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RESEARCH ARTICLE

Trends and determinants of choline alfoscerate use in newly diagnosed Alzheimer's disease patients in Korea

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Abstract

BACKGROUND: Choline alfoscerate, a cholinergic precursor, is widely used in Korea for dementia-related symptoms and is covered by national health insurance (NHI). This study investigates the utilization trends and factors influencing choline alfoscerate prescription in newly diagnosed Alzheimer's disease (AD) patients using real-world data.

METHODS: We analyzed data from the Health Insurance Review and Assessment Service (HIRA) for patients aged 60 years and older who were newly diagnosed with AD between 2012 and 2019. Patients with prescriptions for acetylcholinesterase inhibitors (AChEIs) or memantine within 60 days of diagnosis were included. Choline alfoscerate utilization was defined as prescriptions within 60 days of initial diagnosis. Factors influencing its use were identified through multiple logistic regression analyses, and trends over time were assessed using the Cochran–Armitage Trend test.

RESULTS: Among the 330,326 study participants, 99,845 (33.08%) were prescribed choline alfoscerate, with usage increasing from 15.96% in 2012 to 47.65% in 2019. Factors positively associated with its use included male sex, MedAid insurance, and osteoarthritis. Conversely, usage decreased with comorbidities such as hypertension, congestive heart failure, stroke/transient ischemic attack, chronic kidney disease, and depression.

CONCLUSION: Choline alfoscerate usage in Korea has significantly increased, partly due to its national insurance coverage and the absence of disease-modifying therapies for AD. Given the uncertain efficacy and potential risks of choline alfoscerate, continuous monitoring and rigorous evaluation of its long-term benefits and safety are essential. Further research is necessary to establish definitive evidence for its effectiveness and guide its therapeutic use in AD management.

KEYWORDS
acetylcholinesterase inhibitors, Alzheimer's disease, choline alfoscerate, memantine

Highlights

- Choline alfoscerate usage among newly diagnosed AD patients in Korea increased from 15.96% in 2012 to 47.65% in 2019.
- Male sex (OR = 1.05) and MedAid insurance coverage (OR = 1.07) were associated with higher odds of choline alfoscerate usage.
- Usage was more likely in patients with osteoarthritis (OR = 1.05) and less likely among those with hypertension (OR = 0.96), stroke/TIA (OR = 0.80), chronic kidney disease (OR = 0.80), and depression (OR = 0.93).
- Patients in rural areas had higher odds of using choline alfoscerate (OR = 1.28) compared to those in metropolitan areas (OR = 1.00).
- Despite limited evidence of efficacy, the extensive use of choline alfoscerate highlights the need for continuous monitoring and rigorous evaluation to ensure its safety and therapeutic value in AD management.

1 | INTRODUCTION

Alzheimer's disease (AD), the most common type of dementia, mainly affects individuals aged 65 and older.[1] According to the World Health Organization Global Health Estimates, AD was the 20th leading cause of death in 2000 but rose to the 7th position in 2019,[2] highlighting the escalating social and economic burden of AD worldwide.[3]

The primary pharmacological treatments for AD have been acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists. AChEIs, such as donepezil, galantamine, and rivastigmine, work by enhancing cholinergic function to alleviate the symptoms of AD, particularly in mild-to-moderate stages.[4] NMDA receptor antagonists like memantine help mitigate memory and learning impairments caused by excessive glutamate activity in moderate-to-severe AD.[5,6]

Choline alfoscerate, also known as l-alpha-glycerylphosphorylcholine, is another agent used in AD management. It acts as a cholinergic precursor that supports the synthesis of acetylcholine, a neurotransmitter essential for cognitive function.[7] The ASCOMALVA study suggested that choline alfoscerate may help restore cholinergic transmission, particularly when combined with donepezil, offering modest cognitive benefits in mild-to-moderate AD.[8] It is generally well tolerated, with gastrointestinal symptoms being the most commonly reported side effects. However, despite these potential benefits, robust clinical trials and definitive evidence supporting its efficacy are lacking, limiting its broader use.[9–11]

Choline alfoscerate is sold as a dietary supplement in several countries, including the United States, but is approved as a reimbursed prescription drug in Korea, where it is often prescribed alongside AChEIs. In the first quarter (Q1) of 2023, choline alfoscerate's prescription expenditures reached 152.8 billion Korean won (KRW, approximately 114 million US Dollars), surpassing that of atorvastatin[12] and marking an 18.4% increase from the same period in 2022, despite limited clinical evidence of efficacy.

This study aims to analyze trends in the utilization of choline alfoscerate in Korea among newly diagnosed AD patients, utilizing nationally representative real-world data. By examining prescription patterns and identifying demographic, clinical, and institutional factors influencing its use, we seek to understand the broader implications of its widespread prescription within the national insurance framework, despite limited clinical evidence supporting its efficacy.

