The Preventive and Treatment of the Neuroinflammasome in Sorokdo National Hospital

Jong-Hoon Lee (science@research.re.kr)
Seoul National University
Chul Joong Lee
Zein Pain Clinic Seongbuk
So Jeong Lee
Rice University
Su-Hee Choi
Seoul National University Hospital
Sang-Suk Oh
Ewha Womans University
Jungwuk Park
Chungdam Hospital

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Abstract

Objective: This study investigated leprosy patients with Alzheimer's disease (AD) treated with 4,4'-diaminodiphenyl sulfone (DDS, Dapsone) as a neuroinflammasome competitor.

Method: We searched all the Sorokdo National Hospital medical records and the National Health Insurance Service in South Korea and when the Korean government computerized the International Classification of Diseases (ICD)-9 code and Electronic Data Interchange (EDI). The Seoul study analyzed AD, and anti-AD drugs in the Sorokdo National Hospital's EDI database archived from January 2005 to June 2020 through the ICD-9 and -10 codes with National Health Insurance System.

Result: The relation between DDS and AD each year was analyzed using the chi-square tests. P-values from 2007 to 2020 were significant. (P-value < 0.05) Treatment effects were proved with the T-Test Calculator. Four groups were defined: Treatment (T) 1: DDS prescription (+) AD prevalence (+), T 2: DDS (+) AD non-prevalence (-), T 3: DDS non-prescription (-) AD (+), T 4: DDS (-) AD (-). The results are all significant at $p < .05$. The participants with AD (T1) who took the DDS intervention (Mean (M) = 0.1766, Standard Deviation (SD) = 0.074) compared to the participants without AD (T2) who did not take the DDS in the control group (M = 0.5501, SD = 0.1421) demonstrated significantly lesser AD prevalence rates. The t-value is -8.72515 and the p-value is < .00001. The result is significant at $p < 0.05$.

Conclusion: Our study is the first to prove dapsone as a preventive treatment for AD through observational studies for 15 years. This study demonstrated the neuroinflammasome therapy for AD.

1. Introduction

In 1992, an Alzheimer's disease (AD) research team published a method of preventing and treating human AD dementia with 4,4'-diaminodiphenyl sulfone (DDS, Dapsone), its didextrose sulfonate derivative, and other closely related sulfones (sulfetrone and thiazolsulfone)[1–3]. However, further investigations did not detect any differences in AD prevalence among leprosy patients treated with DDS and failed to demonstrate that it had any protective effects against Aβ neurotoxicity[4]. There have been various claims in autopsy findings and AD interpretations in leprosy patients. Population studies varied in their specific neuropathological findings, but all observed some abnormal neuropathology characteristic of AD despite DDS treatment[5–8].

The Seoul study originated from the Seoul Longitudinal Study of Aging[9] had investigated five patients diagnosed with MCI from February 2008 to December 2020. The production of dapsone was ceased from 2016 to 2018 in South Korea. The reason is that pharmaceutical companies gave up the production of dapsone because the maximum allowance price of the National Health Insurance System was low. Patients were diagnosed with AD in June 2018. The patient suffered from severe side effects after taking anti-AD drugs (AADs)[10,11]. We have found that taking and stopping AAD leads to the development of AD. So, we reviewed the studies on AD, AAD and Dapsone [1–8]. So it suggested whether leprosy patients have

continued to take dapsone should be critical in AD and beta-amyloid neurotoxicity studies. Because dapsone is a drug with side effects, doctors closely monitor the condition of leprosy patients and then prescribe dapsone or not.

The Sorok island as a Japanese 'leper colony' was established in May 1916 to quarantine leprosy patients. It was not easy for them to see a doctor. So they have been taking the prescribed leprosy remedy steadily. Some people lived on Sorok Island for 79 years and took dapsone for more than 50 years from our survey. After graduating from nursing school at the University of Innsbruck Nursing School in Tyrol, Western Austria, Marianne, who worked at a hospital in Innsbruck, joined Sorok Island in February 1962. Sister Margaret entered Sorok Island in October 1967, and they left Sorok island on 21 November 2005, returned to their homeland. Since this study was conducted from 2005 to 2020 based on the medical records of Sorokdo National Hospital, the patient research was initiated by Sister Marianne Stoeger and Sister Margaritha Pissarek from 1962 as a kind of control group. The Seoul study analyzed the AD prevalence in leprosy patients.

2. Methods

Study Design

In the 1990s, a Japanese epidemiological survey of leprosy patients aged 65 years or older revealed dementia in leprosy patients. A neuropathological case series of leprosy patients detected the absence of senile plaques[1–3]. Nevertheless, a similar study the following year showed no difference in discovering senile plaques between the patient and control groups[5–8]. The verification study of the effect of anti-leprosy drugs on Aβ-induced neurotoxicity in vitro for the Japanese Sanatorium Study[4] may be the Null hypothesis. So, the leprosy patients, taking dapsone consistently for decades, were selected as the study's subject.

Inclusion and exclusion criteria

According to the Official Information Disclosure Act in Korea, the Seoul study analyzed all AD, DDS and AAD use in Hansen subjects. We searched all medical records of the Sorokdo National Hospital and the National Health Insurance Service (NHIS) in Korea from the time when the Korean government computerized the International Classification of Diseases (ICD)-9 code and Electronic Data Interchange (EDI). We connected to the medical record database of the Sorokdo National Hospital and archived it from January 2005 to June 2020. With the ICD-9 and − 10 codes, we then analyzed medical data on the correlation between DDS and AD. Informed consent was obtained from all participants or, if participants are under 18, from a parent and/or legal guardian.

