임상의과학과 박사 학위논문

The effect of lithium and valproic acid on the onset of dementia in old age bipolar disorder patients

노인 양극성 장애 환자에서 리튬 및 발프로산이 치매 발생에 미치는 영향

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문 우 리

Abstract

The effect of lithium and valproic acid on the onset of dementia in old age bipolar disorder patients

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Background and Aim: While the number of elderly patients with bipolar disorder is increasing, clinical research for the effect of lithium and valproic acid on dementia is limited. There are prior cohort studies based on US and Danish claim data. However, these studies have several limitations in evaluating the independent effect of lithium or valproic acid.

Methods: This study used claim data of patient ≥ 50 years diagnosed with bipolar disorder from Korean HIRA (Health Insurance Review and Assessment Service) database. We used multi-variable cox proportional hazard model stratified on the

matched pairs with adjustment of factors affecting risk of incident dementia. For accurate estimation of independent effect of lithium and valproic acid on incident dementia, we analyzed the hazard ratio (HR) of dementia in lithium only users, matched valproic acid only users, and matched both lithium and valproic acid users compared to matched nonusers who did not use both medications.

Results: After matching and exclusion, our final subjects included 4,784 old age bipolar disorder patients. We observed 269 dementia cases during average 7 year follow up period. Compared to the nonusers, lithium only users (HR, 1.59; 95% CI, 1.10 - 2.31), valproic acid only users (HR, 1.76; 95% CI, 1.29 - 2.41), and the both users (HR, 1.81; 95% CI, 1.26 - 2.59) reported the higher risk of incident dementia, and the interaction between lithium and valproic acid on the risk of dementia did not show statistical significance ($p = 0.07$). The risk of incident dementia was comparable between the lithium only users, valproic acid only users and both users. Although dose response association in lithium users was not prominent, the risk of dementia became significant above the certain level of total prescription dose ($\geq$22 defined daily dose) or prescription duration ($\geq$56 days) in valproic acid users.

Conclusions: Clinicians should aware risk of dementia in old age bipolar disorder patients using lithium or valproic acid. For old age bipolar disorder patients who are resistant to valproic acid monotherapy, combination of lithium and valproic acid might be considerable in respects of dementia risk.

Keyword: lithium, valproic acid, bipolar disorder, dementia, cognitive impairment, big data, insurance claim data, Korean national health insurance data

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List of Abbreviations

AD: Alzheimer’s disease

MCI: mild cognitive impairment

BDNF: brain-derived neurotrophic factor

CGNs: cerebellar granule neurons

CI: confidence interval

CSF: cerebrospinal fluid

DDD: defined daily dose

CPD: cumulative prescription duration

GSK-3: glycogen synthase kinase-3

HIRA: Health Insurance Review and Assessment Service

HR: hazard ratio

ICD: International Classification of Disease

ISBD: International Society for Bipolar Disorder

NHI: National Health insurance

OABD: Older Age Bipolar Disorder

RCT: randomized controlled trial

Introduction

Study background

Along with population aging, the proportion of older adults aged 60 years or older is also getting larger and reached about 25% among bipolar disorder patients (1). Bipolar disorder patients are at high risk of developing dementia in their late life due to administration of various psychiatric drugs along with frequent mood fluctuation (2-4). Lithium and valproic acid are the most frequently prescribed medications for the elderly bipolar disorder patients (5). However, their effects on risk of developing dementia have been barely investigated.

The International Society for Bipolar Disorder (ISBD) has selected the effect of lithium on the cognitive function of bipolar disorder patients as the future research agenda (6). Evidence for the prophylactic effect of lithium on cognitive function has been reported in several pre-clinical studies. Although the mechanism is not yet clear, inhibition of glycogen synthase kinase-3 (GSK-3) and enhancement of brain-derived neurotrophic factor (BDNF) may play a key role (7-9). In a study with irradiated mice, lithium treatment prevented hippocampal neurons from apoptosis and ameliorated cognitive performance via decreased GSK-3β activity (10). In amyloid precursor protein (APP) mutant mice, lithium enhanced the proliferation and specification of neuron cells and promoted hippocampal neurogenesis by the inhibition of GSK-3β (11).

While substantial number of pre-clinical studies report positive effect of lithium on cognitive function (12-16), clinical studies with bipolar disorder patients have reported neutral or marginally negative impact of lithium on cognitive function. According to a meta-analysis analyzing the effect of lithium on cognitive function, lithium had mild to moderate adverse effect on immediate verbal learning, verbal memory and psychomotor performance (17). In a study comparing bipolar disorder patients who received lithium treatment ≥ 2 month with patients who did not treated

with lithium, lithium showed no significant effect on cognitive function (18).

Valproic acid is another most widely prescribed mood stabilizer in bipolar disorder (19, 20). Recently, prescription in old age bipolar disorder patients has shifted in favor of valproic acid over lithium, due to concern for potential toxicity of lithium (19, 21, 22). Valproic acid has conflicting pre-clinical evidence supporting its effect on cognitive function. While valproic acid was found to induce neurogenesis of neural progenitor cell both in vitro and in vivo via multiple pathways in some studies (23-25), it was found to reduce hippocampal cell proliferation (26, 27). A recent review on one quasi randomized controlled trial (RCT) and 9 cross-sectional studies concluded that valproic acid may negatively affect cognitive functions of bipolar disorder patients (28).

