

Dementia Management Act and Death Toll by Dementia Drug

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Research Article

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Abstract

The Dementia Management Act (DMA) came into effect on August 04, 2011, in South Korea. Medical data on the correlation between Alzheimer's disease (AD) and anti-AD drug (AAD) groups were observed from 2010 to 2019. This study investigated the increase and decrease in deaths and AAD used to treat AD. It is known that psychotropic medicines should not be administered for dementia patients because they increase all-cause mortality. This study demonstrated that acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonist also increase the death toll when used to treat dementia.

Main Text

According to the Dementia Management Act (DMA), the Sorokdo National Hospital, established in May 1916 to treat leprosy, also provides Alzheimer's disease (AD) treatment and preventive services. Hansen's disease (HD) Patient's life expectancy at Sorokdo National Hospital is known to live longer¹. There were HD patients who settled in 2020 to those who had lived for 79 years in Sorokdo Island. Life expectancy is data accumulated over decades. The decrease or increase of life expectancy is fundamental data.

The DMA purposes are to mitigate personal pain and damage from dementia. The DMA came into effect on August 04, 2011, in South Korea, and the Act was amended, June 12, 2018,². Medical personnel, psychiatrists or neurologists of medical institutions, and workers engaged in providing medical services under the Medical Service Act became very active in dementia management programs executed by the state and local governments. According to the DMA policy, AD patients and AAD prescriptions are increasing rapidly, so it is most suitable for analyzing national medical data. AAD group 1 is dementia symptom treatments: donepezil hydrochloride, rivastigmine, galantamine, and N-methyl-D-aspartate (NMDA) receptor antagonist. AAD group 2 is psychotropic medications: haloperidol, Risperidone, Quetiapine, Olanzapine, Aripiprazole, Oxcarbazepine, fluvoxamine, Escitalopram, Trazodone, Sertraline, Escitalopram, and Fluoxetine.

South Korea is the most computerized country. This study investigated the increase and decrease in deaths, and anti-AD drugs (AADs) used to treat AD in the National Health Insurance System (NHIS) of South Korea. With the increasing biomedicalization of dementia, we have announced that it can treat dementia or slow the disease's progression^{3 4 5 6 7 8}. The prescriptions for AAD have increased dramatically, and now the results need to be examined.

Results

Compared with South Koreans' increased life expectancy, there was a gradual decline in HD patients' life expectancy. HD patients taking AAD group 2 together with group 1 had a shorter lifespan than those taking AAD group 1 alone (Fig. 1). The mean age of deaths while taking only dementia symptom treatment (AAD group 1) was blue. The mean age of deaths with taking additional psychiatric drugs (AAD group 2) is red. In 2018-2019, the life expectancies of HD patients taking additional psychotropic medications were suddenly decreased in the Sorokdo National Hospital. The reason is presumed to be because a public health doctor was working 2017-2019 in Sorokdo National Hospital to substitute military services to administer AAD group 2 thoroughly.

However, the life expectancies of HD patients taking the AAD group 1 (blue) were also decreased in the Sorokdo National Hospital. On the other hand, Korean's life expectancy is on the rise. It can be estimated that the AAD group 1 reduces life expectancy.

First-NHIS-retrieval results

From 2010 to June 2019, the DMA increased the diagnosis of patients with MCI or AD by 3.26 times, and AAD prescription by 4.65 times in Korea (Fig. 2).

We requested and analyzed the entire ICD 9 and 10 code data (from 2010 to 2019) of AAD and deaths from the NHIS with the Open Data Mediation Committee of South Korea according to the Official Information Disclosure Act in South Korea. NHIS provided the information of deaths (Table 1). The number of users who took AAD in Korea increased by 2.16 times, and the number of deaths increased by 2.51 times from 2010 to June 2019 (Fig. 3). This number of AAD and deaths is the baseline.

The number of users who took donepezil in Korea increased by 3.48 times, and the number of deaths increased by 3.88 times from 2010 to June 2019. The number of users who took rivastigmine in Korea increased 1.84 times, and the number of deaths increased by 2.36 times from 2010 to June 2019. The number of users who took memantine in Korea increased 2.50 times, and the number of deaths increased by 2.29 times from 2010 to June 2019. The number of users who took risperidone in Korea increased 1.26 times, and the number of deaths increased by 1.35 times from 2010 to June 2019. The number of users who took galantamine and other psychotropic medications in Korea increased 1.55 times, and the number of deaths increased by 1.60 times from 2010 to June 2019 (Fig. 4). It was significant when comparing death among AAD users. Cholinesterase inhibitors (ChEIs; donepezil, rivastigmine, and galantamine) increase mortality when used to treat dementia.

However, rivastigmine had a significant difference in the increase or decrease in users from 2014 to 2019. Moreover, memantine did not show a significant increase in the number of deaths than the increase in users. So we needed a comparison graph for hidden data.

Second-Data-Processing results

We developed an equation to interpret the data for this study. By comparing the rate at which the number of deaths increases when the number of users increases, we can compare deaths caused by dementia medicines.

[Lee's hidden equation for a comparison graph]

X is the year, Y is (death B – death A)/(user B – user A). (1)

If the independent variables are AAD, Donepezil, Rivastigmine, Memantine, Risperidone, Fluoxetine, Olanzapine, Sertraline, Quetiapine, Aripiprazole, Escitalopram, and the others, the dependent variable is Lee's hidden data. It makes to calculate the F-ratio value and the p-value by One-Way Repeated Measures ANOVA Calculator (Fig. 5).

The population is all Koreans. The number of deaths is the independent variable. If the independent variables are five (AAD, Donepezil, Rivastigmine, Memantine, Risperidone), the dependent variable is Lee's hidden data. The output of the ANOVA Calculator is pretty significant. The F-ratio value is 3.2028. The p-value is .023868. (The result is significant at $p < .05$.) (Supplement Section 3. Statistics Table 19-1, One-Way Repeated Measures ANOVA Calculator)

We used AAD as the reference line. Although rivastigmine was rapidly increased and decreased, it was the drug that increased the death rate (Fig. 6). Memantine did not increase the number of deaths compared to the increase of users. However, when the hidden equation was used, memantine also increased the rate of deaths (Fig. 7).

