the new era of availability of disease modifying treatment of AD, including anti-amyloid monoclonal antibodies.²³⁻²⁵ However, identifying factors associated with adherence and compliance with anti-dementia medications is not straightforward because multiple factors, including ethnic-racial, socioeconomic, or regional factors, are intermixed. Furthermore, the heterogeneous status of insurance coverage within a nation may affect medication usage patterns, which limits the generalization of the findings.²⁶ In this study, we utilized a longitudinal claim database in South Korea, which adopted a system of single national health insurance in 2000. The objective was to evaluate healthcare system-related factors that are associated with non-adherence, as well as regional disparities in anti-dementia medication usage patterns by patients with ADRD.

METHODS

Study design and data source

This study is based on a retrospective analysis of a longitudinal cohort extracted from a nationwide claim database. In South Korea, approximately 97% of the population is registered under the obligatory National Health Insurance Service (NHIS), while the remaining 3% is covered by national medical aid based on socioeconomic status. All medical utilization within NHIS and medical aid programs is closely monitored with respect to reimbursement, and health facilities are responsible for submitting claims for reimbursement. The medical data collected by the NHIS are accessible through the National Health Information Database.²⁷

Based on the Korean Standard Classification of Disease Version 7 (a modified version of the International Statistical Classification of Disease and Related Health Problems, 10th Revision, Clinical Modification [ICD-10 CM] codes), ADRD was defined as F00 or G30 for AD, F01 for vascular dementia, and F03 or G31 for other types of dementia. Information related to prescription of anti-dementia medication was retrieved using the prescription claim codes for AChEi (donepezil, galantamine, and rivastigmine) and an NMDA receptor antagonist (memantine). The NHIS mandates cognitive and clinical assessment prior to prescription of AChEi and memantine: a Mini-Mental State Examination (MMSE) score ≤ 26 , and either a Clinical Dementia Rating (CDR) ≥ 1 or a Global Deterioration Scale (GDS) ≥ 3 , are required for AChEi prescription, whereas an MMSE score ≤ 20 and either CDR ≥ 2 or GDS ≥ 4 are necessary for memantine prescription.

Selection of the study population

A flowchart showing selection of the study population is shown in **Fig. 1**. Individuals diagnosed with ADRD and first prescribed anti-dementia medication between 2018 and 2020, and who had not previously been prescribed anti-dementia medication prior to 2017, were screened for eligibility. After excluding those aged < 65 years at the medication index date, and those who were not enrolled in the health insurance service < 1 year after the date of first prescription, the study finally included 508,958 individuals.

Definition of variables

Age at the time of prescription was categorized as 65–74, 75–85, or > 85 years. The Charlson comorbidity index (CCI) was determined from insurance claims (looking back 1-year from the index date); those with a CCI < 2 were determined as having low co-morbidity, while those with a CCI ≥ 2 were determined as having high comorbidity. Insurance type was used as a marker of socioeconomic status because qualification for medical aid is determined by annual income. Hospitals in South Korea are classified into three types (primary, secondary, and tertiary), and patients are referred from primary or secondary class hospitals to tertiary class hospitals. The department that issued the prescription was classified as follows: specialist dementia clinics (e.g., neurology or psychiatry), and non-specialist clinics. Regions were divided into four categories (**Supplementary Fig. 1**): 1) Seoul, a metropolitan capital city; 2) other metropolitan cities (Incheon, Daejeon, Gwangju, Daegu, Ulsan and Busan); 3) a satellite province of Seoul (Gyeonggi-do); and 4) other provinces (Gangwon-do, Chungcheongbuk-do, Chungcheongnam-do, Jeollabuk-do, Jeollanam-do, Gyeongsangbuk-do, Gyeongsangnam-do, Sejong-si, and Jeju-do). The number of neurologist/psychiatrist per 1,000 patients with dementia or the number of tertiary hospitals per 1,000 patients with dementia during the study period (**Supplementary Fig. 2A and B**) were retrieved from Korean Dementia Observatory.²⁸