The effects of lithium and valproic acid on cognitive functions raise the question whether and how they influence the risk of dementia in bipolar disorder patients. However, it is difficult to prove these questions by RCT because the incidence of dementia is very low in younger or middle-age adults. Instead, there are a few cohort studies using health insurance claim data. In such large scale studies, lithium was found to reduce the risk of dementia in bipolar disorder patients while valproic acid raised the risk of dementia. In a study from Denmark on 5,856 patients aged 40 years or over with bipolar disorder, multiple lithium prescription reduced the risk of dementia while anticonvulsants, antidepressants, or antipsychotics did not (29). In another nested case-control study with cohort from US on 41,931 older adults aged 50 years or over with bipolar disorder, continuous use of lithium reduced the risk of dementia while anticonvulsants did not (30). A recent study using national health insurance data of Taiwan reported that valproic acid increased the risk of dementia in bipolar disorder patients aged 20 years or older (31).

However, these studies have several limitations to confirm whether lithium or valproic acid can change the risk of dementia.

First of all, in all three studies, the patients who were taking lithium were included in the control group in the analysis of the effect of valproic acid on the risk

of dementia and vice versa. Since both lithium and valproic acid may influence the risk of dementia, the users of lithium or valproic acid should be excluded from the control group. Second, potential confounding factors are not sufficiently screened or controlled. Especially in Danish study, only sex, age, and calendar period are considered as covariates. Third, the measurements of exposure dose were crude. Danish study only measured number of prescriptions without considering prescription dose or duration. In US study, lithium exposure is measured during only 1 year before the index date. In addition, all three studies did not consider wash-out period to minimize the effect from the exposure before the index date. Lastly, the follow-up periods were shorter than 3 years in the US study. Although follow-up periods were relatively long in Danish or Taiwan study, the age of participants in these studies were too young to evaluate dementia outcome.

Purpose of study

This retrospective cohort study aimed to investigate the effects of lithium and valproic acid on the risk of dementia in the adults aged 50 years or older with bipolar disorder using the Korean National Health Insurance data. We compared the risk of dementia between lithium only users, matched valproic acid only users, matched both users and matched both nonusers within the observation period of 5 - 10 years.

Methods

Data source

In this study, we used the Korean HIRA (Health Insurance Review and Assessment Service) database. Korea has NHI (National Health insurance) program covering the ~59 millions of population in Korea. The medical claim reimbursement information from all health care institutions in country is collected through NHI program. HIRA data provides patient's demographic information, diagnoses code, prescription records, medical procedures and services, types of health care institution, medical utilization information, and admission dates. Prescription records include brand name, generic name, prescription date, duration, does and route of administration (32). Diagnosis is recorded according to the International Classification of Disease, Tenth Revision (ICD-10) (33). For this study, we received claim data from HIRA after removing any identifiable information of individual patients. The present study was approved by Institutional Review Board of Seoul National University Bundang Hospital (IRB no. X-1906-546-901).

Study design and population

We collected claims data (January 1, 2007 – August 31, 2018) of 116, 737 patients who were 1) aged 50 years or older and 2) had once or more in-patient or twice or more out-patient ICD-10 codes of bipolar spectrum disorder (F30, F31, F34.0 and F38.0) as their primary or secondary diagnosis records between January 1, 2008 and August 31, 2013. We included the patients who met the inclusion criteria 1) for the following reasons. First, we intended to avoid selection bias from the patients with bipolar disorder who survived until 60 or 65 years old only. Second, cognitive dysfunction may occur earlier in the patients with bipolar disorder. The ISBD Task Force on Older-Age Bipolar Disorder (OABD) also defined OABD patients as aged 50 years or older for similar reasons (34). We included the patients who met the

inclusion criteria 2) for the following reasons. First, the number retrieved from this definition was aligned with previous epidemiologic studies in Korea (35). Second, patients with bipolar disorder usually have one or more neuropsychiatric comorbidities (36).

We defined the index date as the first day of lithium or valproic acid prescription after the diagnosis of bipolar disorder, and the pre-index period as between January 1, 2007 and the index date. We defined the both users as the patients who were prescribed for both lithium and valproic acid between diagnosis of bipolar disorder and August 31, 2013. The index date of both users was the date of first prescription of the any of lithium or valproic acid. We defined nonusers as the patients who had been never prescribed for lithium or valproic acid between January 1, 2007 and August 31, 2018. We defined the index date in the nonuser by adding the interval between the bipolar disorder diagnosis date and the index date (the date of first medication use) of the matched medication user to the bipolar disorder diagnosis date of the nonuser.

In order to capture the new users, we excluded the patients who were prescribed for lithium or valproic acid before diagnosis of bipolar disorder. To secure at least 1-year wash-out period and 5-year follow up period, we excluded the patients who were first prescribed for lithium or valproic acid before Jan 1, 2008 or after Aug 31, 2013. We also excluded the patients who were diagnosed as or treated for dementia, diagnosed as cerebrovascular disorder, Parkinson disorder, epilepsy, traumatic head injury, and psychotic disorder before the index date. After exclusion, 1,279, 3,626, and 1,776 remained in the lithium only users, valproic acid only users, and both users respectively.