Discussion

ChEIs and memantine do not lower the progression rate to Alzheimer's disease^{9 10 11 12 13}. AD patients who received ChEIs and memantine took them longer, were more functionally impaired, and showed more significant cognitive decline than those who received ChEIs only¹⁴. Amnesic mild cognitive impairment is associated with increased mortality¹⁵. The cohort's mortality was more significant in the galantamine group than in the placebo group in the original per-protocol assessment¹³. Conversely, there have been reports of the duration, and the dose of donepezil or galantamine are not related to an increase in mortality¹⁶. ChEIs' role remains unclear in acute myocardial infarction and heart failure remediation¹⁷.

The DMA reinforced the socialization of elder care, and enduring fear of dependency in old age forced Koreans to cooperate in diagnostic tests and treatments for dementia actively¹⁸. It is well understood that individual Koreans are very active in the prevention of SARS-CoV-2¹⁹.

Korean government's legislative process and medical staff medication

The Korean Government has continuously established national policies for dementia care, and compulsory long-term care insurance for older people was introduced²⁰. The "War against Dementia" was announced, and the First National Dementia Plan in 2008²¹. It facilitates the socialization of long-term care services at a national level. The DMA was legislated in August 2011. The government announced the DMA as a reform plan, emphasizing changes such as increasing coverage and improving the quality of services²⁰. The DMA intended to lighten its burden on society and help enhance national health by establishing and implementing comprehensive policies on preventing dementia, supporting dementia patients, and researching finding a cure for dementia.

As a result of the election in May 2017, the new President announced the National Duty for Dementia²². The proportion of elderly over 65 years exceeded 14% of the entire people in 2018²³, and dementia care became a major national issue. The DMA was strengthened on June 12 2018. The Korean government installed Community Dementia Reassurance Centers successively at all Community Health Centers to establish a community-based dementia management system according to the National Duty for Dementia. Psychiatrists or neurologists of medical institutions engaged in medical diagnosis and treatment under the Medical Service Act²⁴. They strengthened the dementia management programs that administer AAD to mild cognitive impairments or delirium as a preventive and treatment²⁵⁻²⁹. They insisted that the 1-year persistence rate of ChEIs for AD patients should be specially monitored to optimize treatment persistence because patients are less likely to remain on therapy than those in other countries²⁶. The no improvement results of clinical studies on AAD were already published in 2005-2009^{9 10 11 12 30 14}, but in Korea, medical staff started to publish clinical studies of ChEIs and memantine as significant but modest therapeutic improvement the year 2009^{25 31 32}.

Furthermore, they interviewed the media that the administration of AAD is essential to slow down and treat dementia^{33 34}. By Article 12 (1) of the DMA, the government and local governments provided support for the treatment and diagnosis of dementia in consideration of the economic burden of dementia patients. NHIS began to reduce the cost of AAD drugs for dementia patients and became almost free. From 2010 to June 2019, policymakers and medical staffs increased the diagnosis of patients with MCI or AD by 3.26 times and AAD prescription by 4.65 times in Korea.

We should re-examine the life expectancy of dementia patient treated by AAD

All studies from many countries have already confirmed that antipsychotic drugs should not be administered to dementia patients because of the risk of seizures and all-cause mortality³⁵. Deprescribing psychotropic medications are feasible to most people experiencing no withdrawal symptoms in long-term care^{36 37}. Life expectancy is significantly different between AD and AAD groups 1 and 2 in the Sorokdo National Hospital (Fig 1. between 2018 and 2019). It is suspected because the patients were hospitalized in the psychiatric ward, but the life expectancy of AAD group 1 is also decreased.

The neurological side effects of ChEIs for AD patients are similar to neurological symptoms of AD patients. Treated patients had increased disinhibited or compulsive acts, which abated with discontinuation of the ChEIs^{38 39}. Few specialists can distinguish whether they are side effects caused by dementia or donepezil drugs: dizziness, delusions, dream abnormalities, ataxia, convulsive seizures, hemiplegia, hypertonia, and salivation⁴⁰. When connected with the Sorokdo National Hospital's EDI database, we could evaluate AAD prescriptions for fifteen years⁴¹. Three ChEIs are approved for use in mild-to-moderate AD, and their symptomatic benefit in AD has been confirmed via meta-analyses assessing both cognitive performance and global functioning⁴². However, the data analysis on the number of peo

ple who took four FDA-approved therapeutics (three ChEIs and memantine) and the number of fatalities revealed that the number of deaths increased as the number of prescriptions increased. NHIS did not separately provide the number of users and deaths of galantamine, but it can be sufficiently estimated.

Memantine did not show a significant increase in the number of deaths than the increase in users, but the death toll increased in the hidden equation graph (Fig. 6).

We re-evaluated the effects of long-term drug accumulation of four FDA-approved therapeutics. Since ChEIs' neurological side effects are similar to AD symptoms^{38 39,40}, it can be assumed that patients take AAD group 2 quickly when admitted to the hospital. AD medication groups in a US national sample of Medicare beneficiaries were observed, with donepezil being associated with better survival than memantine and oral and transdermal forms of rivastigmine⁴³. This study elucidates the underlying causes of mortality and hospitalization to determine the direct effects of AD medications on mortality in real-world settings.

Many toxins are cholinesterase inhibitors

However, many toxins are cholinesterase inhibitors, and these toxins can cause death if given at high enough dosages. There is no known cumulative effect on AD patients who have taken ChEIs or memantine consistently for long periods. Botulinum toxin blocks the release of acetylcholine hormone from the presynaptic terminal by preventing acetylcholine release⁴⁴. Black widow spider venom is thought to be associated with a wide release of neurotransmitters, especially norepinephrine and acetylcholine, due to spider envenomation. If widow venom exhausts all acetylcholine supplies as the opposite effect of botulinum toxin, paralysis occurs^{45 46}.

Acetylcholine performs various physiologic functions through cholinergic muscarinic receptors, five different types of muscarinic receptors, M1, M2, M3, M4, and M5. The muscarinic receptor M1 is in the cerebral cortex, salivary glands, and gastric glands. The muscarinic receptor M2 is present in smooth muscle as well as cardiac tissue. The muscarinic receptor M3 is found in smooth muscle cells, particularly of the bronchioles, iris, bladder, and small intestines. The muscarinic receptors M4 and M5 have a less clear distribution but have been found in the hippocampus, substantia nigra, and other locations within the brain^{47 48}.