Statistical Analysis

We used the software programs Object-Relational DBMS, Google spreadsheet and SPSS. According to the Official Information Disclosure Act in Korea, we also requested and analyzed the entire ICD 9 and 10 code

data of AD and AAD from the Health Insurance Review & Assessment system. The total number of leprosy patients living in Sorok Island as a control group was investigated. After diagnosis and examination, all leprosy patients diagnosed with AD were examined for drugs being administered.

Standard Code: Korean Standard Classification of Diseases (KCD) disease code

(1) Mental and behavioural disorders, F00-F09, G30

[F00 code Dementia in Alzheimer's disease (G30.-+)]

[F01 code Vascular dementia]

[F02 code Dementia in other diseases classified elsewhere]

[F03 code Unspecified dementia]

[F04 code Organic amnesic syndrome, not induced by alcohol and other psychoactive substances]

[F05 code - Delirium, not induced by alcohol and other psychoactive substances]

[F06 code - Other mental disorders due to brain damage and dysfunction and to physical disease]

[F07 code - Personality and behavioural disorders due to brain disease, damage and dysfunction]

[F09 code - Unspecified organic or symptomatic mental disorder]

[G30 Alzheimer's disease]

(2) For symptomatic relief of Alzheimer's disease

First Group: For symptomatic relief of Alzheimer’s disease

[donepezil hydrochloride] 148603ATB 148602ATD 148602ATB 148601ATD 148601ATB 643401ATD 643402ATD

[rivastigmine] 224501ACH 224503ACH 224504ACH 224505ACH 224506CPC 224507CPC 224508CPC

[galantamine] 385203ACR 385203ATR 385204ACR 385204ATR 385205ACR 385205ATR

[N-methyl-D-aspartate (NMDA) receptor antagonist] 190031ALQ 190001ATB 190003ATD 190004ATB 190004ATD

Second Group: For psychologic symptoms of Alzheimer’s disease

[haloperidol] 167903ATB 167904ATB 167905ATB 167906ATB 167908ATB 167908ATB 168030BIJ

[Risperidone] 224201ATB 224201ATD 224202ATB 224202ATD 224203ATB 224204ATB 224205BIJ 224206BIJ

[Quetiapine] 378601ATB 378602ATB 378603ATB 378604ATB 378605ATB 378605ATR 378606ATR 378607ATR 378608ATR 378608ATR 378610ATB

[Olanzapine]

204001ATB 204001ATD 204002ATB 204002ATD 204004ATB 204005ATB

[Aripiprazole]

451501ATB 451501ATD 451502ATB 451502ATD 451503ATB 451504ATB 451505ATB 451506BIJ 451507BIJ

[Oxcarbazepine] 206330ASS 206301ATB 206302ATB 206303ATB

[fluvoxamine] 162501ATB 162502ATB

[Escitalopram] 474801ATB 474802ATB 474803ATB 474804ATB

[Trazodone] 242901ACH 242901ATB 242902ATB 242903ATR

[sertraline] 227001ATB 227002ATB 227003ATB

[Escitalopram] 474801ATB 474802ATB 474803ATB 474804ATB

[Fluoxetine] 161501ACH 161501ATB 161502ACH 161502ATB 161502ATD

3. Results

From 2010 to June 2020, the diagnosis of patients with MCI and AD in South Korea increased dramatically. From 2010 to June 2019, the Dementia Management Act increased the diagnosis of patients with mild cognitive impairment or AD by 3.26 times and AAD prescription by 4.65 times in South Korea. From 2010 to June 2019. Through rapid diagnosis and prescription changes over ten years, it is possible to monitor how AAD affects dementia. (Table 1) (Fig. 1)

Table 1
Numbers of drug prescriptions for dementia patients in Korea from 2010 to 2019

Year	Total billed quantity of drugs	Total amount billed for drugs (US dollar)	Total number of patients
2010	56,258,246	109,447,004.94	257,385
2011	72,339,833	134,113,060.88	319,327
2012	88,533,271	140,102,940.12	376,126
2013	106,422,008	160,202,046.28	435,538
2014	127,120,294	187,253,891.03	497,676
2015	154,734,543	215,276,823.70	562,844
2016	181,226,560	240,267,890.56	627,823
2017	207,303,641	265,949,723.52	692,531
2018	234,480,000	296,443,092.12	767,282
2019	261,621,750	328,425,770.98	839,413
(Currency data provided by Morningstar on 07 February, 12:58 AM UTC)			

Study Population

Korean leprosy patients continue to take DDS throughout their lives. Based on the relative prevalence of AD in patients who have been prescribed DDS and those who have not, dapsone has a preventive effect against AD. AD diagnosed (+) group has increased DDS non-prescription (-) Group and has the lower prevalence in the DDS (-) Group from January 2005 to June 2020. The regression analysis value through linear analysis of the trend line is R^2 = Total (0.989), DDS (-) (0.979), DDS (+) (0.606) (Fig. 2). The proportion of the DDS prescription (+) group has been increased, and the proportion of the DDS (-) group has been decreased significantly in the AD no (-) group. There is a significant relationship between DDS and the differential prevalence proportion of AD in patients. The regression analysis value through linear analysis of the trend line is R^2 = Total (0.988), DDS (-) (0.988), DDS (+) (0.939) (Fig. 3)