2 | METHODS

2.1 | Data source

Data for this study were obtained from the Korean Health Insurance Review and Assessment Service (HIRA) database (https://opendata.hira.or.kr/home.do). Most Koreans are covered by the National Health Insurance (NHI), which provides comprehensive healthcare services. Under this system, all healthcare institutions submit insurance claims to HIRA for review and approval. Therefore, HIRA has several datasets consisting of de-identified claims information, including patient characteristics, medical treatments, diseases, drug prescriptions, and healthcare facility details.[13] These data are available to researchers for study purposes.

2.2 | Study population

The study population consisted of individuals aged ≥ 60 years newly diagnosed with AD between 2012 and 2019 based on KCD codes (F00 and G30). Patients were included if they had a prescription for AChEI (donepezil, galantamine, or rivastigmine) or memantine within 60 days

of the initial AD diagnosis (index date). Patients with a history of AD diagnosis or recent use of AChEIs, memantine, or choline alfoscerate within the year preceding the first diagnosis date were excluded from the study. Medications and comorbidities were identified using specific codes as detailed in Table S1.

Data on the age, sex, insurance types (NHI and Medical Aid [MedAid]), comorbidities, and characteristics of healthcare institutions were assessed to define covariates. NHI is the universal healthcare system that covers the majority of the Korean population and is funded by contributions based on income levels. MedAid, on the other hand, provides healthcare coverage to low-income individuals who meet certain eligibility criteria, including those with disabilities and the elderly who are economically disadvantaged.[14] This difference in coverage and the socioeconomic conditions of the insured populations may influence treatment patterns.

All patients were categorized into five age groups: 60–64, 65–69, 70–74, 75–79, and ≥ 80 years old. Healthcare institutions were grouped according to their geographical regions: metropolitan, urban, and rural. They were also classified based on their type: tertiary hospitals, general hospitals, hospitals, and clinics. Physicians were also classified based on their specialties: general physicians, internal medicine (IM), family medicine (FM), rehabilitation medicine (RM), neurology, and psychiatry. For simplicity, IM, FM, and RM were combined and analyzed as a single group. Patient comorbidities were investigated by referencing the major chronic diseases of the elderly in Korea based on the 2020 National Survey of Living Conditions and Welfare Needs of Older Koreans by the Ministry of Health and Welfare.[15]

2.3 | Choline alfoscerate utilization

We identified patients who were prescribed choline alfoscerate within 60 days of the index date. Utilization of choline alfoscerate was defined as the outcome variable, and patients were categorized into two groups: those taking choline alfoscerate and those not taking choline alfoscerate.

2.4 | Statistical analyses

Categorical variables, including the underlying characteristics of the patients, such as sex, age group, insurance type, comorbidities, AD drug type, region, location, type of medical institution, and annual choline alfoscerate usage, were expressed as absolute values and percentages. These variables were compared using a chi-squared test.

Multiple logistic regression analyses were performed to identify the factors affecting the use of choline alfoscerate. To evaluate the goodness of fit of the logistic model, C-statistics and the Hosmer–Lemeshow test were performed. Trends of choline alfoscerate use across the years were determined using the Cochran–Armitage Trend test.

RESEARCH IN CONTEXT

1. **Systematic review**: Choline alfoscerate, an acetylcholine precursor, is widely prescribed in South Korea for cognitive support in AD, despite limited clinical trial evidence of efficacy. While acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists remain the mainstay pharmacologic treatments in AD, choline alfoscerate is also frequently prescribed under national insurance coverage. This study utilizes real-world data to examine trends and determinants of choline alfoscerate use among newly diagnosed AD patients in Korea.
2. **Interpretation**: Our analysis of data from the Health Insurance Review and Assessment Service (HIRA) shows a notable increase in choline alfoscerate prescriptions for AD patients from 2012 to 2019. Higher use was associated with factors such as male sex, MedAid coverage, and comorbid osteoarthritis, while lower use was observed among patients with conditions like hypertension, stroke, and chronic kidney disease. These findings underscore the need for ongoing monitoring and critical evaluation of choline alfoscerate's long-term safety and efficacy, particularly given its continued insurance coverage.
3. **Future directions**: Future research should include large-scale controlled trials to rigorously assess choline alfoscerate's efficacy and safety in AD. Cost-effectiveness analyses are also essential to determine its financial sustainability within national health systems, guiding policymakers on its appropriate place in AD treatment and insurance coverage.

Data and statistical analyses were performed using the R software (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Characteristics of the study population

HIRA database includes the data of 1,155,699 patients diagnosed with AD between 2012 and 2019. Among them, 1,131,046 were aged ≥ 60 years and 548,896 had no prior AD diagnosis or drug use in the previous year. After further exclusion, a final cohort of 324,277 patients administered AD drugs within 60 days of the index date was included in the analysis.

More than half of the study population was aged ≥ 80 years (51.22%), followed by those aged 75–79 years (24.88%) and 70–74 years (14.49%). Female patients accounted for more than twice the number of male patients. Most patients were covered by NHI (89.44%). The most prevalent comorbidity was hypertension (64.01%), followed

by osteoarthritis (45.18%), hyperlipidemia (42.56%), and diabetes mellitus (34.71%).