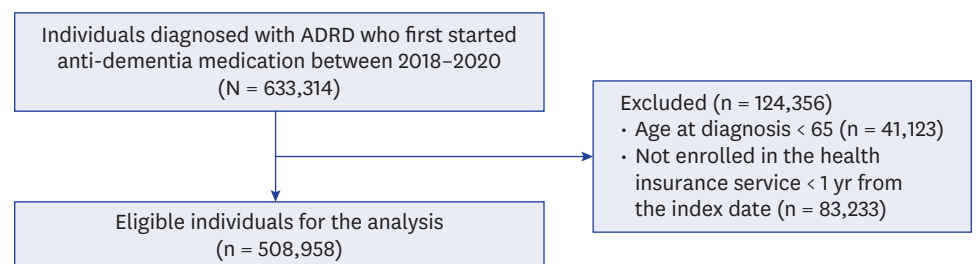


Fig. 1. Flowchart showing selection of the study population. ADRD = Alzheimer's disease and related dementia.

Definition of medication prescription patterns

The initial fill date was defined as the day on which the anti-dementia medications were first prescribed. Refill dates are the days on which patients re-visited the clinic to refill their anti-dementia medications. Run-out dates are the days when the prescribed medications need to be refilled, which is computed by the days of supply of medication after initial fill or following refill dates. The mean possession ratio is the ratio of the sum of prescribed medication supply over fixed pre-defined duration and was calculated as $\text{Days covered by prescription} / 365 \text{ days} \times 100 (\%)$. Non-adherence is defined as mean possession ratio $< 80\%$.^{14,15} Discontinuation is defined as no prescription of anti-dementia medications, or no switch to other anti-dementia medications, within 45 days after the run-out date.^{13,14} The index discontinuation date was defined as the run-out date on which the first discontinuation occurred.

Statistical analysis

Statistical analyses were performed using R statistical software (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria). The cumulative incidence of discontinuation of anti-dementia medication was estimated and then plotted using the Kaplan-Meier method. Univariable logistic regression was performed to evaluate the effect of baseline characteristics on non-adherence to anti-dementia medication. We further explored the potential nonlinear association between age or CCI and the risk of non-adherence to anti-dementia medication using natural cubic splines in the logistic regression models. Multivariable logistic regression analyses were performed using factors that were significant in the univariable analysis. Because nationwide data are nested within the 17 administrative regions of South Korea, logistic regression analyses were conducted using multilevel hierarchical models. To further evaluate regional disparities regarding medication usage patterns, the population was further divided by hospital class (tertiary vs. non-tertiary) or clinic specialty (neurology/psychiatry vs. other). The effect of region on non-adherence to anti-dementia medications in each subgroup was then evaluated. Seoul, the metropolitan capital city of South Korea, was used as reference for comparison among regions. Relationship between odds ratio for non-adherence and the number of neurologists/psychiatrists per 1,000 patients with dementia or the number of tertiary hospitals per 1,000 patients with dementia was evaluated using Pearson's correlation coefficients (r).

Ethics statement

The study was approved by the Institutional Review Board (IRB) of the Ilsan Paik Hospital, Inje University College of Medicine (IRB No. 2023-08-017). The requirement for written informed consent was waived due to the retrospective nature of the study, and the fact that data were extracted from a fully anonymized secondary database.

RESULTS

Demographic and clinical characteristics

The demographic and clinical characteristics of the study participants ($N = 508,958$) are summarized in **Table 1**. At the index date (start of anti-dementia medication), the median age was 80 years (interquartile range = 9); 68.7% of the cohort was female. Among all participants, 66,754 (13.1%) were enrolled by medical aid type insurance. Most participants (42.8%) were prescribed anti-dementia medication in tertiary class hospitals; 330,709 participants (65.0%) were prescribed medication by a specialist clinic (neurology or