Then we matched age, sex, health insurance type, index year and the use of antipsychotics between the lithium only users, valproic acid only users, both users and nonusers. We matched use of antipsychotics for following reasons. First, as recommended and approved medication for bipolar disorder, antipsychotics are commonly prescribed for bipolar disorder to treat mood and behavioral symptoms

(29, 37-39). Therefore, matching of antipsychotics helps balancing the severity of bipolar disorder between lithium or valproic acid users and nonusers. In addition, as administration of antipsychotics can cause cognitive impairment (40-42), the use of antipsychotics needs to be matched for precise evaluation of independent effect of lithium or valproic acid. In case of the nonusers, we first matched the nonusers to the lithium users to determine the index date for the nonusers, and then applied the same exclusion criteria as were applied to the medication users. Finally, 621 lithium only users, 1,164 valproic acid users, 621 both users and 2,378 nonusers were included in the current analyses. The overall study design is illustrated in Figure 1 and Figure 2.

Exposure

The exposure to lithium (ATC; N05AN01) or valproic acid (ATC; N03AG01) was evaluated by ATC code. Each group's prescription period and dose data were collected from index date until the end of the follow-up period. To assess dose-response relationship, we calculated cumulative defined daily dose (DDD), cumulative prescription duration (CPD) of lithium or valproic acid (in days) during follow-up period. When calculating DDD, we adapted widely used drug standardization method developed by World Health Organization (43). We divided the level of exposure into tertiles of cumulative DDD and CPD.

Outcome

The primary outcome was an incident diagnosis of dementia. Follow-up was started from the index date until 1) incidence of dementia, 2) drop out from NHIS (including death), or 3) date of August 31, 2018. The incident dementia was defined as having once or more in-patient or twice or more out-patients ICD-10 codes of dementia (F00, F02, F03, G30 or G31) as his or her primary diagnosis code 1 year or more after the index date, and were prescribed one or more cognitive enhancers (donepezil, meantime, rivastigmine or galantamine) for 7 days or longer. The 1-year lag-time is

applied to avoid protopathic bias due to pre-existing undiagnosed dementia and to address disease latency for drug-induced dementia.

Covariates

We defined the presence of the comorbidities as having once or more in-patient or twice or more out-patient ICD-10 codes of comorbidities (Hypertension : I100, I150, I152, I158, I159, Atrial fibrillation: I48, Coronary artery disease : I20-25, Peripheral vascular disease : I739, I790, R02, Z958, Z959, Diabetes : E10-14, Hyperlipidemia : E780-785, Depressive disorder : F32-33, F341, Substance related disorder : F11-19, Alcohol related disorder : F10) in the pre-index period as his or her primary diagnosis code, and the comedications as being prescribed for 7 days or longer during pre-index period.

Statistical analyses

We calculated the incidence of dementia per 10,000 person years by dividing the number of dementia events by the sum of person years followed in each group and then multiplied by 10,000. We built multivariable cox proportional hazard model stratified on the matched pairs to estimate hazard ratio (HR) and the 95% confidence interval (CI) in each group compared to the matched nonusers. To select the covariates to be adjusted in the cox proportional hazard models, we first run univariable cox regression for each of the potential confounding factors described above, and chose the factors that were significantly associated with the risk of dementia as covariates. We did not include the variables used for matching (age, sex, insurance type, use of antipsychotics) in the covariates of cox proportional hazard models. In order to examine the dose-response relationship, we calculated the HR according to CPD and DDD. For sensitivity analyses, the hazard ratio is calculated with 1) modified definition of dementia outcome, 2) lithium or valproic acid users matched with nonuser of each. All statistical analyses were performed by SAS

Enterprise 7.1 for windows (SAS Institute Inc., Cary, NC, USA). A two-tailed value of $p < 0.05$ is regarded as statistical significance.