Outcome Measures with the p-values between treatment groups

The relation between DDS and AD each year was analyzed using the chi-square test. P-value was significant from 2007 to 2020 when P-value < 0.05 was considered significant. (Table 2)The AD prevalence (+/-) group was rearranged based on the DDS prescription (+/-) group again. (Table 3)

Table 2
Alzheimer's Disease patients in the DDS prescription (+) /non-prescription (-) group from January 2005 to June 2020

Year	DDS (+)	DDS (-)	AD (+) Total	DDS (+)	DDS (-)	AD(-) Total	P-value*
2005	18	19	37	290	417	707	.3583
2006	20	37	57	302	363	665	.1324
2007	22	51	73	317	332	649	.0024**
2008	22	58	80	310	312	622	.00028**
2009	19	66	85	300	283	583	< .00001**
2010	25	82	107	270	286	556	< .00001**
2011	35	98	133	255	268	523	< .00001**
2012	39	135	174	238	241	479	< .00001**
2013	34	172	206	195	248	443	< .00001**
2014	25	190	215	172	236	408	< .00001**
2015	26	242	268	167	168	335	< .00001**
2016	33	255	288	154	149	303	< .00001**
2017	37	268	305	143	115	258	< .00001**
2018	45	292	337	132	87	219	< .00001**
2019	46	334	380	114	40	154	< .00001**
2020	32	352	384	109	4	113	< .00001**

*The relation between DDS and Alzheimer's Disease each year was analyzed using the chi-square test. A P-value < 0.05 was considered significant. ** indicates a P-value < 0.05.

Table 3
Alzheimer's Disease prevalencs and the DDS prescription (+) /non-prescription (-) group from January 2007 to June 2020

Year	T1: DDS(+)/AD(+)total	T2: DDS(+)/AD (-)total	T3: DDS(-)/AD (+)total	T4: DDS(-)/AD(-)total
2007	0.3014	0.4884	0.6986	0.5116
2008	0.2750	0.4984	0.7250	0.5016
2009	0.2235	0.5146	0.7765	0.4854
2010	0.2336	0.4856	0.7664	0.5144
2011	0.2632	0.4876	0.7368	0.5124
2012	0.2241	0.4969	0.7759	0.5031
2013	0.1650	0.4402	0.8350	0.5598
2014	0.1163	0.4216	0.8837	0.5784
2015	0.0970	0.4985	0.9030	0.5015
2016	0.1146	0.5083	0.8854	0.4917
2017	0.1213	0.5543	0.8787	0.4457
2018	0.1335	0.6027	0.8665	0.3973
2019	0.1211	0.7403	0.8789	0.2597
2020	0.0833	0.9646	0.9167	0.0354

The values of f and p were calculated using ANOVA calculator. Four groups were defined: Treatment (T) 1: DDS (+) AD (+), T 2: DDS (+) AD (-), T 3: DDS (-) AD (+), T 4: DDS (-) AD (-). The f-ratio value is 58.43, the p-value is < .00001 in the one-way repeated measures. The f-ratio value is 77,90, the p-value is < .00001 in the independent-measures (one-factor). The results are all significant at $p < .05$. However, there were caveats to Tukey's honestly significant difference. The pairwise comparisons within our ANOVA data (T1:T2, T1:T3, T1:T4, T2:T3, T2:T4, T3:T4) is all applicable except T2:T4. (Supplement Sect. 1)

T-Test

The participants with AD (T1) who took the DDS intervention (Mean (M) = 0.1766, Standard Deviation (SD) = 0.074) compared to the participants without AD (T2) who did not take the DDS in the control group (M = 0.5501, SD = 0.1421) demonstrated significantly lesser AD prevalence rates. The *t*-value is -8.72515 and the *p*-value is < .00001. The result is significant at $p < 0.05$. Fewer people have AD in the group who regularly took DDS from 2007 to 2020 in the DDS (+) Group. There are far more people in the group taking DDS who do not develop AD. The regression analysis value through the 6th-order polynomial analysis of the trend line is R^2 = AD (+) (0.958), AD (-) (0.987) (Fig. 4).

The participants with AD (T1) who took the DDS intervention (Mean (M) = 0.1766, Standard Deviation (SD) = 0.074) compared to the participants with AD (T3) who did not take the DDS in the control group (M = 0.8234, SD = 0.074) demonstrated significantly lesser AD prevalence rates. The t-value is -23.13483. The p-value is < .00001. The result is significant at p < .05. (Supplement Sect. 1). DDS (-) Group shows a steady increase in the number of people with AD. It suggests an increase in AD is associated with not taking DDS. The regression analysis value through the 6th-order polynomial analysis of the trend line is R^2 = AD (+) (0.958), AD (-) (0.958) (Fig. 5).

DDS' treatment effects can be conjectured by comparing the AD prevalence in leprosy patients who have been prescribed metronomic DDS and those who have not .

4. Discussion

Because of the Dementia Management Act in Korea, the Sorokdo National Hospital strengthened the diagnosis of dementia for old leprosy patients. Korean doctors perform standard treatment according to AD diagnosis and neuropsychiatric examinations results for leprosy patients. They strengthened the prescription of AADs and discontinued DDS in patients with inactive leprosy. As a result, it became possible to separate the group taking DDS from the group not taking DDS among AD patients for fifteen years. The relationship between AD and Dapsone become clear. Suppose any studies do not distinguish groups who have been prescribed from the other groups discontinued to take dapsone in the statistical data. In those cases, the effects of dapsone as an inflammasome competitor are mixed in the pathologic findings like previous confused pathologic findings[1–8].