Table 1. Demographic characteristics of the study participants

Characteristics	Values
No. of participants	508,958
Median age at the start of medication (IQR)	80 (9)
Female	349,695 (68.7)
Insurance type	
NHIS	
Medical aid	66,754 (13.1)
Hospital class	
Tertiary hospital	217,911 (42.8)
Non-tertiary hospital	291,047 (57.2)
Clinic specialty	
Neurologist or psychiatrist	330,708 (65.0)
Others	178,250 (35.0)
Region	
Seoul	70,873 (13.9)
Other metropolitan cities	127,974 (25.1)
A satellite province of Seoul (Gyeonggi-do)	93,317 (18.3)
Other provinces	216,794 (42.6)
Mean Charlson Comorbidity Index (SD)	2.9 (2.4)
Low co-morbidity [< 2]	166,962 (32.8)
High co-morbidity [≥ 2]	341,996 (67.2)
Mean possession ratio (SD)	77.0 (45.7)
Non-adherence [MPR < 80]	207,854 (40.8)
Discontinuation	221,899 (43.6)

Values are presented as number (%) unless otherwise indicated.

IQR = interquartile range, NHIS = National Health Insurance Service, SD = standard deviation, MPR = mean possession ratio.

psychiatry). The mean CCI was 2.9 (standard deviation [SD] = 2.4), and approximately 67.2% of participants had high levels of co-morbidity (CCI ≥ 2).

Non-adherence and discontinuation of anti-dementia medication within 1 year

During 1-year of follow-up, the mean possession ratio was 77.0% (SD = 45.7) and the non-adherence ratio was 40.8%, while the discontinuation ratio was 43.6% (Table 1). During first year after the start of anti-dementia medication, approximately 30% of patients discontinued medication within 90 days after initiation (Fig. 2).

Effects of baseline characteristics on non-adherence of anti-dementia medication

Univariable multilevel logistic regression analysis revealed that the older age was associated with a lower risk of non-adherence to anti-dementia medication within one year of initiation. Specifically, individuals aged 75–85 years had a lower risk compared to those aged 65–74 years (odds ratio [OR], 0.945; 95% confidence interval [CI], 0.932–0.959), and those aged 85 years or older also had a lower risk compared to the 65–74 age group (OR, 0.940; 95% CI, 0.924–0.955). In the logistic regression model incorporating natural cubic splines of age, there was a linear decrease in the risk of non-adherence in 65–75 and 85+ age groups, with a plateau observed in the 75–85 age group (Supplementary Fig. 3A). Similarly, higher co-morbidity (CCI > 2) was associated with a reduced risk of non-adherence (OR, 0.959; 95% CI, 0.948–0.971). For the model using natural cubic splines of CCI, the risk of non-adherence decreased linearly with increasing CCI up to approximately 2, after which the risk stabilized, forming a plateau (Supplementary Fig. 3B).

In contrast, certain factors were associated with a higher risk of non-adherence during the first year of anti-dementia medication use. These included female sex (OR, 1.085; 95%