The non-neuronal cholinergic systems are involved in the pathophysiology of diseases⁴⁹. The cardiovascular system determines generalized vasodilation, negative chronotropic effects, and negative inotropic effects. It has a less pronounced negative dromotropic effect in the specialized tissue of the sinoatrial and atrioventricular nodes at the ventricular level than other organs. Muscarinic receptor 2 is not the only functional subtype found within the heart, and muscarinic receptors 1 and 3 mediate both dilation and constriction in the vasculature⁵⁰.

When a patient taking dapsone, mainly used in clinical studies on inflammasome competitors^{41 51 52}, stopped it for stroke treatment and administered acetylcholine precursors for dementia care, the patient's courses were rapidly progressed to severe hypertension and neurologic abnormalities⁴⁰.

AADs administered to the elderly are closely related to health insurance policies. If the elderly die early, health insurance companies will benefit. However, health insurance policies have been implemented to improve the health of the elderly⁵³. Long-term administration of ChEIs to patients with dementia has increased mortality. The effects of ChEIs on cardiovascular systems should be analyzed and studied.

Materials And Methods

Experimental Design

According to the Official Information Disclosure Act in Korea, the Seoul study analyzed AD and anti-Alzheimer's disease drug (AAD) use in Hansen subjects. We searched all medical records of the National Health Insurance Service (NHIS) in Korea when the Korean Government computerized the International Classification of Diseases (ICD)-9 (10) code and Electronic Data Interchange (EDI). We also connected the medical record database of the Sorokdo National Hospital and archived it from January 2005 to June 2020. The Sorokdo National Hospital was established and operated exclusively for HD patients. Since HD patients take therapeutics for leprosy, a Seoul cohort runs to study AD and AAD correlations.

With the ICD-9 and -10 codes, medical data on the correlation between AD and AAD were then analyzed for cohort correlational possibility. AAD First group, according to Korea Drug Code Medicine, First Group: For symptomatic relief of Alzheimer's disease (donepezil hydrochloride, rivastigmine, galantamine, N-methyl-D-aspartate (NMDA) receptor antagonist). AAD Second group is according to Korea Drug Code Medicine Second Group: For psychologic symptoms of Alzheimer's disease (haloperidol, Risperidone, Quetiapine, Olanzapine, Aripiprazole, Oxcarbazepine, fluvoxamine, Escitalopram, Trazodone, Sertraline, Escitalopram, Fluoxetine). (Supplement 1. Korea Drug Code Medicine) The mean age of death of AD patients was classified into the first or second group.

Through the coordination of the Open Data Mediation Committee, data on the number of deaths among people taking AAD from 2010 to 2019 were available from the NHIS. We analyzed the entire ICD 9 and 10 code data (from 2010 to 2019) of AAD and death from NHIS. We used the software programs Object-Relational DBMS and Google spreadsheet for R² analysis and power series calculations. (Supplement 2. DATA)

Declarations

Code availability

We used Google spreadsheets for R² calculation and drawing the trend lines.

Data availability

The authors declare that all primary data generated or analyzed during this study supporting the findings are available within the article and its supplementary information files. Additional data that support the findings of this study are available from the corresponding author upon reasonable request. Source data are provided with this paper.

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This study deals with society's pathology that I learned during a long journey to treat Alzheimer's disease person, who went to heaven on January 3 this year—published through the branch journal of Nature journal, replacing the person's obituary.

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Author Contributions: JL designed the study, developed the hidden equation, analyzed the data, and wrote it.

Competing Interests

The authors declare that they have no competing interests.

Data and Materials Availability

According to the Official Information Disclosure Act in Korea, it is possible to provide public access to a dataset based on the linkage of data from nationwide public registries. Access to the National Health Insurance Service (NHIS) and the Sorokdo National Hospital, and the Health Insurance Review & Assessment system's registry data can be granted to individual researchers only upon seeking approval, according to the National Agency for Data Protection. We, therefore, cannot place the dataset in a public repository. However, pooling of aggregated data is possible and would be of interest to the research group.

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Tables

Table 1. NHIS Dementia Medicines: Users and Deaths Toll.

Year	ADD		Donepezil		Rivastigmine		Memantine		Risperidone		Fluoxetine		Olanzapine		Sertraline		Quetiapine	
	User	Death	User	Death	User	Death	user	death	user	death	user	death	user	death	user	death	user	dea
2010	1,496,235	78,528	96,820	12,575	8,070	780	31,965	5,559	181728	8945	156,899	1,802	37,810	1,654	71,494	1,341	140,218	10,6
2011	1,624,963	87,053	123,101	15,797	9,788	850	35,315	5,945	186077	8976	151,252	1,580	45,177	2,001	76,809	1,319	172,218	13,4
2012	1,793,974	100,711	150,128	19,604	11,218	1,103	37,138	6,419	191121	9519	150,654	1,582	54,344	2,681	85,193	1,377	202,486	17,6
2013	1,879,280	109,772	176,440	22,941	11,935	1,170	38,391	6,403	189702	9354	140,194	1,439	59,184	3,112	86,931	1,427	228,140	21,1
2014	2,028,410	119,542	204,724	26,636	13,705	1,291	43,165	6,568	190178	9271	134,013	1,395	63,444	3,276	89,114	1,565	259,635	24,5
2015	2,191,614	135,524	236,834	32,084	15,542	1,847	52,358	8,134	195951	10052	133,262	1,373	64,123	3,036	92,676	1,522	290,105	27,9
2016	2,373,538	148,351	267,241	36,375	15,103	1,682	58,626	9,080	199776	10396	137,846	1,329	66,902	3,368	103,099	1,684	331,811	32,9
2017	2,598,416	167,853	294,203	42,187	14,443	1,716	65,605	10,718	203635	10822	144,496	1,268	75,153	3,700	115,370	1,853	384,209	39,9
2018	2,880,654	185,099	319,751	47,487	14,777	1,839	70,873	11,597	208994	11179	157,170	1,369	81,868	4,042	129,710	1,982	439,704	46,2
2019	3,234,536	197,232	336,683	48,830	14,964	1,840	79,770	12,714	228123	12044	173,284	1,405	87,565	4,359	142,660	2,005	540,397	51,7