The results of many epidemiologic studies and limited clinical evidence suggest that NSAIDs should delay the onset and hinder AD's progression[12,13]. The results of long-term clinical trials were negative. Still, these drugs affect the periphery of the inflammatory reaction[14]. The components of the neurovascular unit harmoniously working influence the BBB's properties. The brain capillary phenotypes have differences in a lack of fenestration and low pinocytotic activity. They mostly have the presence of tight junctions with low permeability between cells. Since most central nervous system (CNS) diseases are caused by inflammation and oxidative stress, the efficiency of drugs acting on CNS is essential[15]. DDS passes through the BBB, and high-dose sulfadiazine results in an effective CSF concentration in humans[16]. DDS appears to have more significant anti-inflammatory effects than NSAIDs. Moreover, DDS does not have the side effects of NSAIDs, such as gastrointestinal disorders; therefore, it is possible to administer adequate doses of DDS (100–300 mg/day) while monitoring other side effects.

DDS can regulate the production of hypochlorous acid, which is associated with myeloperoxidase, a kind of reductase enzyme. It reduces inflammatory reactions[10,11]. DDS may regulate NLRP3 inflammasome activators and a common signaling pathway. The specific NLRP3 target may act through a competitive therapeutic mechanism to counter the progression of MCI to AD[17]. Our work corroborates a finding reported in 1994: antibodies could inhibit this activation against complement receptors in the nanomolar

range. DDS and indomethacin are weakly inhibitory (10^{-4} M range) therapeutic agents in AD[3]. Clinical trials were conducted in 2013, and DDS increases the viability of brain cells in acute Stroke; statistics were significant [18]. It was very effective and economical in treating acute ischemic stroke patients[19]. In 2016, MRI results were published to compensate for functional loss after brain cell damage[20], and DDS has been reported to protect brain cells and increase viability in various experiments[21].

DDS reduced doxorubicin's cardiac toxicity from free radicals and inflammatory cytokines[22]. As an NLRP3 inflammasome competitor(17), DDS has been a substitute for colchicine treatment for familial Mediterranean fever[23,24]. As a treatment for immune thrombocytopenia with a median treatment duration with dapsone of six months and a median follow-up period of 3.4 years, a retrospective study of 122 patients reported a sustained response observed in 51% of patients, including 24% of complete responses[25].

There were different interpretations of the commonly cited 'Decreased Aβ and Increased Abnormal Tau Deposition in the Brain of Aged Patients with Leprosy[26] between the first review[27]: DDS was a therapeutic, preventive agent in AD[5,6,26], and the second review[28]: DDS was not[8,26]. It has reported that amyloid-beta protein (Aβ) depositions were significantly lower in the temporal cortex and hippocampal formation, and T-type leprosy patients exhibited slightly more Aβ deposition than L-type leprosy. Because T-type leprosy patients did not take Dapsone and Dapsone did not remove the Aβ, *Mycobacterium leprae* was assumed to cause a low incidence of AD in both type leprosy patients[29].

However, the subsequent researchers regarded it as the null hypothesis because the Aβ removal of DDS is irrelevant[10]. As an inflammasome competitor, DDS shows a reaction pattern that can explain the autopsy findings of AD brain pathology of the sanatorium in Japan, sometimes different. The molecular properties, including electron density and its Laplacian delocalization index, have explained the DDS' chemical bonding and atomic and molecular details[30,31]. The redox properties of DDS dependent on amine and sulfone moieties can explain the oxidation mechanism by electron transfer conferring potential biological properties, mainly electron transfer or oxidation for DDS—NHOH formation [32]. We can understand the various neuropathological findings of AD brain pathology. DDS regulates NLRP3 inflammasome activators and a common signalling pathway of SARS-CoV-2 inflammasome activators in the medulla oblongata[17,33]. DDS showed the exact competitive therapeutic mechanism to counter the progression of MCI to AD[10,11]. Leprosy patients on Sorok Island continue to take DDS throughout their lives. DDS appears to have a preventive effect against AD. From 1995 to this study, all researchers and all medical staff are overcoming bias information. It has long been known that a wide variety of factors characterizes Alzheimer's disease. The causality law could not be applied because the research analysis was conducted on patients who lived in various environments.

The Japanese Sanatorium study has arisen about dapsone, which has been proven therapeutic by this study. Coincidentally, in Japan, the team developed donepezil and used it as a therapeutic agent[34]. It was a cure for the team leader's severe AD patient[35]. However, donepezil has been turned into a treatment for

mild AD and has been found to be ineffective[36–41]. Also, conflicting researches have been announced that it can treat dementia or slow the disease's progression[42–47], but it is now being verified to increase the death toll[10,11,48–50].

In order to prove a causal relationship for the treatment of Alzheimer's disease, only the record of administering certain drugs in a very isolated environment is meaningful. This study overcomes the limitations of the diverse studies. The specific targeting of the NLRP3 inflammasome by DDS may be responsible for its observed preventive effects of AD[10,17]. Nevertheless, the paradoxical limitation of this study is that it was conducted in an isolated island area. In order to derive universal research results later, a large-scale population survey study in which dapsone is prescribed as preventive medicine for dementia and the results observed over a long time is required.