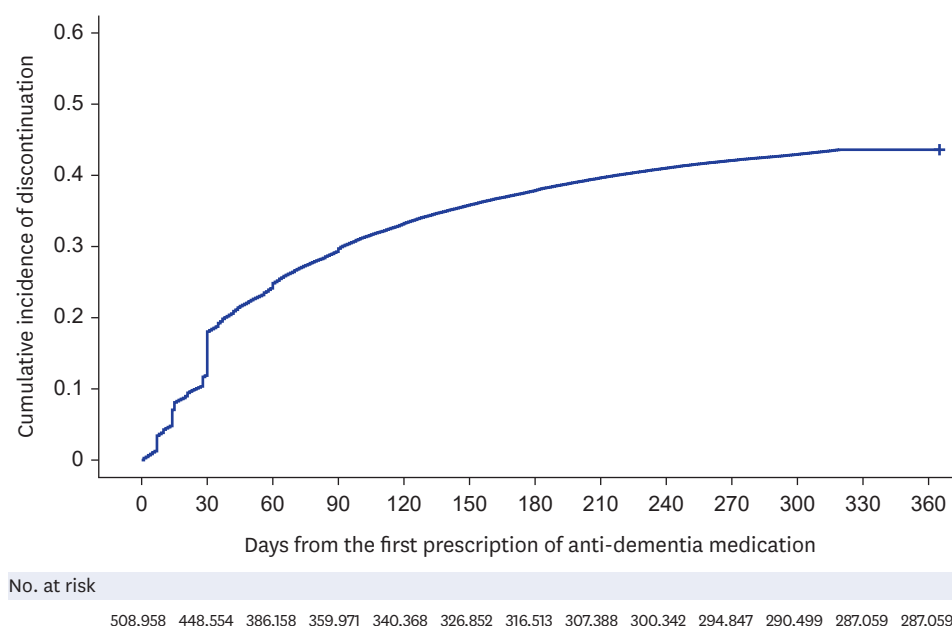


Fig. 2. Cumulative incidence of discontinuation of anti-dementia medication. The proportion of patients who discontinued anti-dementia medications was estimated using the Kaplan-Meier method. Discontinuation was defined as cessation of medication, or no switch to other anti-dementia medication, for more than 45 days beyond the expected refill date.

CI, 1.072–1.099), medical aid type insurance (OR, 1.075; 95% CI, 1.059–1.092), treatment at non-tertiary hospital (OR, 1.727; 95% CI, 1.707–1.748), and treatment by clinical specialties other than neurology or psychiatry (OR, 1.157; 95% CI, 1.143–1.171).

Multivariable multilevel logistic regression analysis revealed a significant negative interaction between hospital class and clinic specialty with respect to the risk of non-adherence to anti-dementia medication (OR, 0.497; 95% CI, 0.484–0.511; **Table 2**). Subgroup analysis according to hospital class and clinic specialty identified the highest risk of non-adherence in those prescribed medication by a neurologist or psychiatrist at a non-tertiary hospital (**Supplementary Fig. 4**). The cumulative incidence of discontinuation showed that the discontinuation rate of those prescribed anti-dementia medication at neurology or psychiatry clinics at tertiary class hospitals reached 20% at 90 days, compared with over 35% of those prescribed medications at neurology or psychiatry clinics at non-tertiary class hospitals (**Supplementary Fig. 5**).

Effect of region on non-adherence to anti-dementia medications

Multivariable logistic regression analysis revealed a significant interaction effect between regions and clinic specialty or hospital class (**Supplementary Table 1**). Subgrouping according to clinic specialty and hospital class revealed regional differences with respect to the risk of non-adherence to anti-dementia medications were most pronounced in the subgroup prescribed medications by neurology and psychiatry clinics or a tertiary hospital; compared with Seoul, there was a 75% increase in the risk of non-adherence in other provinces (i.e., there was a 35% and 25% increased risk of non-adherence in the satellite province of Seoul and in metropolitan cities, respectively; **Fig. 3**). Subgrouping according to clinical specialty (neurology or psychiatry) revealed a strong correlation between the number of neurologists or psychiatrists per 1,000 dementia patients in each region and

Table 2. Effect of demographic factors on non-adherence to anti-dementia medication

Variables	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, yr				
65–74	Reference		Reference	
75–85	0.945 (0.932–0.959)	< 0.001	0.919 (0.905–0.933)	< 0.001
85+	0.940 (0.924–0.955)	< 0.001	0.864 (0.849–0.879)	< 0.001
Sex				
Male	Reference		Reference	
Female	1.085 (1.072–1.099)	< 0.001	1.061 (1.048–1.075)	< 0.001
Charlson Comorbidity Index				
Low co-morbidity (< 2)	Reference		Reference	
High co-morbidity (≥ 2)	0.959 (0.948–0.971)	< 0.001	0.971 (0.959–0.983)	< 0.001
Insurance type				
NHIS	Reference			
Medial aid	1.075 (1.059–1.092)	< 0.001	1.021 (1.005–1.038)	0.012
Hospital class				
Tertiary hospital	Reference		Reference	
Non-tertiary hospital	1.727 (1.707–1.748)	< 0.001	2.113 (2.082–2.144)	< 0.001
Clinic specialty				
Neurology/Psychiatry clinic	Reference		Reference	
Other clinics	1.157 (1.143–1.171)	< 0.001	1.610 (1.573–1.647)	< 0.001
Hospital class × Clinic specialty				
Tertiary hospital × Neurology/Psychiatry clinic			Reference	
Non-tertiary hospital × Other clinics			0.497 (0.484–0.511)	< 0.001

Data are derived from a multilevel linear regression model assessing the risk of non-adherence to anti-dementia medications.