Most patients (94.33%) received AChEIs as monotherapy, commonly recommended for mild-to-moderate AD. The prescription rates for memantine/AChEI combination therapy and memantine monotherapy were low (3.38 and 2.29%, respectively).

General hospitals were the most common treatment facilities (41.43%), followed by clinics (24.38%), and hospitals (20.70%). In terms of physician specialties, most were in neurology (56.79%), followed by psychiatry (26.29%) and the combined IM/FM/RM group (8.50%; Table 1).

3.2 | Choline alfoscerate utilization

Among the 330,326 patients prescribed AD medication within 60 days of the index date, 99,845 (33.08%) were taking choline alfoscerate as an additional medication (Figure 1).

Choline alfoscerate utilization was higher in males than in females (32.21 vs. 30.17%; $p < 0.001$) and compared to the 60- to 64-year age group, the use of choline alfoscerate was slightly lower in other age groups. Patients covered by NHI were prescribed choline alfoscerate at a lower frequency than those covered by MedAid (30.59 vs. 32.50%; $p < 0.001$).

Choline alfoscerate use was higher in patients with hyperlipidemia and osteoarthritis and lower in those with hypertension, coronary artery disease, stroke/TIA, chronic kidney disease, depression, and insomnia. Choline alfoscerate use was the highest in the memantine/AChEI combination therapy group (41.68%), followed by the AChEI monotherapy (30.52%) and memantine monotherapy (25.96%) groups.

Choline alfoscerate utilization was higher in rural areas (33.67%) than metropolitan areas (28.42%). Moreover, highest utilization was observed in hospitals (36.24%) and the lowest in other facilities, such as nursing hospitals or health centers (15.54%). Choline alfoscerate was most commonly prescribed by specialists categorized as "others" (38.55%), followed by those in neurology (35.09%), IM/FM/RM (24.70%), and psychiatry (21.25%; Table 1).

3.3 | Factors affecting the use of choline alfoscerate

Multiple logistic regression analysis showed that patients aged 80 years and older had lower odds of using choline alfoscerate compared to the reference age group of 60–64 years (odds ratio [OR] = 0.910; 95% confidence interval [CI] = 0.868–0.954). Women were less likely to use choline alfoscerate than men (OR = 0.949; 95% CI = 0.933–0.966), and those covered under MedAid exhibited higher odds of using choline alfoscerate than those covered under NHI (OR = 1.069; 95% CI = 1.042–1.097).

Osteoarthritis was associated with a higher likelihood of choline alfoscerate use (OR = 1.051; 95% CI = 1.034–1.069) compared to other comorbidities. Conversely, stroke/TIA was the main negative influencing factor (OR = 0.795; 95% CI = 0.777–0.814), followed by chronic kidney disease (OR = 0.797; 95% CI = 0.759–0.836), depression (OR = 0.932; 95% CI = 0.911–0.952), hypertension (OR = 0.957; 95% CI = 0.940–0.975), and congestive heart failure (OR = 0.957; 95% CI = 0.932–0.982).

Patients receiving memantine/AChEI combination therapy were more likely to use choline alfoscerate (OR = 1.298; 95% CI = 1.248–1.3529) compared to those on AChEI monotherapy, while those receiving memantine monotherapy had lower odds of choline alfoscerate use (OR = 0.907; 95% CI = 0.858–0.958).

Patients in rural areas had a higher OR for being prescribed choline alfoscerate (OR = 1.283; 95% CI = 1.259–1.306) than those in metropolitan areas. Patients in urban areas also had a slightly higher OR (OR = 1.024; 95% CI = 1.002–1.047) of utilizing choline alfoscerate compared to their metropolitan counterparts.

Regarding healthcare facilities, the odds of being prescribed choline alfoscerate were higher in hospitals (OR = 1.996; 95% CI = 1.920–2.076) and general hospitals (OR = 1.833; 95% CI = 1.767–1.902) than in tertiary hospitals.

Physician specialties also influenced prescription patterns. Compared to general physicians, neurologists had significantly higher odds of prescribing choline alfoscerate (OR = 1.253; 95% CI = 1.093–1.439), while psychiatrists (OR = 0.568; 95% CI = 0.495–0.653) and IM/FM/RM group (OR = 0.771; 95% CI = 0.672–0.888) had lower odds.

The odds of receiving a prescription for choline alfoscerate increased steadily throughout the study period. In 2019, patients with AD exhibited four-fold greater odds of utilizing choline alfoscerate (OR = 4.828; 95% CI = 4.662–5.000) than those in 2012 (Table 2).