Table 2. Lee's hidden data and results of calculation

Year	AAD		Donepezil		Rivastigmine		Memantine		Risperidone		Fluoxetine		Olanzapine		Sertalin	
	User (B-A)	Death (B-A)	User (B-A)	Death (B-A)	User (B-A)	Death (B-A)	User (B-A)	Death (B-A)	User (B-A)	Death (B-A)	User (B-A)	Death (B-A)	User (B-A)	Death (B-A)	User (B-A)	Death (B-A)
2010	128,728	8,525	26,281	3,222	1,718	70	3,350	386	4349	31	-5,647	-222	7,367	347	5,31	
2011	169,011	13,658	27,027	3,807	1,430	253	1,823	474	5044	543	-598	2	9,167	680	8,38	
2012	85,306	9,061	26,312	3,337	717	67	1,253	-16	-1419	-165	-10,460	-143	4,840	431	1,73	
2013	149,130	9,770	28,284	3,695	1,770	121	4,774	165	476	-83	-6,181	-44	4,260	164	2,18	
2014	163,204	15,982	32,110	5,448	1,837	556	9,193	1,566	5773	781	-751	-22	679	-240	3,56	
2015	181,924	12,827	30,407	4,291	-439	-165	6,268	946	3825	344	4,584	-44	2,779	332	10,42	
2016	224,878	19,502	26,962	5,812	-660	34	6,979	1,638	3859	426	6,650	-61	8,251	332	12,27	
2017	282,238	17,246	25,548	5,300	334	123	5,268	879	5359	357	12,674	101	6,715	342	14,34	
2018	353,882	12,133	16,932	1,343	187	1	8,897	1,117	19129	865	16,114	36	5,697	317	12,95	
2019	-3,234,536	-197,232	-336,683	-48,830	-14,964	-1,840	-79,770	-12,714	-228123	-12044	-173,284	-1,405	-87,565	-4,359	-142,66	

Results of the hidden equation for a comparison graph

Year	AAD	Donepezil	Rivastigmine	Memantine	Risperidone	Fluoxetine	Olanzapine	Sertalin
2010	0.0662	0.1226	0.0407	0.1152	0.0071	0.0393	0.0471	-0.004
2011	0.0808	0.1409	0.1769	0.2600	0.1077	-0.0033	0.0742	0.006
2012	0.1062	0.1268	0.0934	-0.0128	0.1163	0.0137	0.0890	0.028
2013	0.0655	0.1306	0.0684	0.0346	-0.1744	0.0071	0.0385	0.063
2014	0.0979	0.1697	0.3027	0.1703	0.1353	0.0293	-0.3535	-0.012
2015	0.0705	0.1411	0.3759	0.1509	0.0899	-0.0096	0.1195	0.015
2016	0.0867	0.2156	-0.0515	0.2347	0.1104	-0.0092	0.0402	0.013
2017	0.0611	0.2075	0.3683	0.1669	0.0666	0.0080	0.0509	0.009
2018	0.0343	0.0793	0.0053	0.1255	0.0452	0.0022	0.0556	0.001
2019	0.0610	0.1450	0.1230	0.1594	0.0528	0.0081	0.0498	0.014

Figures

The life expectancy of Hansen's disease patients of Sorokdo (island)

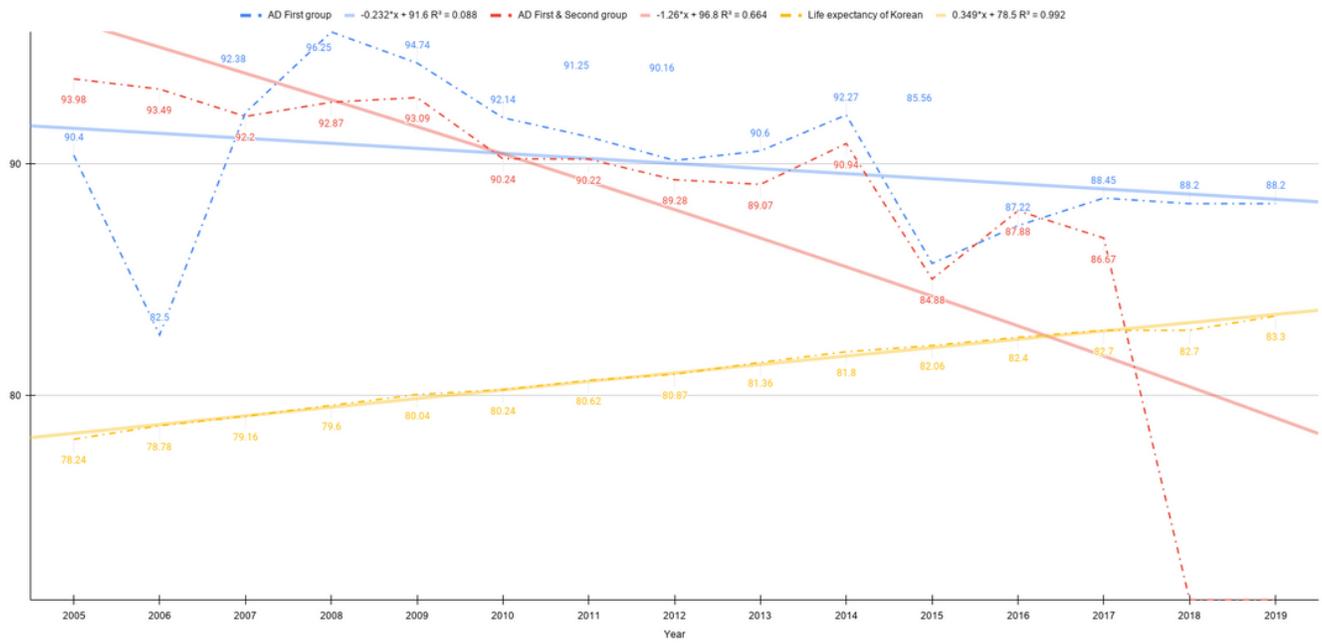


Figure 1

The life expectancy of Hansen's disease patients with Alzheimer's disease at Sorokdo National Hospital. In the group of patients diagnosed with Alzheimer's disease, the mean age of deaths while taking only dementia symptom treatment was blue. The mean age of deaths with taking additional psychiatric drugs is red. In 2018-2019, the life expectancies of Hansen's disease (HD) patients taking additional psychotropic medications were suddenly decreased in the Sorokdo National Hospital. On the other hand, Korean's life expectancy is on the rise (see yellow). The life expectancies of HD patients taking the AAD first group (blue) were decreased in the Sorokdo National Hospital.