OR = odds ratio, CI = confidence interval, NHIS = National Health Insurance Service.

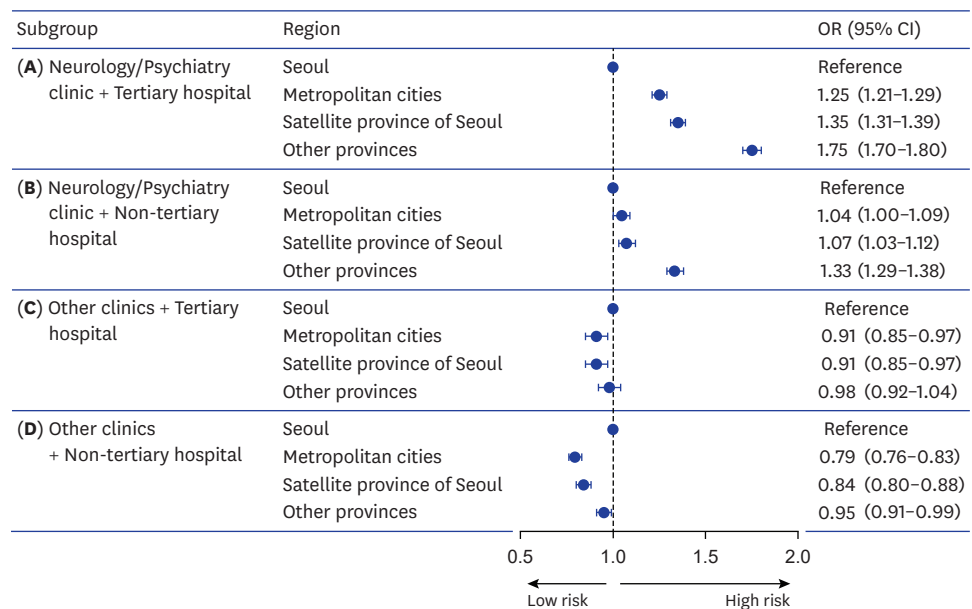


Fig. 3. Regional disparities in non-adherence to anti-dementia medication. Regional differences in the odds ratio for non-adherence in subgroups prescribed treatments at (A) a neurology/psychiatry clinic at a tertiary hospital, (B) a neurology/psychiatry clinic at a non-tertiary hospital, (C) a clinic with another specialty at a tertiary hospital, or (D) a clinic with another specialty at a non-tertiary hospital. The metropolitan capital city of South Korea, Seoul, was used as a reference. OR = odds ratio, CI = confidence interval.

the risk of non-adherence by patients ($r = -0.64$, $P = 0.005$; Fig. 4A); however, the number of tertiary hospitals per 1,000 dementia patients in each region did not correlate with the risk of non-adherence ($r = 0.02$, $P = 0.949$; Fig. 4B).