5. Conclusion

A group has been taking dapsone consistently for a long time in South Korea, and this study concludes that dapsone must be a preventive therapeutics for AD. Our study is the first to prove the causal relationship or association between dapsone and AD through observational studies. And dapsone is a drug that is not easy to take consistently: The reasoning that overlooked that point was the cause of having to prove it so late.

Declarations

Standard Protocol Approvals, Registrations

The National Agency approved this study for Management of Life-sustaining Treatment, which certified that the life-sustaining treatments were managed properly (Korea National Institute for Bioethics Policy (KoNIBP) approval number P01-202007-22-006). The KoNIBP approved the observational study of patients ethically based on FDA guidelines following the World Medical Association Declaration of Helsinki. We carried out all methods following relevant ethical guidelines, regulations and reported the study results. Sorokdo National Hospital obtained informed consent from all participants or, if participants are under 18, from a parent and/or legal guardian.

Data availability

According to the Official Information Disclosure Act in Korea, it is possible to access a dataset based on data linkage from nationwide public registries. Access to the National Health Insurance Service (NHIS) in Korea 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 Official Information Disclosure Act in Korea. We, therefore, presented the data through the pooling of aggregated data.

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Soon Joe (09-12-1931 ~ 03-01-2021) contributed to making treatment method for MCI & AD, SARS-CoV-2 ARDS: So naming is Soon, Joe's treatment.

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Figures

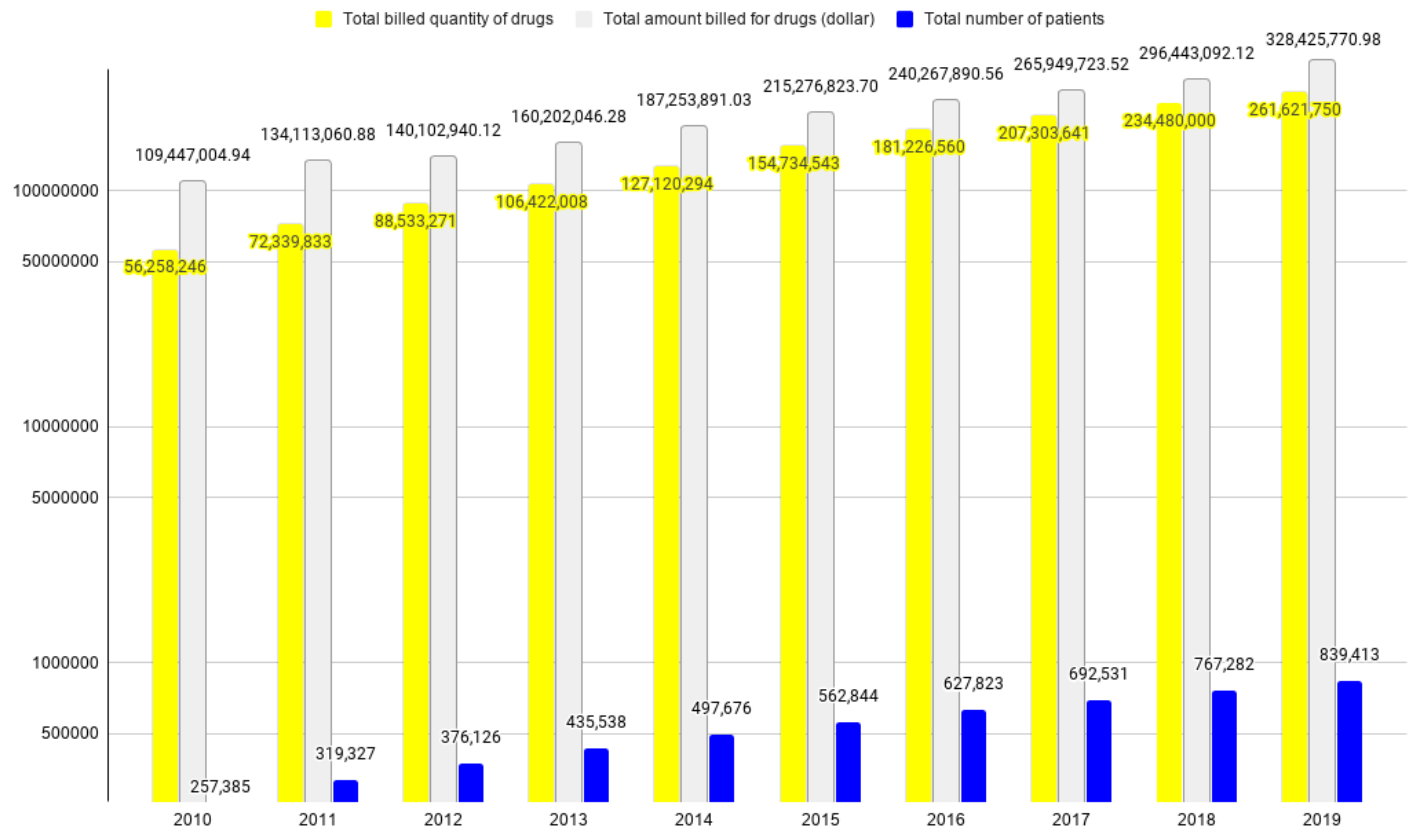

Figure 1

The Dementia Management Act had a significant influence on the diagnosis and treatment of dementia. The Dementia Management Act increased the diagnosis of patients with MCI or AD by 3.26 times. Anti-Alzheimer's Disease Drug (AAD) prescription was increased by 4.65 times in South Korea From 2010 to June 2019. Through rapid diagnosis and prescription changes over ten years, it is possible to monitor how AAD affects dementia.