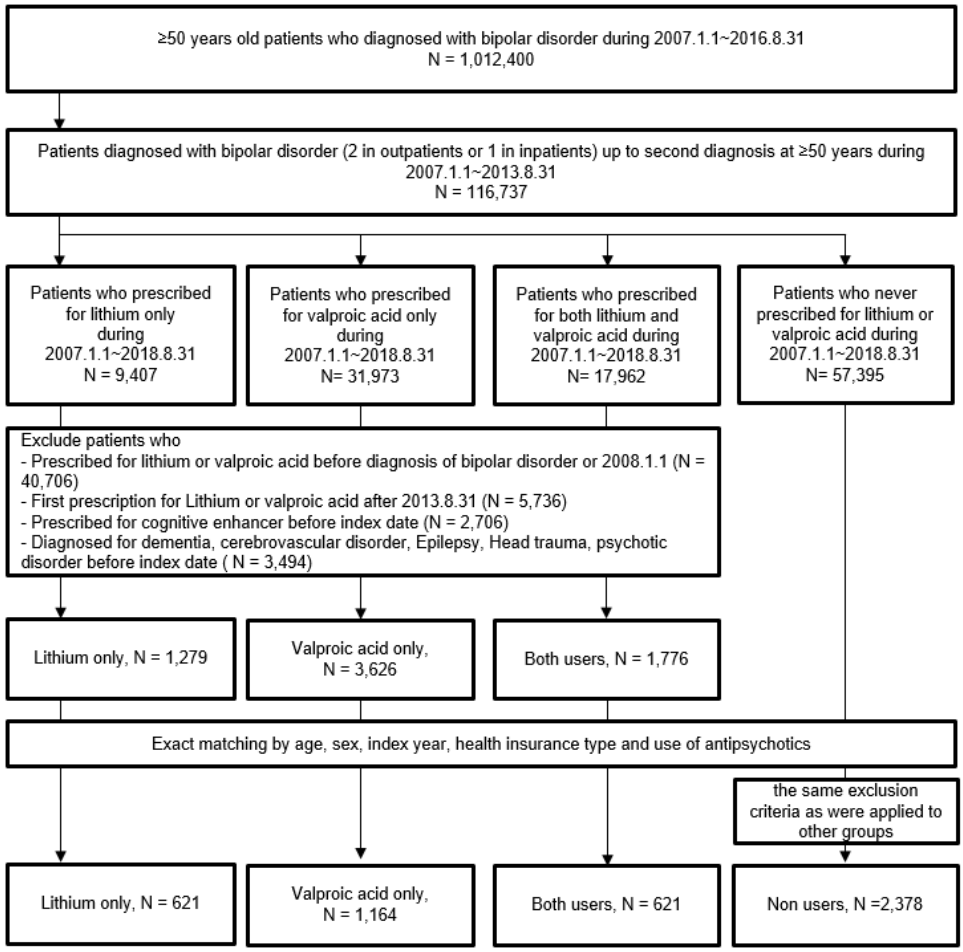
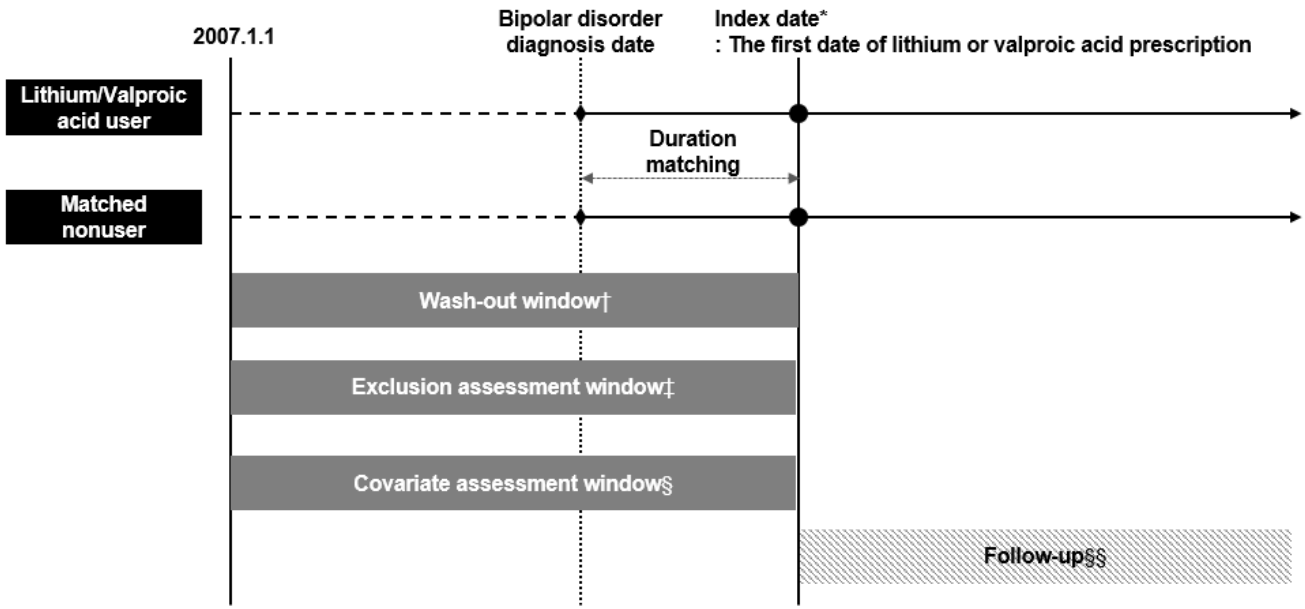


Figure 1. Assembly of study cohort.



* Date of the first medication use for medication users
† Minimum 1 year, prescribed or lithium or valproic acid
‡ Minimum 1 year, diagnosed as or treated for dementia, diagnosed as cerebrovascular disorder, Parkinson disorder, epilepsy, traumatic head injury, and psychotic disorder
§ Minimum 1 yea, covariates including prescription of comedication(≥7days), presence of comorbidities (1 inpatients or 2 outpatients as primary diagnosis code)
§§ Follow up until 1) incidence of dementia, 2) drop out from NHIS (including death), or 3) date of August 31, 2018

Figure 2. Description of study design

Results

Characteristics of the participants (Table 1)

The mean follow-up durations in all four groups were over 6.6 years. As summarized in Table 1, the average age of each group was around 58 years old, and females were more dominant in all groups. Most of covariates were well balanced between four groups with some exceptions in nonusers. Nonusers had more coronary artery disorder, depressive disorder and use more medications (SSRI/SNRI, TCA, benzodiazepine, anti-inflammatory agents, narcotics, H2 receptor antagonist, statin, platelet aggregation inhibitor, antihypertensive, and flourquinolones) than medication users.