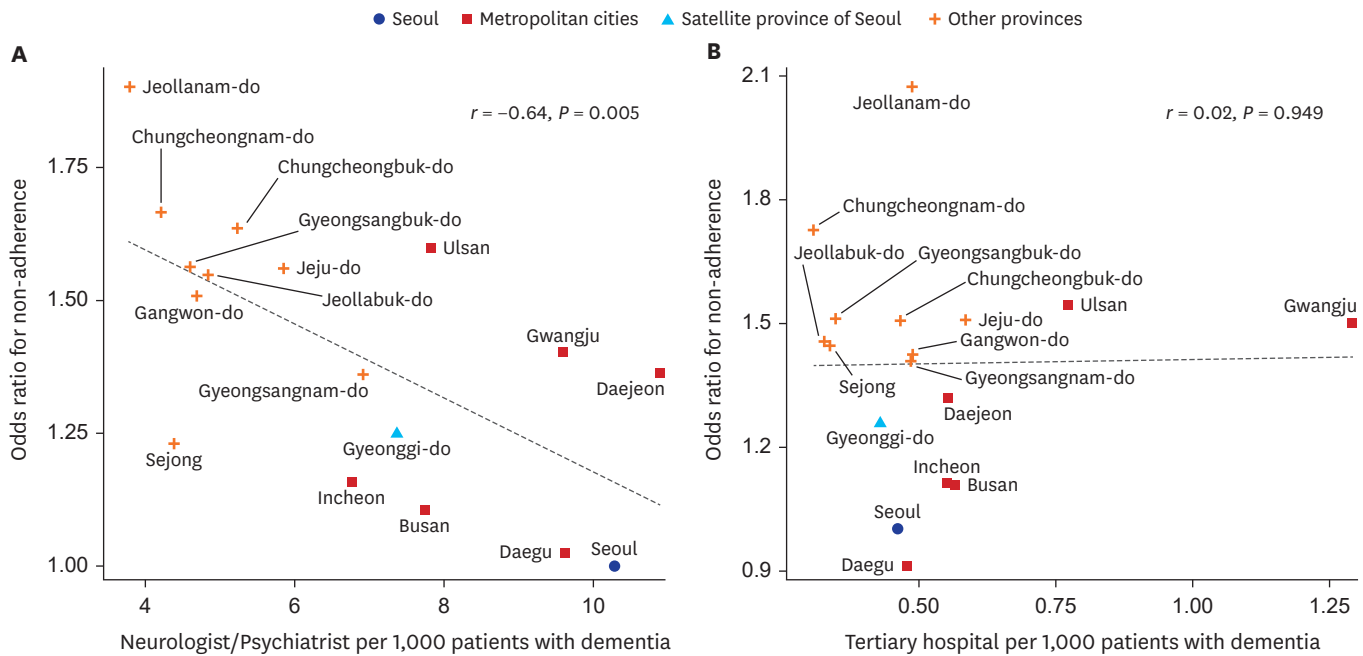


Fig. 4. Correlation between regional characteristics and the risk of non-adherence to anti-dementia medication. **(A)** Correlation between the odds ratio for non-adherence and the number of neurologists/psychiatrists per 1,000 patients with dementia in a subgroup of patients prescribed medication by a neurology/psychiatry clinic. **(B)** Correlation between the odds ratio for non-adherence and the number of tertiary hospitals per 1,000 patients with dementia in a subgroup prescribed medication at a tertiary hospital.

DISCUSSION

Here, we extracted data from a nationwide claim database in South Korea to evaluate use of anti-dementia medications by patients with ADRD. Within 1 year after initiating anti-dementia medication, the mean possession rate over 12 months was 77.0%; the non-adherence and discontinuation rates were 40.8% and 43.6%, respectively. At baseline, younger age, female sex, medical aid type insurance, non-tertiary hospital, and clinic specialty other than neurology or psychiatry were associated with suboptimal use of the drugs. Among those who started anti-dementia medications after attending neurology/psychiatry clinics, regional disparities in the level of non-adherence were pronounced; these disparities showed a strong correlation between the number of neurologists or psychiatrists relative to the number of dementia patients in each region.

Several population-based studies reported non-adherence and discontinuation rates related to anti-dementia medication. A study of 127,896 patients with dementia in Austria reported that 26% of patients discontinued anti-dementia medication within 1 year after initiation.¹² Another study based on Medicare data for approximately 1,343 patients with ADRD in the United States reported a discontinuation rate of 24% and a non-adherence rate of 44%,¹⁴ which are similar to our own results. Furthermore, our study revealed that over two-thirds of discontinuations occurred within the first 90 days. These observations suggest that readily available drugs for ADRD are not being taken properly⁹; thus, close observation and careful follow-up during the early period post-prescription is required.