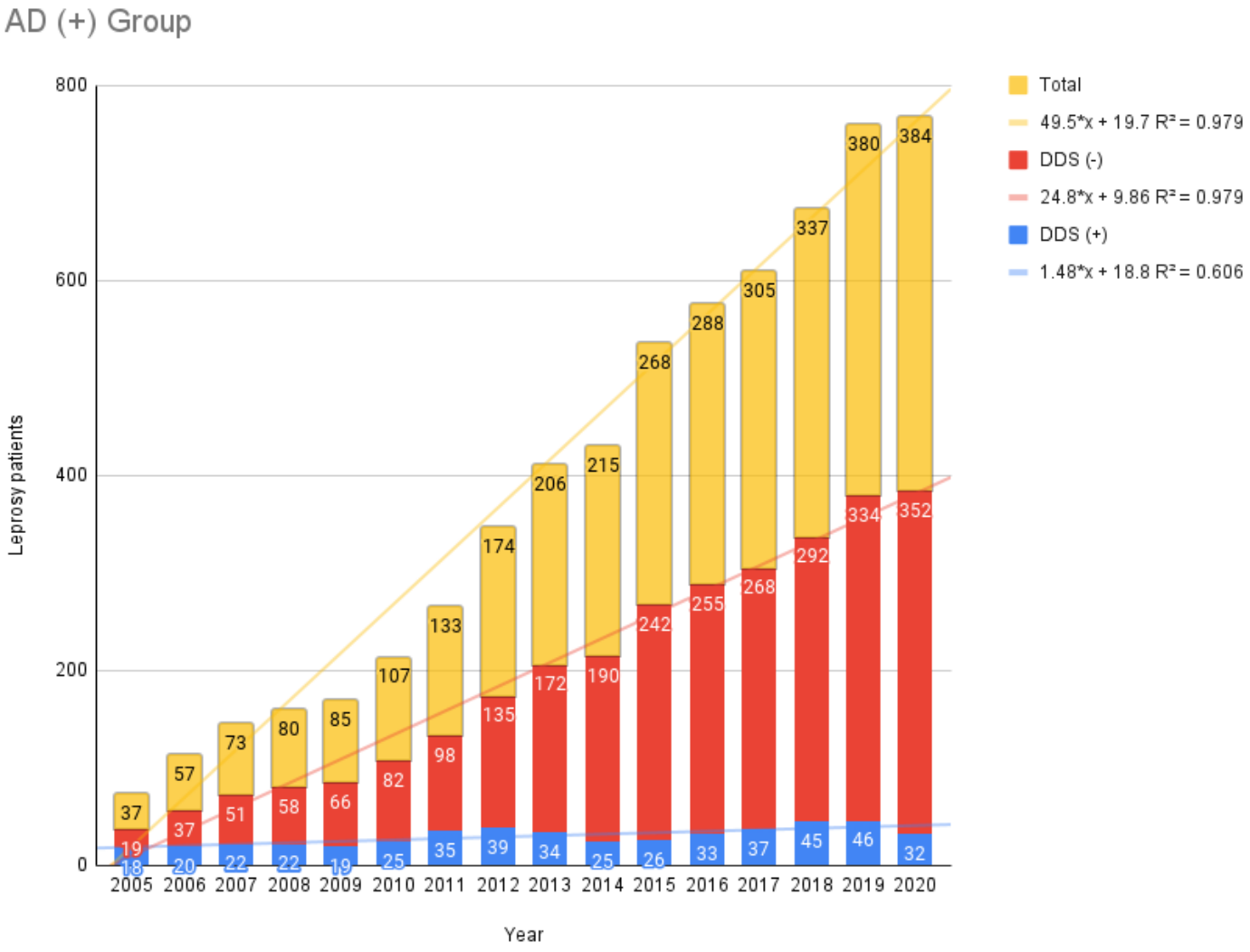

Figure 2

AD diagnosed (+) Group in Hansen's disease patients at Sorokdo National Hospital in Korea. The relevant Korean Standard Classification of Diseases (KCD) codes of the International Classification of Diseases (ICD-9, 10) are F00-F99 (mental and behavioural disorders), G30 (Alzheimer's disease), and DDS (140501ATB). The data are archived from January 2005 to June 2020. The graph suggests that the DDS prescription (+) group (blue) and DDS non-prescription (-) group (red) have the differential prevalence of AD in patients who have been prescribed DDS and those who have not. DDS acts as a neuroinflammasome competitor for AD.