3.4 | Prescription trends of choline alfoscerate by year

The number of individuals who started choline treatment within 60 days of their first AD diagnosis showed a remarkable upward trajectory. In 2012, the proportion of patients starting choline alfoscerate therapy was 15.96%, which increased to 47.65% in 2019. The Cochran–Armitage test confirmed a statistically significant difference in choline alfoscerate utilization across the years ($p < 0.001$; Figure 2).

4 | DISCUSSION

This study used nationally representative real-world data to investigate the prescribing trends of choline alfoscerate in patients newly diagnosed with AD. Utilization of choline alfoscerate was observed in 33.08% of the total study population, with its use consistently increasing from 15.96% in 2012 to 47.65% in 2019. The increased utilization of choline alfoscerate can be attributed to the limited therapeutic options available during the study period, particularly before the advent of disease modifying therapies (DMTs).[16,17]

TABLE 1 Demographic characteristics of the study population.

	Study population		Choline alfoscerate users		
Variable	***N***	**(%)**	***N***	**(%)**	***p*-value**
Overall	324,277	100	99,845	30.79	
Age (years)					< 0.001
60–64	9282	2.86	2953	31.81	
65–69	21,240	6.55	6583	30.99	
70–74	46,980	14.49	13,921	29.63	
75–79	80,683	24.88	24,961	30.94	
≥ 80	166,092	51.22	51,427	30.96	
Sex					<0.001
Male	98,358	30.33	31,681	32.21	
Female	225,919	69.67	68,164	30.17	
Insurance					<0.001
NHI	290,040	89.44	88,719	30.59	
MedAid	34,237	10.56	11,126	32.50	
Coexisting disease					
Hypertension					<0.001
No	116,693	35.99	36,920	31.64	
Yes	207,584	64.01	62,925	30.31	
Diabetes mellitus					0.580
No	211,706	65.29	65,254	30.82	
Yes	112,571	34.71	34,591	30.73	
Hyperlipidemia					<0.001
No	186,271	57.44	56,319	30.24	
Yes	138,006	42.56	43,526	31.54	
Coronary artery disease					<0.001
No	258,767	79.80	80,250	31.01	
Yes	65,510	20.20	19,595	29.91	
Congestive heart failure					0.153
No	285,807	88.14	88,122	30.83	
Yes	38,470	11.86	11,723	30.47	
Stroke/TIA					<0.001
No	276,313	85.21	87,379	31.62	
Yes	47,964	14.79	12,466	25.99	
Osteoarthritis					<0.001
No	177,757	54.82	53,665	30.19	
Yes	146,520	45.18	46,180	31.52	
Rheumatoid arthritis					0.254
No	308,679	95.19	95,107	30.81	
Yes	15,598	4.81	4,738	30.38	
Chronic kidney disease					<0.001
No	314,814	97.08	97,212	30.88	
Yes	9,463	2.92	2,633	27.82	
COPD					0.168
No	263,166	81.16	81,171	30.84	
Yes	61,111	18.84	18,674	30.56	

(Continues)

TABLE 1 (Continued)

Variable	Study population		Choline alfoscerate users		
	N	(%)	*N*	(%)	*p*-value
Depression					<0.001
No	270,272	83.35	84,209	31.16	
Yes	54,005	16.65	15,636	28.95	
Insomnia					<0.001
No	280,465	86.49	87,046	31.04	
Yes	43,812	13.51	12,799	29.21	
Prescription type					<0.001
AChEI	305,873	94.33	93,346	30.52	
Memantine	7454	2.29	1935	25.96	
COMBI	10,950	3.38	4564	41.68	
Region					<0.001
Metropolitan	119,248	36.77	33,888	28.42	
Urban area	67,631	20.86	19.690	29.11	
Rural area	137,398	42.37	46,267	33.67	
Level of healthcare facility					<0.001
Tertiary hospitals	22,318	6.88	4237	18.99	
General hospitals	134,359	41.43	47,283	35.19	
Hospitals	67,116	20.70	24,324	36.24	
Clinics	79,055	24.38	20,670	26.15	
Others	21,429	6.61	3331	15.54	
Medical department					<0.001
General physician	1355	0.42	282	20.81	
IM/FM/RM	27,573	8.50	6810	24.70	
Neurology	184,165	56.79	64,639	35.10	
Psychiatry	85,267	26.29	18,122	21.25	
Others	25,917	7.99	9992	38.55	
Year					<0.001
2012	34,442	10.62	5496	15.96	
2013	38,228	11.79	6843	17.90	
2014	37,930	11.70	8382	22.10	
2015	39,046	12.04	9643	24.70	
2016	40,260	12.42	12,491	31.03	
2017	40,697	12.55	15,323	37.65	
2018	45,837	14.14	18,874	41.18	
2019	47,837	14.75	22,793	47.65	

Abbreviations: AChEI, acetylcholinesterase inhibitor; COMBI, memantine/AChEI combination therapy; COPD, chronic obstructive pulmonary disease; FM, family medicine; IM, internal medicine; NHI, National Health Insurance; RM, rehabilitation medicine; TIA, transient ischemic attack.