Baseline clinical and socioeconomic factors were associated with adherence to anti-dementia medication. We found that female sex was associated with a higher risk of

discontinuation and non-adherence, consistent with previous studies reporting higher non-adherence in females.^{11,18,29} However, some studies found no significant associations between sex and adherence to anti-dementia medications.^{10,17} One previous study suggested that the sex of caregivers, rather than the sex of patients, plays a significant role in adherence to anti-dementia medications.³⁰ While we were unable to evaluate caregiver characteristics in this study, it is possible that the caregiving dynamic in married couples, where the caregiver is often of the opposite sex in South Korea, may influence adherence. This interaction remains speculative and warrants further investigation in future research. We also observed that older patients were less likely to discontinue medications. While some studies reported higher discontinuation rates in older patients, possibly reflecting concerns about increased side effects,^{11,17} others found higher adherence in older individuals.^{18,29} Several hypotheses may explain this trend. First, older adults may have fewer competing responsibilities, allowing better adherence.²⁹ Second, greater engagement with healthcare providers or caregivers in older age may contribute to improved medication adherence.³¹

Interestingly, we found that higher co-morbidity (CCI > 2) was associated with a lower risk of non-adherence, which aligns with previous studies demonstrating greater adherence among individuals with higher levels of co-morbidities.^{18,19} Several hypotheses may explain this paradoxical relationship between co-morbidity and adherence to anti-dementia medication. First, patients with multiple chronic conditions are often more engaged with healthcare providers and tend to be better educated in terms of compliance. Second, frequent visits to healthcare facilities provide opportunities for regular monitoring and reinforcement of adherence. One prior study found that frequent physician visits were associated with higher adherence, suggesting that increased exposure to the healthcare system may contribute to improved adherence.¹⁸ Third, patients with a higher CCI may benefit from tools or caregiver support to manage complex medication regimens, thereby enhancing adherence.²⁹ Our analysis, which utilized cubic splines of CCI as predictors, revealed that the risk of non-adherence was higher at lower CCI scores, particularly around a CCI index of 2. Beyond this point, the risk of non-adherence stabilized and plateaued, suggesting the presence of a co-morbidity threshold that may influence adherence to anti-dementia medications.

Healthcare service-related factors such as hospital class and clinic specialty were associated with adherence to anti-dementia medications. Hospital class and clinic specialty may be expected to affect compliance because clear communication and monitoring compliance after prescription of drugs are important for maintaining adherence. Reflecting this, higher hospital class and prescription by a specialist (i.e., neurologist or psychiatrist) are associated with lower rates of discontinuation and greater adherence to anti-dementia medications. Interestingly, we found a negative interaction between hospital class and clinic specialty with respect to the risk of non-adherence; for example, those prescribed anti-dementia medication by a neurologist or psychiatrist at a non-tertiary class hospital were at highest risk of displaying suboptimal usage patterns. We speculate that in contrast to more specialized clinics at tertiary hospitals in South Korea, not all neurology or psychiatry clinics are not specialized for differential diagnosis of AD/DRD. In addition, tertiary hospitals often have the infrastructure to perform cerebrospinal fluid tests, blood tests, and nuclear medicine tests for differential diagnosis of AD/DRD. This suggests that even in specialized fields such as neurology or psychiatry, compliance is better when drugs are prescribed by hospitals that can perform tests for differential diagnoses.

With respect to disparities regarding hospital class and availability of dementia specialists in South Korea (**Supplementary Fig. 2B and C**),³² we also evaluated regional disparities that may affect adherence to anti-dementia medication. Among those first prescribed anti-dementia medication by a neurologist or psychiatrist, we found a 75% increased risk of non-adherence in the other provinces compared with Seoul. Other metropolitan cities and a satellite province of Seoul had risk of non-adherence rates of 25% and 35%, respectively. A study from the United States also showed that participants in southern areas were less likely to adhere to anti-dementia medications than those from western areas^{29,33}; however, the regional differences in the previous study may have been confounded by the heterogeneous status of insurance coverage, racio-ethnic effects, and socioeconomic differences between regions.¹⁴ South Korea is a country with a homogenous ethnic population; thus, cultural background does not differ much by region. South Korea does have a national insurance system, but the regional disparities found in our study could be attributable to regional disparities in healthcare system-related factors. Supporting this hypothesis, we found that the number of neurologists or psychiatrists per 1,000 patients with ADRD correlated positively with the odds ratio for non-adherence to anti-dementia medications within a region; however, the number of tertiary class hospitals did not correlate with regional differences. These findings suggest that regional disparities with respect to adherence to anti-dementia medications is driven largely by the availability of clinics specializing in management of ADRD.