Incidence of dementia (Table 2)

As described in Table 2, the total follow-up person-years for the lithium only users, valproic acid only users, both users and nonusers were 4,265, 7,728, 4,279, and 16,660 respectively. The overall incidence of dementia in the lithium only users (105.51 per 10,000 person years), the valproic acid only users (99.63 per 10,000 person years), and the both users (109.84 per 10, 000 person years) were higher than that in the both nonusers (60.02 per 10,000 person years, $p < 0.01$).

Table 1. Characteristics of the study population

	Lithium only (n=621)	Valproic acid only (n=1,164)	Both users (n=621)	Both nonusers (n=2,378)	P value	Post-hoc*
Mean follow-up duration (y)	6.87 ± 2.66	6.64 ± 2.80	6.89 ± 2.62	7.01 ± 2.51	< 0.01	d > b
Total follow up person-years	4,265	7,728	4,279	16,660		
Age (y)	58.08 ± 6.95	57.92 ± 6.82	58.08 ± 6.95	58.05 ± 6.93	0.94	
50-60	410 (66.02)	780 (67.01)	410 (66.02)	1,574 (66.19)	0.99	
60-70	157 (25.28)	292 (25.09)	157 (25.28)	597 (25.11)		
70-80	54 (8.70)	92 (7.90)	54 (8.70)	207 (8.70)		
> 80	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)		
Sex					0.99	
Male	237 (38.16)	447 (38.40)	237 (38.16)	898 (37.76)		
Female	384 (61.84)	717 (61.60)	384 (61.84)	1,480 (62.24)		
Type of insurance					< 0.01	
Health insurance	545 (87.76)	1,031 (88.57)	545 (87.76)	2,177 (91.55)		d > a, b, c
Medicaid	76 (12.24)	133 (11.43)	76 (12.24)	201 (8.45)		
CCI score					< 0.01	
≤ 1	346 (55.72)	634 (54.47)	359 (57.81)	1,155 (48.57)		a, b, c > d
2	123 (19.81)	210 (18.04)	107 (17.23)	464 (19.51)		
≥ 3	152 (24.48)	320 (27.49)	155 (24.96)	759 (31.92)		

Comorbidities						
Hypertension	9 (1.45)	28 (2.41)	13 (2.09)	57 (5.40)	0.52	
Atrial fibrillation	4 (0.64)	9 (0.77)	3 (0.48)	10 (0.42)	0.53	
Coronary artery disorder	25 (4.03)	74 (6.36)	29 (4.67)	189 (7.95)	< 0.01	d > a, c
Peripheral vascular disease	9 (1.45)	19 (1.63)	8 (1.29)	33 (1.39)	0.93	
Diabetes	94 (15.14)	175 (15.03)	86 (13.85)	386 (16.23)	0.47	
Hyperlipidemia	47 (7.57)	96 (8.25)	49 (7.89)	235 (9.88)	0.14	
Psychotic disorder						
Depressive disorder	261 (42.03)	475 (40.81)	241 (38.81)	1,328 (55.85)	< .01	d > a, b, c
Substance related disorder	1 (0.16)	9 (0.77)	3 (0.48)	11 (0.46)	0.38	
Alcohol related disorder	60 (9.66)	168 (14.43)	51 (8.21)	159 (6.69)	< 0.01	b > a > d
Medication						
Anticholinergics	294 (47.34)	523 (44.93)	305 (49.11)	1,034 (43.48)	0.05	
Antipsychotics	483 (77.78)	935 (80.33)	483 (77.78)	1,862 (78.30)	0.44	
SSRI/SNRI	310 (49.92)	607 (52.15)	284 (45.73)	1,491 (62.70)	< 0.01	d > a, b, c
Antiepileptics	141 (22.71)	277 (23.80)	126 (20.29)	548 (23.04)	0.40	
TCA	228 (36.71)	432 (37.11)	211 (33.98)	1,084 (45.58)	< 0.01	d > a, b, c
Benzodiazepine	551 (88.73)	1,064 (91.41)	567 (91.30)	2,209 (92.89)	< 0.01	d > a
Anti-inflammatory analgesics	515 (82.93)	1,002 (86.08)	518 (83.41)	2,146 (90.24)	< 0.01	d > a, b, c
Narcotic analgesics	383 (61.67)	786 (67.53)	395 (63.61)	1,708 (71.83)	< 0.01	d > a, b, c
H2RA	430 (69.24)	862 (74.05)	446 (71.82)	1,886 (79.31)	< 0.01	d > a, b, c

ERT	48 (7.73)	100 (8.59)	49 (7.89)	215 (9.04)	0.66	
Antidiabetic agents	87 (14.01)	191 (16.41)	97 (15.62)	402 (16.90)	0.36	
Statin	141 (22.71)	297 (25.52)	152 (24.48)	710 (29.86)	< 0.01	d > a, b, c
Anticoagulant	95 (15.30)	206 (17.70)	105 (16.91)	413 (17.37)	0.60	
Platelet aggregation inhibitors	137 (22.06)	337 (28.95)	160 (25.76)	799 (33.60)	< 0.01	d > a, b, c
Antihypertensive	336 (58.94)	674 (57.90)	358 (57.65)	1,533 (64.47)	< 0.01	d > b, c
Fluorquinolones	205 (33.01)	413 (35.48)	202 (32.53)	995 (41.84)	< 0.01	d > a, b ,c
Others**	188 (30.27)	347 (29.81)	177 (28.50)	960 (40.37)	< 0.01	
Index year					0.72	
2008	103 (16.59)	187 (16.07)	103 (16.59)	448 (18.84)		
2009	165 (26.57)	300 (25.77)	165 (26.57)	541 (22.75)		
2010	94 (15.14)	177 (15.21)	94 (15.14)	350 (14.72)		
2011	106 (17.07)	204 (17.53)	106 (17.07)	417 (17.54)		
2012	107 (17.23)	210 (18.04)	107 (17.23)	433 (18.21)		
2013**	46 (7.41)	86 (7.39)	46 (7.41)	189 (7.95)		