The effect of Dementia Magement Act

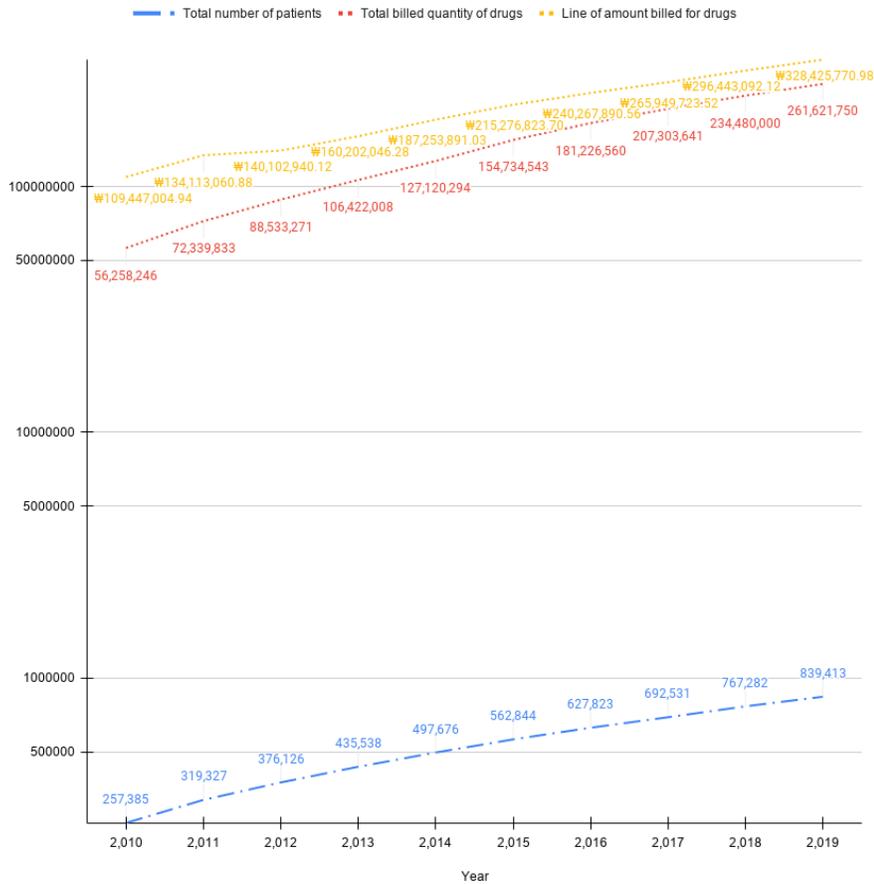


Figure 2

Numbers of drug prescriptions for dementia patients in Korea from 2010 to 2019. The state or a local government subsidizes dementia patients for expenses incurred in the treatment and diagnosis of dementia from its budget, considering each dementia patient's capability to bear such costs. The AD and AAD data were reported from the Health Insurance Review & Assessment system. From 2010 to June 2020, the diagnosis and prescription of patients with MCI and AD in Korea increased 3.26 times and 4.65 times, respectively.

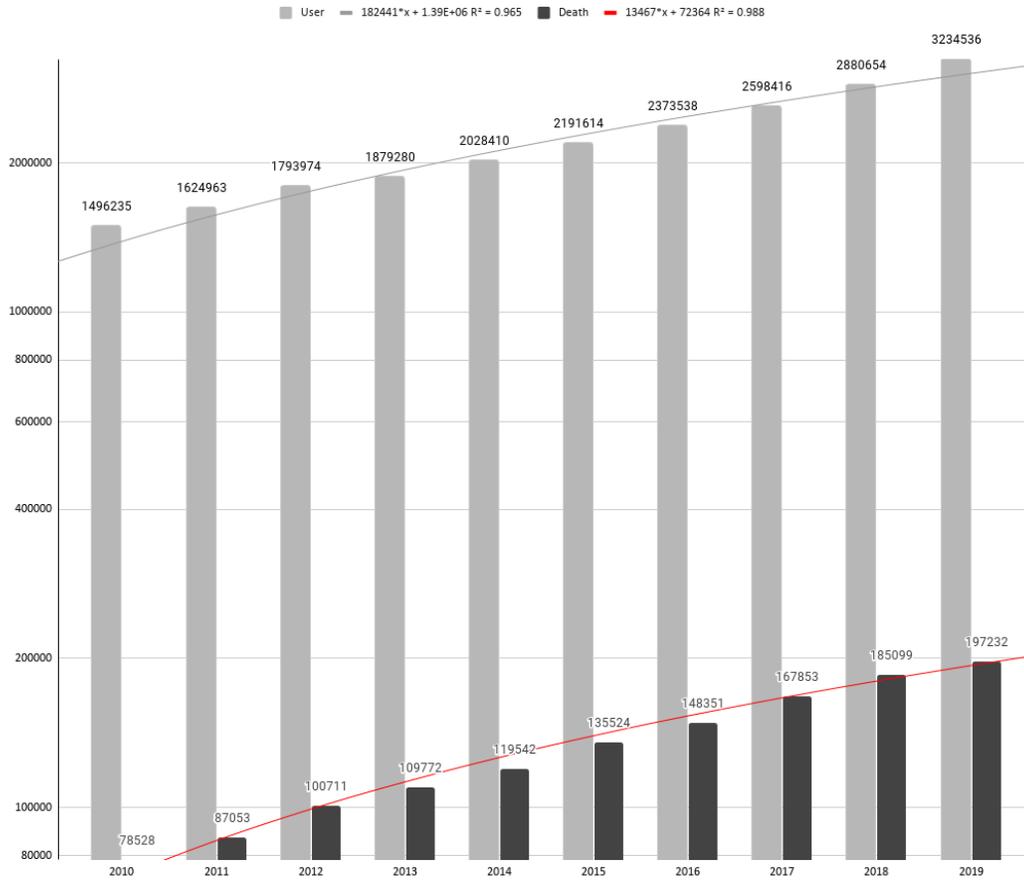


Figure 3

Graph with AAD users and deaths in Korea from 2010 to 2019. The number of users who took AAD in Korea increased 2.16 times, and the number of deaths increased by 2.51 times from 2010 to June 2019. The life expectancy between AD and AAD was significantly observed between 2017 and 2019. It is because the DMA was strengthened on June 12 2018.