Choline alfoscerate's inclusion in Korea's NHI formulary reflects a unique regulatory situation. Approved for reimbursement prior to the Drug Expenditure Rationalization Plan (DERP) and the Positive List System (PLS) in 2007, it entered the formulary under a "negative list" system.[18] This earlier system allowed all drugs approved by the Korea Food and Drug Administration to qualify for reimbursement, with few exceptions. It was only later, with the DERP, that stricter requirements were introduced, mandating that new drugs demonstrate clinical and economic value to be listed. Since choline alfoscerate's approval predated the PLS, it bypassed these evaluations and remains widely prescribed despite not having been reassessed under the updated criteria.[18]

As the AD treatment landscape evolves with novel DMTs, such as monoclonal antibodies lecanemab and donanemab, new therapeutic

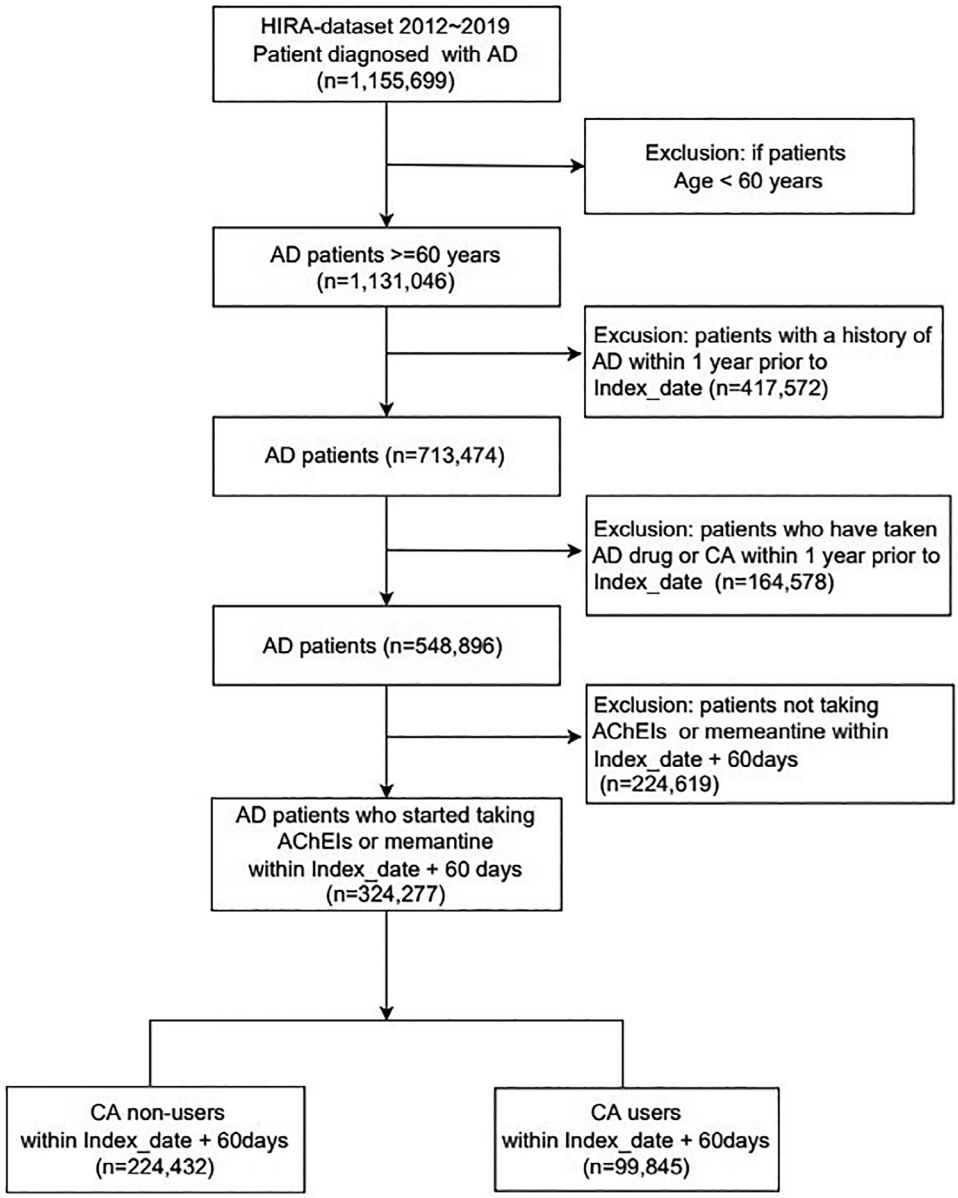

FIGURE 1 Flowchart showing the selection criteria for the study population.