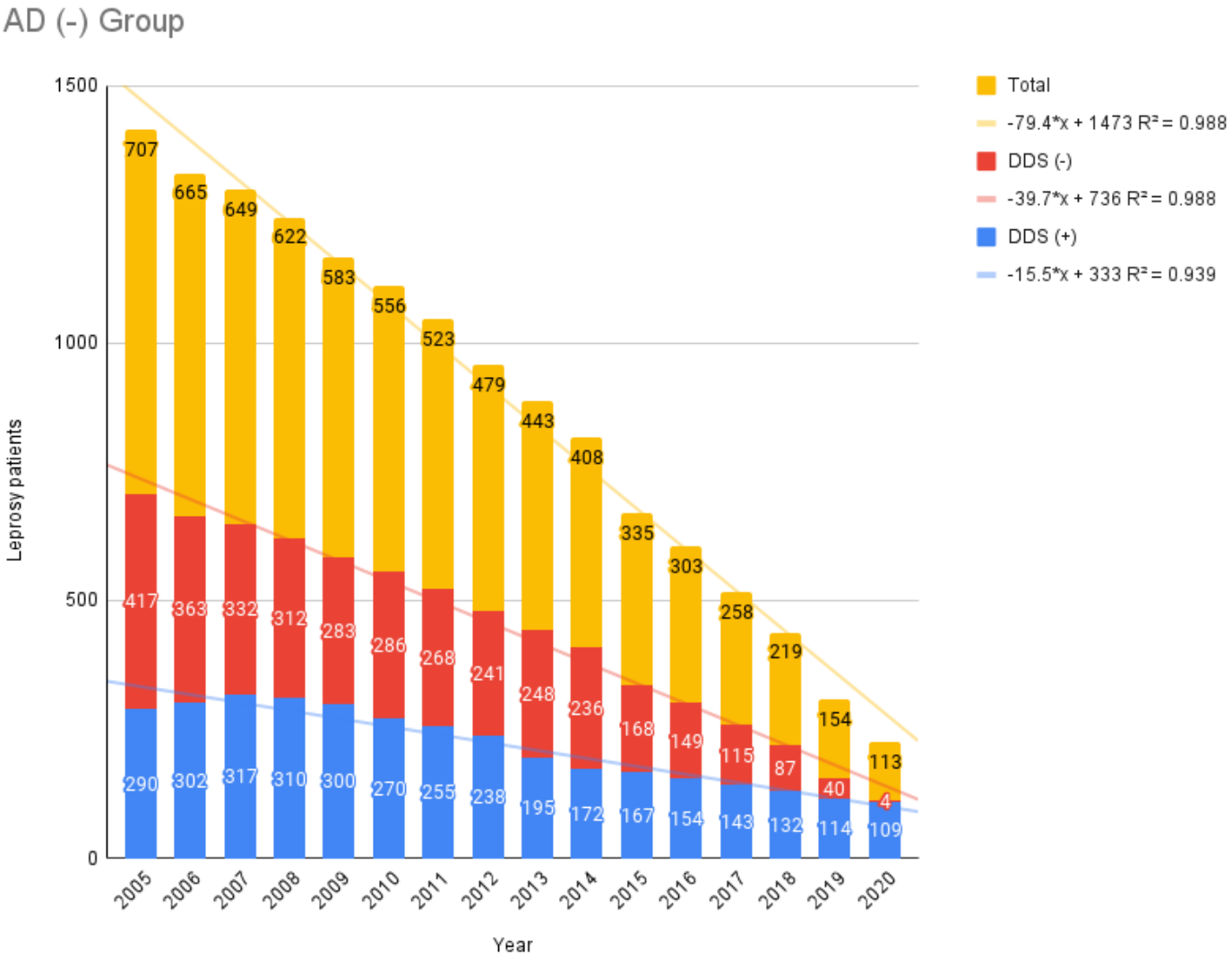

Figure 3

AD free (-) group in Hansen's disease patients at Sorokdo National Hospital. From January 2005 to June 2020, The graph suggests that in the AD (-) group, the proportion of the DDS prescription (+) group (green) increased, and the proportion of the DDS non-prescription (-) Group (red) decreased significantly. DDS acts as the differential prevalence proportion of AD in patients who have been prescribed DDS and those who have not.