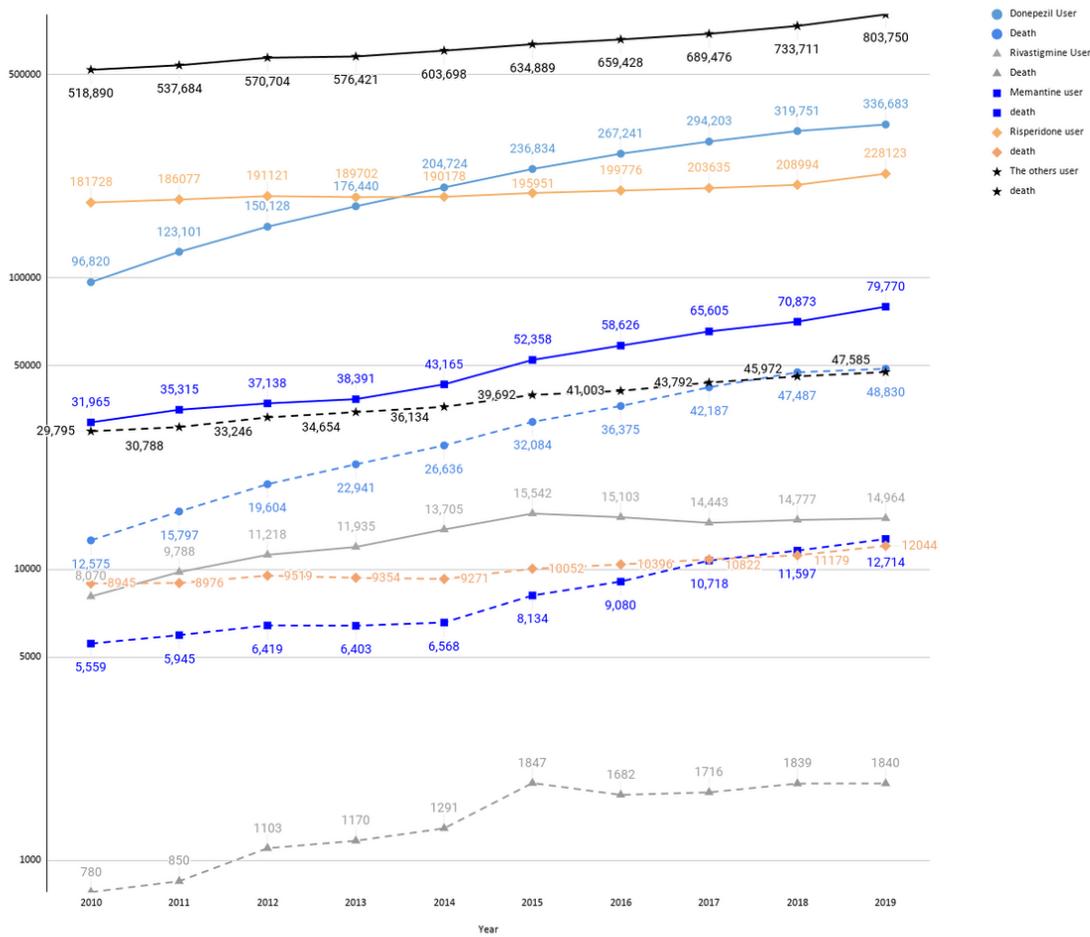


Figure 4

Graph of AAD users and deaths in Korea from 2010 to 2019. The DMA was strengthened on June 12 2018. The number of users who took donepezil in Korea increased 3.48 times, and the number of deaths increased 3.88 times from 2010 to June 2019. Donepezil users' life expectancies were significantly observed between 2017 and 2019 (Supplement Figure 2-1). The number of users who took rivastigmine in Korea increased 1.85 times, and the number of deaths increased 2.36 times from 2010 to June 2019. The number of users who took memantine in Korea increased 2.50 times, and the number of deaths increased by 2.29 times from 2010 to June 2019. It is prescribed to treat moderate-to-severe AD. The number of users who took risperidone in Korea increased 1.26 times, and the number of deaths increased by 1.35 times from 2010 to June 2019. Risperidone is an antipsychotic medication prescribed to treat schizophrenia and bipolar disorder. The number of users who took galantamine and other psychotropic medications in Korea increased 1.55 times, and the number of deaths increased by 1.60 times from 2010 to June 2019.