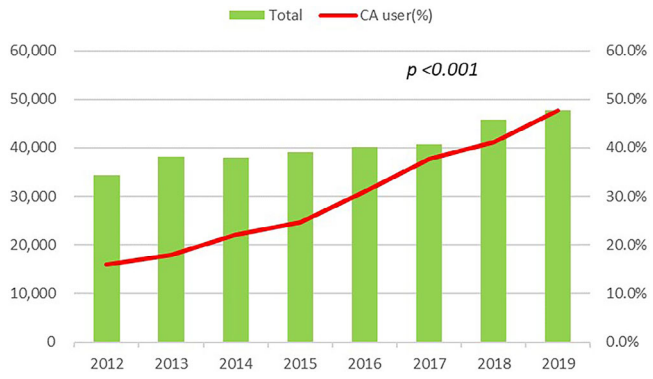

FIGURE 2 Prescription trends of choline alfoscerate analyzed using the Cochran–Armitage trend test.

options are emerging for early-stage AD.[16,17] These therapies, though expensive and limited by narrow indications and concerns over long-term efficacy, represent a shift toward addressing AD's underlying pathology rather than just symptomatic relief.[17] In Korea, lecanemab has been approved but is not yet available on the market.

Given these advancements, the continued reimbursement of choline alfoscerate by the Korean NHI system warrants careful re-evaluation. Current evidence supporting the efficacy of choline alfoscerate remains limited, and it has not been shown to possess disease-modifying effects.[18,19] As more targeted and effective therapies become available, it becomes increasingly difficult to justify allocating healthcare resources to choline alfoscerate. At the very least, its inclusion in the national formulary should be reconsidered to ensure that healthcare spending is directed toward treatments with proven benefits.

TABLE 2 Adjusted ORs and 95% CIs from multiple logistic regression analyses of choline alfoscerate prescription.

Variable	Choline alfoscerate utilization		
	OR	95% CI	*p*-value
Age (years)			
60–64(R)			
65–69	0.998	0.945–1.055	0.954
70–74	0.989	0.941–1.041	0.679
75–79	0.971	0.925–1.020	0.239
≥ 80	0.910	0.868–0.955	<0.001
Sex			
Male (R)			
Female	0.949	0.933–0.966	<0.001
Insurance			
NHI (R)			
MedAid	1.069	1.042–1.097	<0.001
Coexisting disease			
Hypertension			
No (R)			
Yes	0.957	0.940–0.975	<0.001
Diabetes mellitus			
No (R)			
Yes	0.999	0.981–1.017	0.885
Hyperlipidemia			
No (R)			
Yes	0.993	0.974–1.011	0.426
Coronary artery disease			
No (R)			
Yes	0.986	0.965–1.008	0.204
Congestive heart failure			
No (R)			
Yes	0.957	0.932–0.982	<0.001
Stroke/TIA			
No (R)			
Yes	0.795	0.777–0.814	<0.001
Osteoarthritis			
No (R)			
Yes	1.051	1.034–1.069	<0.001
Reumatoid arthritis			
No (R)			
Yes	1.018	0.980–1.056	0.354
Chronic kidney disease			
No (R)			
Yes	0.797	0.759–0.836	<0.001
COPD			
No (R)			
Yes	1.005	0.985–1.026	0.624
Depression			
No (R)			
Yes	0.932	0.911–0.953	<0.001
Insomnia			
No (R)			
Yes	0.983	0.960–1.007	0.159
Prescription type			
AChEI (R)			
Memantine	0.907	0.858–0.958	<0.001
COMBI	1.298	1.246–1.352	<0.001
Region			
Metropolitan (R)			
Urban area	1.024	1.002–1.047	0.035
Rural area	1.283	1.260–1.306	<0.001
Level of healthcare facility			
Tertiary hospitals (R)			
General hospitals	1.833	1.767–1.902	<0.001
Hospitals	1.996	1.920–2.076	<0.001
Clinics	1.793	1.722–1.867	<0.001
Others	0.736	0.698–0.775	<0.001
Medical department			
General physician (R)			
IM/FM/RM	0.771	0.672–0.888	<0.001
Neurology	1.253	1.093–1.439	0.001
Psychiatry	0.568	0.495–0.653	<0.001
Others	1.382	1.205–1.591	<0.001
Year			
2012 (R)			
2013	1.163	1.118–1.209	<0.001
2014	1.515	1.458–1.574	<0.001
2015	1.736	1.672–1.802	<0.001
2016	2.393	2.307–2.482	<0.001
2017	3.244	3.130–3.363	<0.001
2018	3.713	3.585–3.847	<0.001
2019	4.804	4.639–4.975	<0.001
C-statistic	0.697		
p-Value of Hosmer–Lemeshow test	<0.001		

Abbreviations: AChEI, acetylcholinesterase inhibitor; CI, confidence interval; COMBI, memantine/AChEI combination therapy; COPD, chronic obstructive pulmonary disease; FM, family medicine; IM, internal medicine; MEM, concomitant memantine use; NHI, National Health Insurance; OR, odds ratio; RM; rehabilitation medicine; TIA, transient ischemic attack.