CCI: Charlson comorbidity index, SSRI: selective serotonin receptor inhibitor, SNRI: serotonin norepinephrine receptor inhibitor, TCA: ticyclic antidepressants; H2RA: histamine 2 receptor antagonists, ERT: estrogen replacement therapy.
Values are presented as mean ± standard deviation, number only, or number (%).
*a : Lithium only users, b : Valproic acid only user, c : both users, d : both nonusers
**Others included bicalutamide, buspirone, digoxinm and tirpramide.
***Until August

Table 2. Incidence of dementia stratified by the uses of lithium and valproic acid in the patients with bipolar disorder

	n	Person-years	Event	Incidence*
Lithium only	621	4,265	45	105.51 (74.68 - 136.33)
Valproic acid only	1,164	7,728	77	99.63 (77.38 - 121.89)
Both users	621	4,279	47	109.84 (78.44 - 141.25)
Both nonusers	2,378	16,660	100	60.02 (48.26 - 71.79)

*Number of cases per 10,000 person years with 95% confidence intervals

Hazard ratio for dementia (Table 3, Table 4)

In order to select covariates for adjustment, we ran univariate cox regression analyses for the factors listed Table 1. As a result, diabetes, alcohol related disorder, and use of antiepileptics were selected as covariates that should be adjusted in the analysis on the associations of lithium and valproic acid with the risk of dementia (Table 3).

Compared to the nonusers, the lithium only users (HR, 1.59; 95% CI, 1.10 - 2.31), valproic acid only users (HR, 1.76; 95% CI, 1.29 - 2.41), and both users (HR, 1.81; 95% CI, 1.26 - 2.59) showed the higher risk of incident dementia. However, the risk of dementia was comparable between the lithium only users, valproic acid only users and both users (Table 4). According to hazard ratio analysis including interaction term, there was no significant interaction between lithium and valproic acid on the onset of dementia (p for interaction term = 0.0678) in OABD patients.

Dose-response analyses (Table 5, Figure 3)

When we analyzed the risk of incident dementia by DDD in the lithium only users, low DDD group showed higher risk of dementia (T33: HR = 1.84, p = 0.05) than the nonusers while the mid DDD, and high DDD group showed comparable risk of dementia to the nonusers (T66 : HR = 1.55, p = 0.15, T100 : HR = 1.46, p = 0.27). In the valproic acid only users, the risk of incident dementia tended to increase dose-dependently. Although the low DDD group showed the comparable risk of dementia to the nonusers (T33: HR = 1.12, p = 0.70), the middle and high dose groups showed the higher risk of dementia than the nonusers (T66: HR = 2.28, p < 0.01, T100: HR =2.02, p < 0.01).

These dose-response patterns observed in the DDD-based analyses were not observed in CPD based analyses in lithium users. In the lithium only users, the long CPD users showed the higher risk of incident dementia (T100: HR = 1.86, p = 0.05), but it became non-significant in short-term (T33: HR=1.71, p = 0.10), and mid-term users (T66: HR =1.33, p = 0.35). In the valproic acid only users, CPD based dose-response analyses showed similar tendency with that from DDD based

analysis. The risk of dementia in short-term group was comparable with nonusers (T33: HR = 1.08, p = 0.79), the mid and long-term group showed the significantly higher risk of dementia than nonusers (T66: HR = 2.52, p < 0.01, T100: HR = 1.89, p < 0.01). The results from dose response analyses are illustrated in Figure 3.

Table 3. Hazard ratios for dementia of potential confounding factors[*]

Variable	HR (95% CI) [†]	P value
No. of admission	1.01 (0.96 - 1.05)	0.84
CCI score		
≤ 1	Ref	
2	1.01 (0.71 - 1.45)	0.94
≥ 3	1.21 (0.90 - 1.64)	0.21
Comorbidities		
Hypertension	1.12 (0.45 - 2.80)	0.81
Atrial fibrillation	1.14 (0.23 - 5.72)	0.87
Coronary artery disorder	0.56 (0.30 - 1.05)	0.07
Peripheral vascular disease	2.18 (0.99 - 4.81)	0.05
Diabetes[‡]	1.43 (1.03 - 1.99)	0.03
Hyperlipidemia	0.89 (0.54 - 1.46)	0.63
Depressive disorder	1.16 (0.87 - 1.55)	0.32
Substance related disorder	2.38 (0.58 - 9.79)	0.23
Alcohol related disorder[‡]	1.98 (1.13 - 3.48)	0.02
Medication		
Anticholinergics	1.16 (0.88 - 1.52)	0.29
SSRI/SNRI	1.02 (0.75 - 1.38)	0.92
Antiepileptics[‡]	1.42 (1.05 - 1.93)	0.02
TCA	1.09 (0.83 - 1.44)	0.52
Benzodiazepine	0.96 (0.59 - 1.56)	0.87
Anti-inflammatory analgesics	0.87 (0.58 - 1.32)	0.52
Narcotic analgesics	0.89 (0.66 - 1.21)	0.46
H2RA	0.95 (0.69 - 1.31)	0.76
ERT	0.65 (0.32 - 1.33)	0.24
Antidiabetic agents	1.26 (0.91 - 1.74)	0.17
Statin	0.85 (0.62 - 1.16)	0.31
Anticoagulant	0.98 (0.69 - 1.37)	0.89
Platelet aggregation inhibitors	0.95 (0.72 - 1.26)	0.73
Antihypertensive	1.07 (0.80 - 1.43)	0.64
Fluorquinolones	0.92 (0.69 - 1.23)	0.57
Others[§]	1.16 (0.87 - 1.54)	0.31