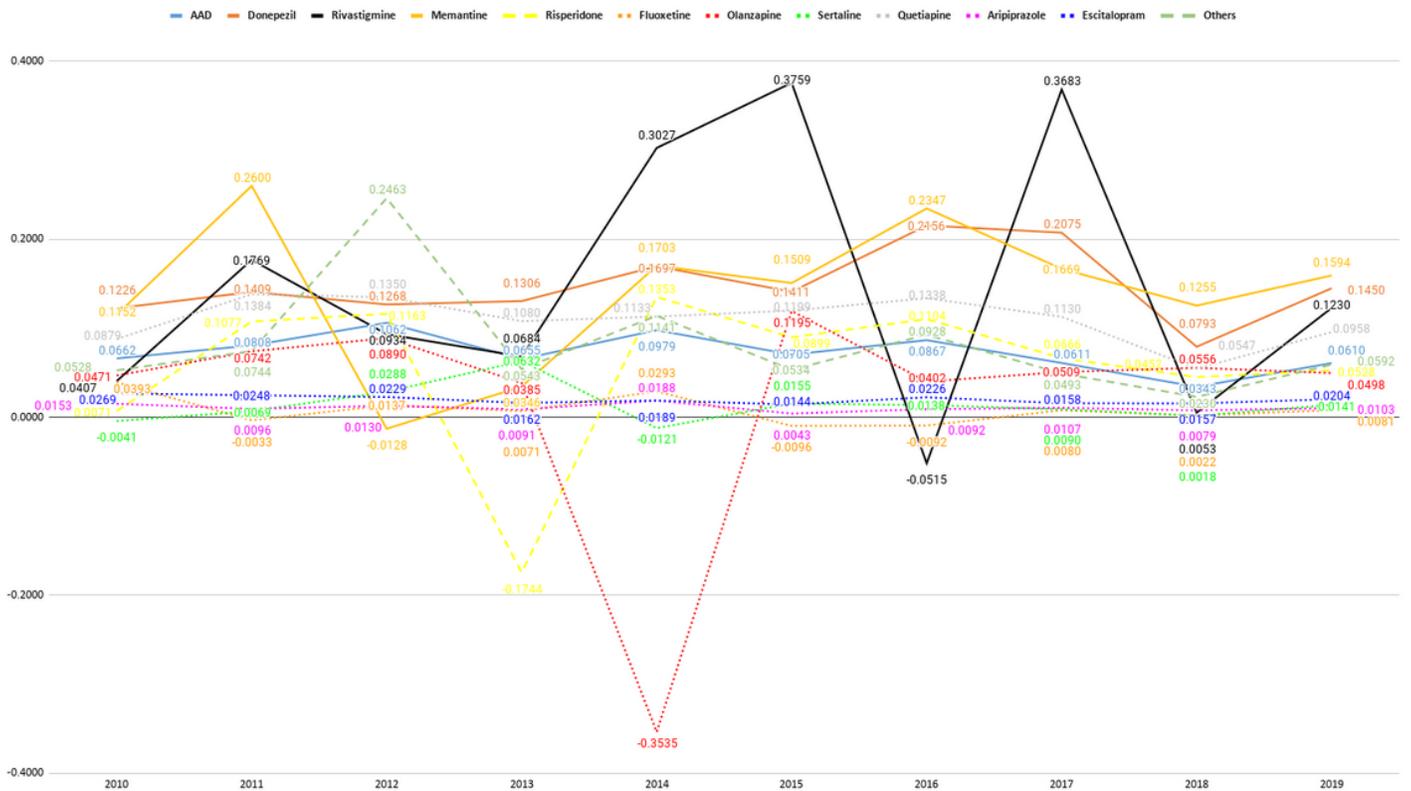


Figure 5
 Graph by Lee's hidden equation with AAD users and deaths in Korea from 2010 to 2019. The number of deaths is the independent variable. Lee's hidden equation follows. X is the year, Y is $(\text{death B} - \text{death A}) / (\text{user B} - \text{user A})$. By comparing the rate at which the number of deaths increases when the number of users increases, we can compare deaths caused by dementia medicines. The population is all Koreans. If the independent variables are AAD, Donepezil, Rivastigmine, Memantine, Risperidone, Fluoxetine, Olanzapine, Sertraline, Quetiapine, Aripiprazole, Escitalopram, and the others, the dependent variable is Lee's hidden data. It makes to calculate the F-ratio value and the p-value by One-Way Repeated Measures ANOVA Calculator.