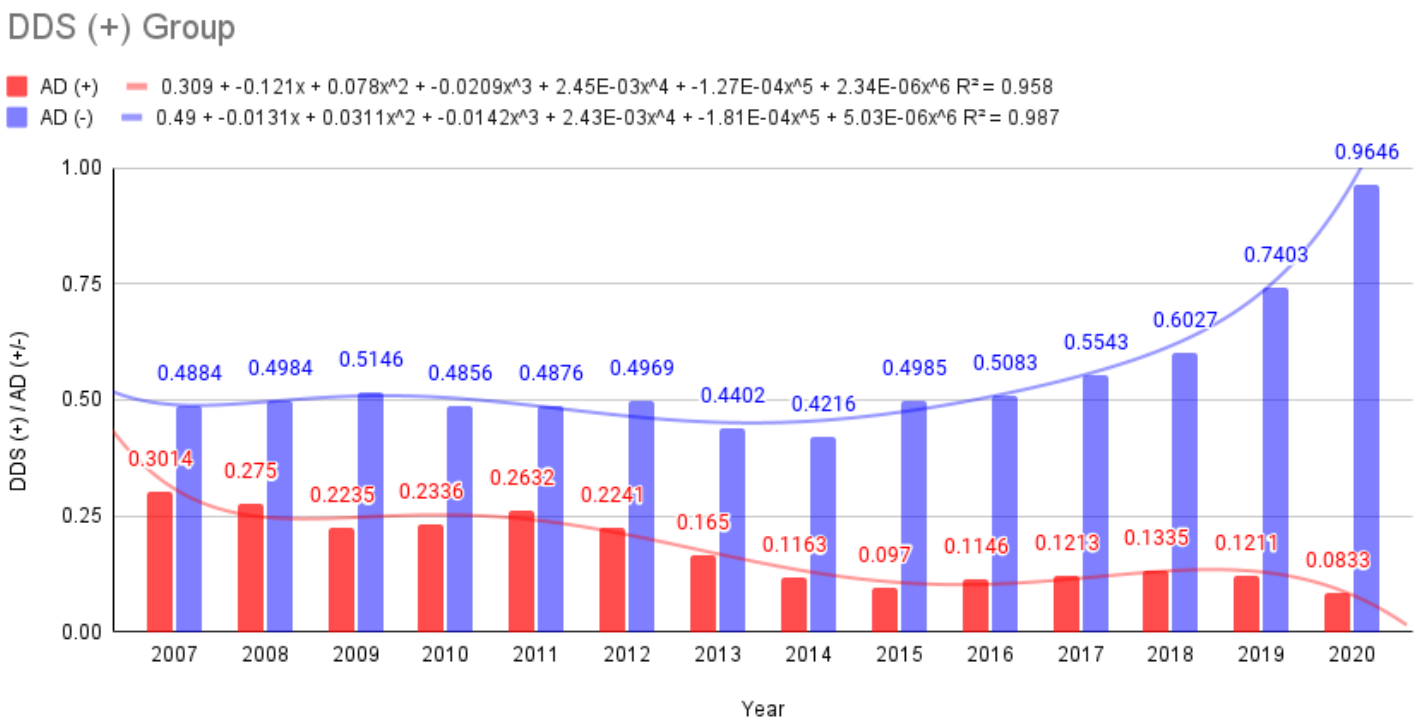

Figure 4

Alzheimer's disease prevalence graph from 2007 to 2020 from DDS prescription (+) group. There are far more people in the group taking DDS who do not develop Alzheimer's disease. This graph shows a clear relationship that fewer people have Alzheimer's disease in the group who regularly took DDS with R2 of 0.958 and 0.987.

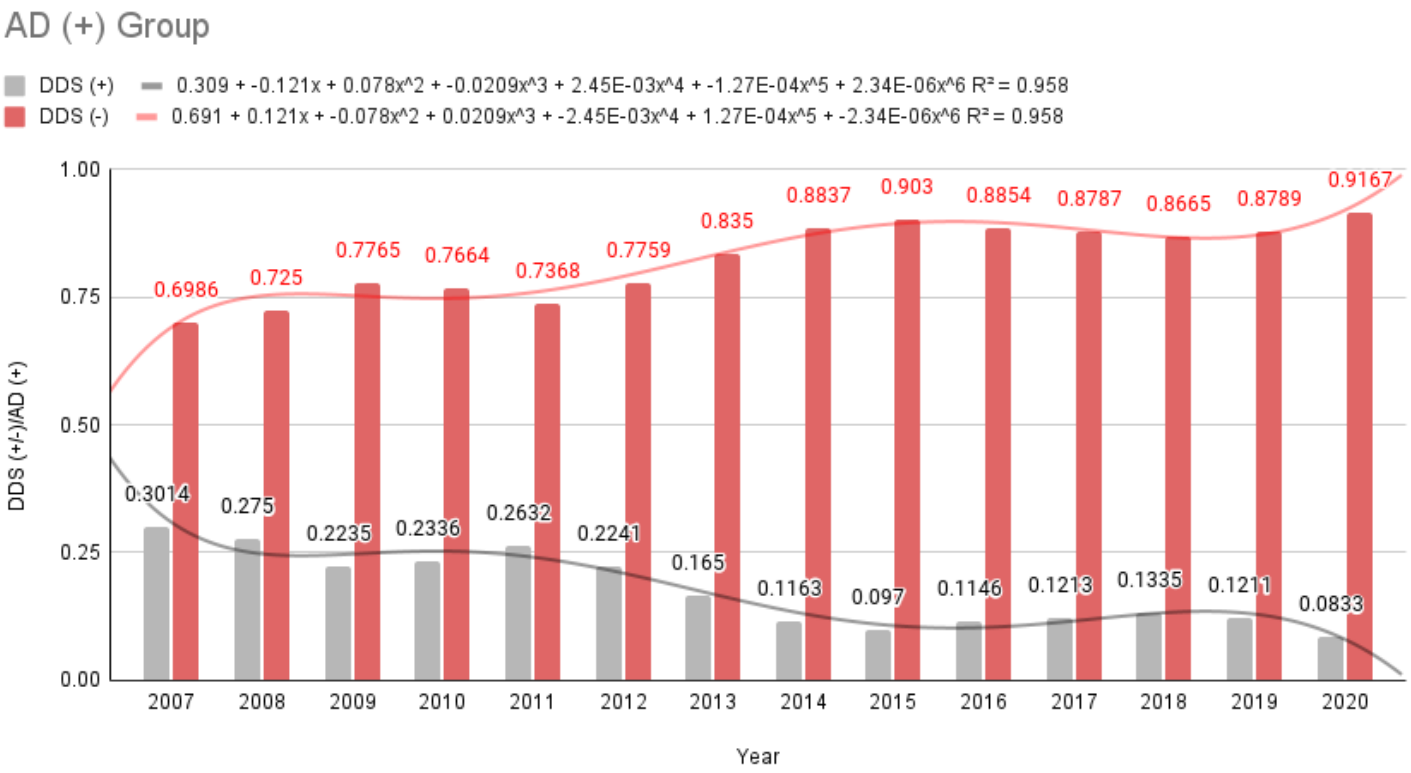

Figure 5

Alzheimer's disease prevalence graph from 2007 to 2020 from DDS (+/-) Group. It shows a steady increase in people with Alzheimer's disease in the group not taking DDS (red) with R2 of 0.958 and 0.958. It has also been shown that very few people (black) in the DDS non-prescription (-) Group do not get Alzheimer's disease simultaneously. It suggests that an increase in Alzheimer's disease is associated with not taking DDS.

Supplementary Files

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