The increasing utilization of choline alfoscerate, despite limited clinical evidence raises significant concerns.[11,19] In response, the Korean Ministry of Health and Welfare has requested that manufacturers conduct a phase IV clinical trial to evaluate its efficacy and safety in patients with mild-to-moderate AD, with data submission expected by 2025. Therefore, a cautious prescription of choline alfoscerate is warranted until more convincing evidence emerges.

This study also explored demographic and clinical factors influencing choline alfoscerate prescribing. Age group analysis revealed that as age increased, the odds of choline alfoscerate use decreased, especially in patients aged over 80 years. Early-stage use of choline alfoscerate may be attributed to studies showing its effectiveness in improving cognitive function in mild-to-moderate AD.[7,20]

Gender differences were also noted, with women being less likely than men to receive choline alfoscerate, a pattern consistent with a previous report.[21] One possible explanation is that AD-related cognitive decline is more rapid and severe in women than in men at the time of initial diagnosis, which may contribute to lower utilization of choline alfoscerate in women.[22]

Insurance status was another key factor influencing prescription rates. Patients covered under MedAid were more likely to receive choline alfoscerate compared to those under the NHI system. This is likely due to differences in healthcare utilization, as MedAid patients, who generally face lower co-payments and have poorer socioeconomic conditions, access more healthcare services, including medications.[23,24] This suggests that socioeconomic factors play a significant role in driving prescription behaviors, highlighting the need for policy-driven research to better understand these patterns.[25]

Finally, we identified that certain comorbidities influenced choline alfoscerate use. Patients with osteoarthritis were more likely to receive the drug, possibly due to the association between osteoarthritis and neuroinflammation, a contributing factor in AD progression.[26] Conversely, patients with conditions such as hypertension, heart failure, stroke/TIA, chronic kidney disease, and depression were less likely to be prescribed choline alfoscerate. This reduced utilization could be related to concerns about polypharmacy in these populations, where adding choline alfoscerate may not be favored due to potential drug interactions or limited perceived benefit.[27]

This study has several limitations. First, there may be potential inaccuracies in diagnosis coding, which could affect the identification of AD cases. Second, the study lacks detailed patient information, such as physical characteristics and lifestyle factors (e.g., height, weight, smoking, and exercise), which may have influenced the analysis of risk factors. Third, the reliance on prescription data may not fully reflect actual medication adherence, as prescriptions do not guarantee that patients consistently take the medications as prescribed. Nonetheless, the use of nationally representative claims data provides valuable insights into the real-world prescribing patterns of choline alfoscerate.

Future research should focus on assessing the long-term safety, efficacy, and cost-effectiveness of choline alfoscerate, particularly in the context of healthcare policies and economic factors. Real-world evidence can play a critical role in determining whether continued spending on this drug is justified, or whether these resources should be redirected toward therapies with greater potential to improve patient outcomes.

5 | CONCLUSION

The use of choline alfoscerate in Korea has consistently increased over the years due to the absence of DMTs for AD and its inclusion in the country's insurance coverage system. However, its use is limited by the unclear efficacy and risk profile of this drug. Positive factors influencing the utilization of choline alfoscerate included MedAid insurance coverage, osteoarthritis, area and level of institutions, use of combination therapy with AChEIs and memantine, and prescription by neurology specialists. Negative factors affecting its utilization included advanced age, female sex, hypertension, congestive heart failure, stroke/TIA, chronic kidney disease, depression, use of memantine, and prescription by psychiatry specialists.

AUTHOR CONTRIBUTIONS

Yeon Hee Kim and Nam Kyung Je conceived and designed the study; Yeon Hee Kim and Nam Kyung Je performed the analysis; Yeon Hee Kim drafted the manuscript; all authors participated in writing the manuscript and approved the final version to be submitted for publication.

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CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflicts of interest related to the research, authorship, and/or publication of this article. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

The dataset used in this study can be accessed using the Health Insurance Review and Assessment website (https://opendata.hira.or.kr).

ETHICS STATEMENT

This study was performed using a HIRA dataset that did not contain any personal patient information and was exempt from review by the Institutional Review Board of Pusan National University College in Korea (PNU IRB/2022_46_HR).