HR: hazard ratio, CI: confidence interval, CCI: Charlson comorbidity index, SSRI, selective serotonin receptor inhibitor, SNRI: serotonin norepinephrine receptor inhibitor, TCA: ticyclic antidepressants, H2RA: histamine 2 receptor antagonists, ERT: estrogen replacement therapy.

[*]Univariate Cox proportional hazards regression analyses

[†] Hazard ratio compared to 50-60 age group in age category, Hazard ratio compared to Male group in sex category, Hazard ratio compared to health insurance group in type of insurance category, Hazard ratio compared to no admission in No of admission category, Hazard ratio compared to CCI score ≤ 1 in CCI score category, Hazard ratio for patients with each of comorbidity compared to patient without that comorbidity in comorbidities category, Hazard ratio for patients who used each of medication compared to patients who did not use that medication in medication category

[‡]Selected for adjustment in multivariable hazard ration analysis.

[§]included bicalutamide, buspirone, digoxinm and tirpramide.

Table 4. Risk of dementia associated with lithium or valproic acid use in the patients with bipolar disorder

	Unadjusted		Adjusted	
	HR (95% CI)	p value	HR (95% CI)	p value
Lithium user	1.60 (1.11 - 2.31)	< 0.01	1.59 (1.10 - 2.31)	< 0.01
Valproic acid user	1.78 (1.31 - 2.43)	< 0.01	1.76 (1.29 - 2.41)	< 0.01
Both user	1.74 (1.21 - 2.49)	< 0.01	1.81 (1.26 - 2.59)	< 0.01
Matched nonuser	Ref		Ref	

HR: hazard ratio, CI: confidence Interval.
*Adjusted for diabetes, alcohol related disorder, and use of antiepileptics,

Table 5. Dose-response relationship in the risk of dementia due to lithium and valproic acid use in the patients with bipolar disorder

	N(event)	Mean daily dose	Unadjusted*	P value	Adjusted*,†	P value
By defined daily dose						
Lithium						
T33 (<140)	205 (22)	538	1.93 (1.06 - 3.52)	0.03	1.84 (1.00 - 3.38)	0.05
T66 (140-722)	208 (26)	653	1.60 (0.89 - 2.86)	0.11	1.55 (0.86 - 2.81)	0.15
T100 (≥722)	204 (21)	724	1.37 (0.70 - 2.65)	0.36	1.46 (0.75 - 2.86)	0.27
Valproic acid						
T33 (<22)	379 (21)	645	1.23 (0.71 - 2.14)	0.47	1.12 (0.64 - 1.96)	0.70
T66 (22-103)	393 (40)	675	2.30 (1.39 - 3.80)	< 0.01	2.28 (1.37 - 3.79)	< 0.01
T100 (≥103)	382 (59)	1,185	1.96 (1.27 - 3.04)	< 0.01	2.02 (1.30 - 3.13)	< 0.01
By days of prescription						
Lithium						
T33 (<42)	203 (21)	645	1.84 (0.97 - 3.49)	0.06	1.71 (0.90 - 3.27)	0.10
T66 (42-205)	210 (25)	620	1.37 (0.76 - 2.47)	0.29	1.33 (0.73 - 2.43)	0.35
T100 (≥205)	204 (23)	651	1.74 (0.94 - 3.22)	0.08	1.86 (1.00 - 3.45)	0.05
Valproic acid						
T33 (<56)	377 (33)	900	1.22 (0.69 - 2.16)	0.49	1.08 (0.61 - 1.93)	0.79

T66 (56-226)	394 (41)	825	2.49 (1.52 - 4.08)	< 0.01	2.52 (1.53 - 4.14)	< 0.01
T100 (≥226)	383 (60)	765	1.84 (1.19 - 2.84)	< 0.01	1.89 (1.22 - 2.92)	< 0.01

*Hazard ratio with 95% confidence intervals compared to the nonusers (number = 2,378, event = 100)