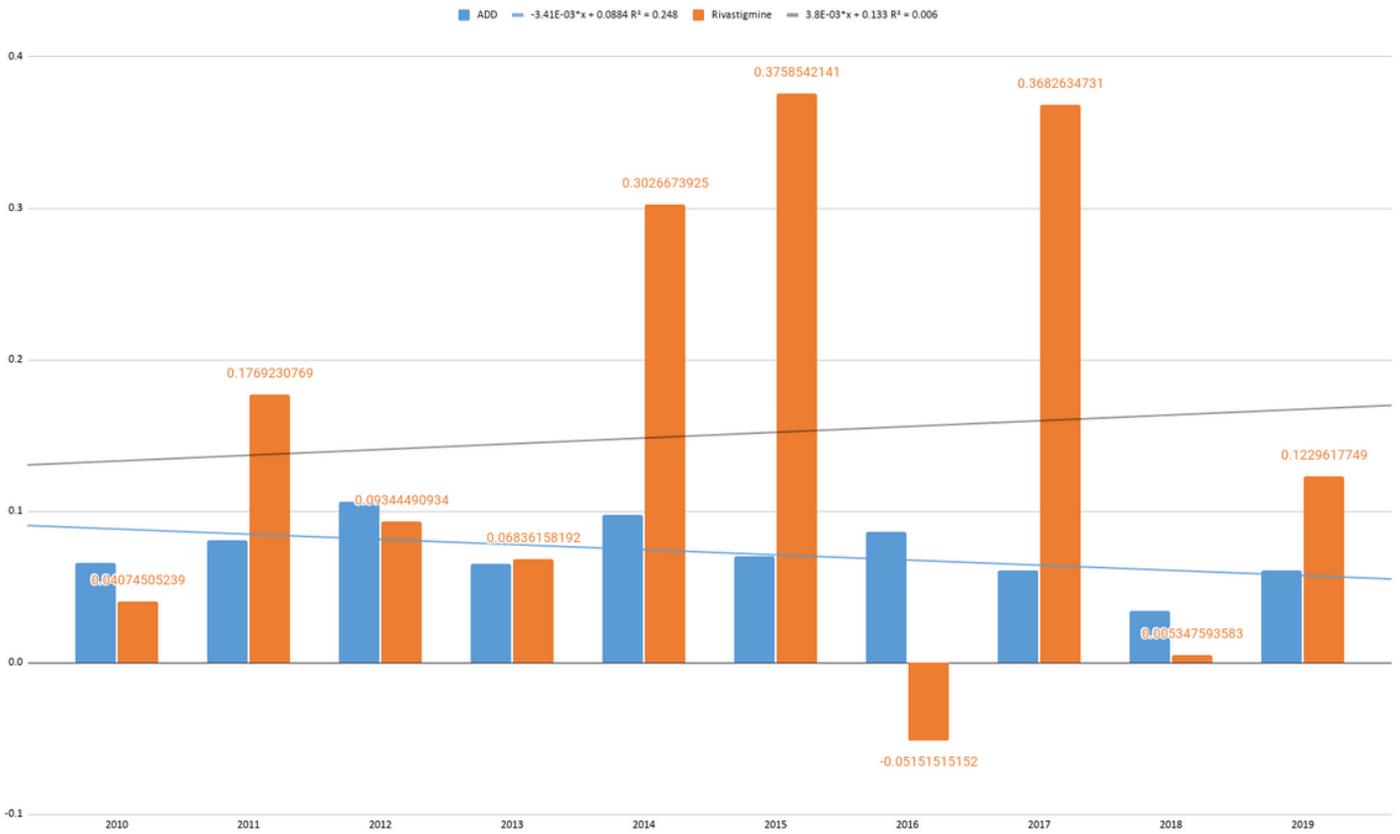


Figure 6

Lee's Hidden Equation Graph with rivastigmine users and deaths in Korea from 2010 to 2019. The number of users who took rivastigmine in Korea increased 1.84 times, and the number of deaths increased by 2.36 times from 2010 to June 2019. The number of users who took AAD in Korea increased 2.16 times, and the number of deaths increased by 2.51 times from 2010 to June 2019. The rivastigmine trend line is black. The trend line of AAD, the reference line, is blue. The increase or decrease of rivastigmine is jagged in the hidden equation graph, but the death toll increases.

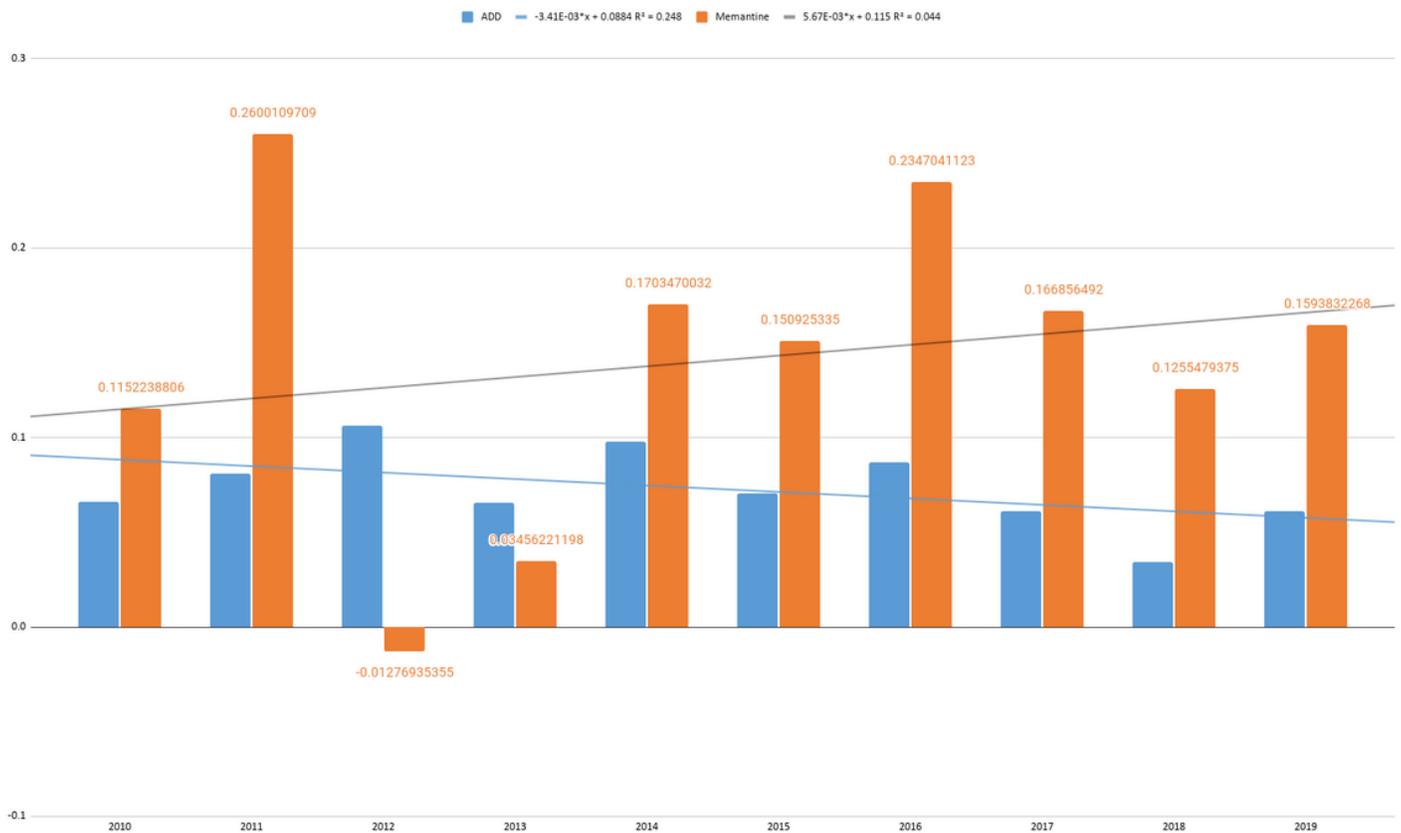


Figure 7

Lee's Hidden Equation Graph with memantine users and deaths in Korea from 2010 to 2019. The number of users who took memantine in Korea increased 2.50 times, and the number of deaths increased by 2.29 times from 2010 to June 2019. Memantine is an uncompetitive NMDA receptor modulator. It is prescribed to treat moderate-to-severe AD. The number of users who took AAD in Korea increased 2.16 times, and the number of deaths increased by 2.51 times from 2010 to June 2019. The memantine trend line is black. The trend line of AAD, the reference line, is blue. Memantine did not significantly increase the number of deaths than the increase in users, but the death toll increases in the hidden equation graph.

Supplementary Files

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- [SupplementaryMaterialsfinal.docx](#)