This study had several limitations. First, we used ICD-10 codes to define dementia and there is lack of diagnostic or clinical data. However, since there are score criteria for MMSE, CDR, and GDS for prescribing antidementia drugs, it can be assumed that the minimum examination was performed to define dementia patients who needed symptom-modifying drugs that this study analyzed. Second, this study excluded patients who stopped all medical claims related to or not related to dementia treatment within 1 year after starting anti-dementia medication. As these participants were likely to have had medical claims discontinued due to death and presumed to be in advanced stage of dementia, caution is required in interpretation. Third, the study could not fully account for factors contributing to regional differences in non-adherence. Although we found an association between the availability of neurologists or psychiatrists and regional non-adherence risks, the absence of data on regional disparities in terms of socioeconomic status, geographic accessibility, and public health resources other than hospital limits causal inference. These unmeasured variables may play a significant role in shaping adherence patterns and should be considered in future research to provide a more comprehensive understanding of regional disparities. Fourth, the reasons for non-adherence, particularly due to cholinergic side effects, could not be comprehensively assessed. Claims data lack clinical details to differentiate between temporary discontinuations from manageable side effects and permanent discontinuations due to unresolved adverse effects. While we attempted to address this by defining drug discontinuation as the absence of prescriptions for any anticholinesterase inhibitors or memantine within 45 days of the expected refill date, this approach may not fully account for patients who discontinue treatment due to persistent side effects. These limitations should be considered when interpreting the findings and applying them to clinical practice.

To summarize, we extracted data from a nationwide claim database in South Korea and evaluated factors associated with non-adherence to anti-dementia medication within 1 year after initiating treatment. Regional disparities in adherence to anti-dementia medications were pronounced and were related to prescription of medication by specialist clinics

and to the number of neurologists or psychiatrists per 1,000 patients with ADRD. Thus, future policies should consider addressing factors associated with non-adherence to anti-dementia medication, as well as regional disparities.

ACKNOWLEDGMENTS

The authors are grateful to all the participants in this study.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Effect of region, hospital class, and clinic specialty on non-adherence to anti-dementia medication

Supplementary Fig. 1

Categorization of administrative regions in South Korea. The regions of South Korea were divided into four categories: 1) Seoul, a metropolitan capital city; 2) other metropolitan cities (Incheon, Daejeon, Gwangju, Daegu, Ulsan, and Busan); 3) a satellite province of Seoul (Gyeonggi-do); and 4) other provinces (Gangwon-do, Chungcheongbuk-do, Chungcheongnam-do, Jeollabuk-do, Jeollanam-do, Gyeongsangbuk-do, Gyeongsangnam-do, Sejong-si, and Jeju-do).

Supplementary Fig. 2

The number of neurologists or psychiatrists and tertiary hospital per 1,000 patients with ADRD. Differences in the availability of neurologists/psychiatrists (A) and tertiary hospitals (B) per 1,000 patients with ADRD in each of the 17 administrative region of South Korea were mapped.

Supplementary Fig. 3

Risk of non-adherence to anti-dementia medications according to age and co-morbidity. Data are the results of univariable logistic regression models for non-adherence to anti-dementia medication using natural cubic splines of age (A) and Charlson comorbidity index (B) as predictors. The dashed orange lines indicate 95% confidence interval.

Supplementary Fig. 4

Subgroup comparison of non-adherence to anti-dementia medications according to hospital class and clinic specialty. Data are derived from multilevel linear regression analysis of the risk of non-adherence to anti-dementia medication.

Supplementary Fig. 5

Cumulative incidence of discontinuation of anti-dementia medication. The proportion of patients in each subgroup (according to hospital class and clinic specialty) who discontinued anti-dementia medications was estimated using the Kaplan-Meier method. Discontinuation was defined as cessation of medication, or no switch to another anti-dementia medication for more than 45 days beyond the expected refill date.

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