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REFERENCES

1. Bhushan I, Manjot K, Guneet K, Shriya G, Supriya S, Arvind Y. Alzheimer's disease: causes & treatment–a review. *Ann Biotechnol*. 2018;1(1):1002.
2. WHO fact sheets-the top 10 causes of death. Published August 7, 2024. Accessed August 1, 2024. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
3. Takizawa C, Thompson PL, Van Walsem A, Faure C, Maier WC. Epidemiological and economic burden of Alzheimer's disease: a systematic literature review of data across Europe and the United States of America. *J Alzheimers Dis*. 2015;43(4):1271-1284.
4. Marucci G, Buccioni M, Ben DD, Lambertucci C, Volpini R, Amenta F, Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease. *Neuropharmacology*. 2021;190:108352.
5. Rogawski MA, Wenk GL. The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease. *CNS Drug Rev*. 2003;9(3):275-308.
6. Lo D, Grossberg GT. Use of memantine for the treatment of dementia. *Expert Rev Neurother*. 2011;11(10):1359-1370.
7. De JM Moreno M, Cognitive improvement in mild to moderate Alzheimer's dementia after treatment with the acetylcholine precursor choline alfoscerate: a multicenter, double-blind, randomized, placebo-controlled trial. *Clin Ther*. 2003;25(1):178-193./bib>
8. Amenta F, Carotenuto A, Fasanaro AM, Rea R, Traini E. The ASCOMA-LVA trial: association between the cholinesterase inhibitor donepezil and the cholinergic precursor choline alphoscerate in Alzheimer's disease with cerebrovascular injury: interim results. *J Neurol Sci*. 2012;322(1-2):96-101.
9. Traini E, Bramanti V, Amenta F. Choline alphoscerate (alpha-glyceryl-phosphoryl-choline) an old choline- containing phospholipid with a still interesting profile as cognition enhancing agent. *Curr Alzheimer Res*. 2013;10(10):1070-1079.
10. Sagaro GG, Traini E, Amenta F, Activity of choline alphoscerate on adult-onset cognitive dysfunctions: a systematic review and meta-analysis. *J Alzheimers Dis*. 2023;92(1):59-70.
11. Parnetti L, Mignini F, Tomassoni D, Traini E, Amenta F. Cholinergic precursors in the treatment of cognitive impairment of vascular origin: ineffective approaches or need for re-evaluation? *J Neurol Sci*. 2007;257(1-2):264-269.
12. Surging demand for choline alfoscerate: leading outpatient prescriptions amid efficacy controversies. Accessed May 8, 2023. http://www.dailypharm.com/Users/News/NewsView.html?ID=299934.2023.05.08
13. Kyoung DS, Kim HS. Understanding and utilizing claim data from the Korean National Health Insurance Service (NHIS) and Health Insurance Review & Assessment (HIRA) database for research. *J Lipid Atheroscler*. 2022;11:103-110.
14. Kim L, Kim J-A, Kim S. A guide for the utilization of Health Insurance Review and Assessment Service National Patient Samples. *Epidemiol Health*. 2014;36:e2014008.
15. Baek JiY, Lee E, Jung HW, Jang IY. Geriatrics fact sheet in Korea 2021. *Ann Geriatr Med Res*. 2021;25(2):65-71.
16. Jin M, Noble JM. What's in it for me? Contextualizing the potential clinical impacts of lecanemab, donanemab, and other anti-β-amyloid monoclonal antibodies in early Alzheimer's disease. *eNeuro*. 2024;11(9):ENEURO.0088-24.2024
17. Noorda K, Noorda K, Sabbagh MN, Bertelson J, Singer J, Decourt B. Amyloid-directed antibodies: past, present, and future. *J Alzheimers Dis*. 2024;101(s1):S3-s22.
18. Bae EY, Lee EK. Pharmacoeconomic guidelines and their implementation in the positive list system in South Korea. *Value Health*. 2009;12(Suppl 3):S36-41.
19. Debate intensifies over the efficacy of choline alfoscerate at medical conference. Published December 9, 2019. Accessed August 1, 2024. https://www.medicaltimes.com/Main/News/NewsView.html?ID=1130754
20. Scapicchio PL. Revisiting choline alphoscerate profile: a new, perspective, role in dementia? *Int J Neurosci*. 2013;123(7):444-449.
21. Hwang SG, Park H. An analysis on prescribing patterns of Alzheimer's dementia treatment and choline alfoscerate using HIRA claims data. *Korean J Clin Pharm*. 2019;29(1):1-8.
22. Pradier C, Sakarovitch C, Le Duff F, et al. The mini mental state examination at the time of Alzheimer's disease and related disorders diagnosis, according to age, education, gender and place of residence: a cross-sectional study among the French National Alzheimer database. *PLoS One*. 2014;9(8):e103630.
23. Park YH, Lee YJ. Qualitative analysis of medical usage patterns of medical aid patients. *J Korea Content Assoc*. 2017;17(9):39-49.
24. Choi Y, Cho HJ, Kim D-S, Yoon S-H. The Polypharmacy status and factor analysis of the elderly of medical aid: a nationwide cohort study using health insurance claims data. *Public Health Aff*. 2022;6(1):e5.
25. Shin SM, Kim MJ, Kim ES, Lee HW, Park CG, Kim HK. Medical aid service overuse assessed by case managers in Korea. *J Adv Nurs*. 2010;66(10):2257-2265.
26. Kyrkanides S, Tallents RH, Miller JN, et al. Osteoarthritis accelerates and exacerbates Alzheimer's disease pathology in mice. *J Neuroinflammation*. 2011;8:112.
27. Allaham K, Feyasa MB, Govender RD, et al. Medication adherence among patients with multimorbidity in the United Arab Emirates. *Patient Prefer Adherence*. 2022;16:1187-1200.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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