†Adjusted for diabetes, alcohol related disorder, and use of antiepileptics,

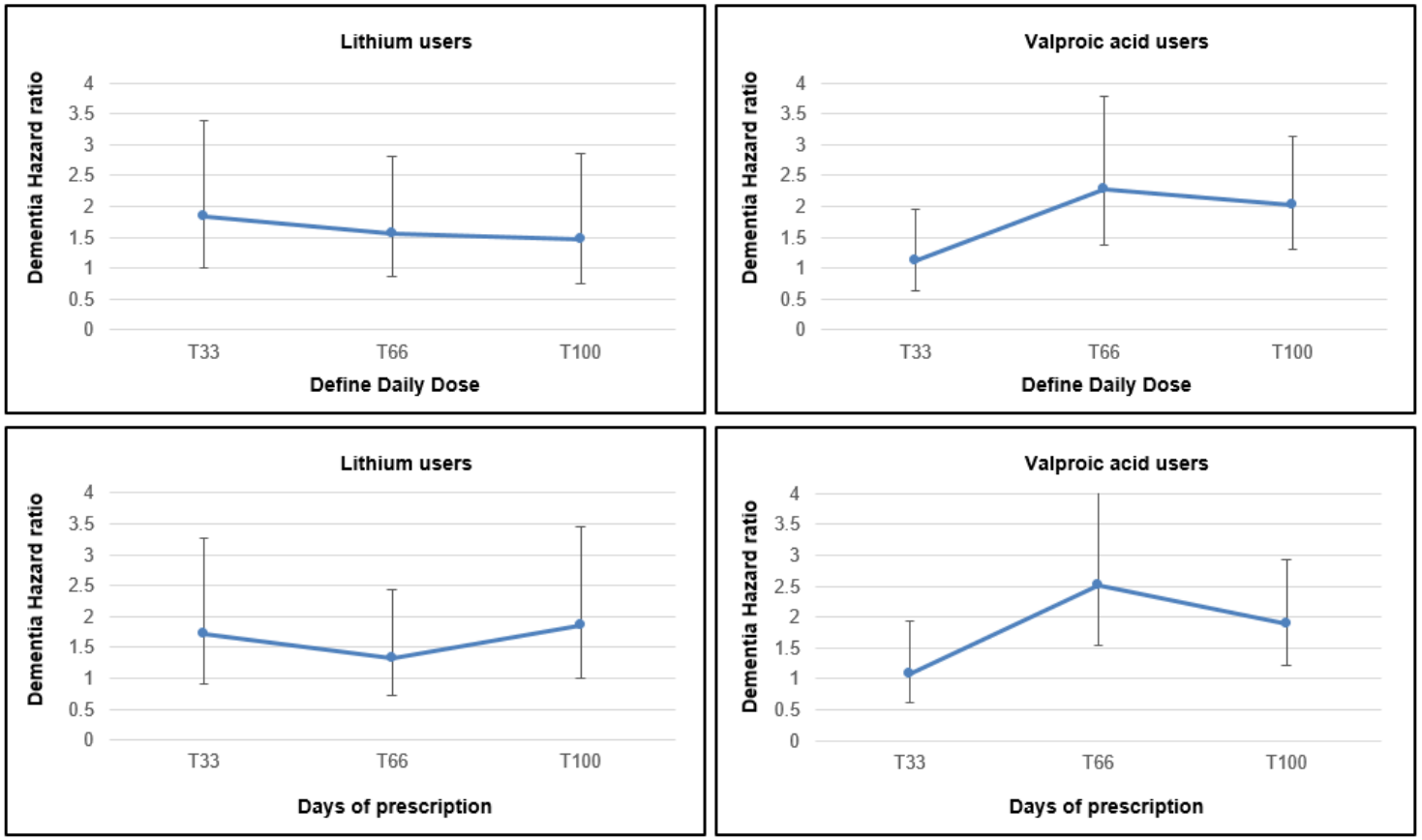


Figure 3. Hazard ratio of dementia due to lithium and valproic acid use in the patients with bipolar disorder

Secondary analyses (Table 6 - 10)

In order to test the validity of the results, we ran several secondary analyses.

First, we tested several definitions of dementia because of the uncertainties in claim data-based case identification. In the main analyses, we defined dementia as having once or more in-patient or twice or more out-patient ICD-10 codes of dementia (F00, F02, F03, G30 or G31) as his or her primary diagnosis code 1 year or more after the index date, and were prescribed one or more cognitive enhancers (donepezil, meantime, rivastigmine or galantamine) for 7 days or longer. We applied a couple of modified definitions as below; a) having once or more in-patient or twice or more out-patient ICD-10 codes of dementia (F00, F02, F03, G30 or G31) as his or her primary diagnosis code 1 year or more after the index date, b) having once or more in-patient or twice or more out-patient ICD-10 codes of dementia (F00, F02, F03, G30 or G31) as his or her primary or secondary diagnosis code 1 year or more after the index date, and were prescribed one or more cognitive enhancers (donepezil, meantime, rivastigmine or galantamine) for 7 days or longer, c,d) having once or more in-patient or twice or more out-patient ICD-10 codes of dementia (F00, F02, F03, G30 or G31) as his or her primary diagnosis code 2 year (c) / 3 year (d) or more after the index date, and were prescribed one or more cognitive enhancers (donepezil, meantime, rivastigmine or galantamine) for 7 days or longer. The results from the main analyses were not significantly changed when we applied these two modified definitions of dementia (Table 6 -Table 9).

Second, we re-identified the lithium users, valproic acid users, and nonusers. In main analyses, we defined the nonusers as taking neither lithium nor valproic acid. In this secondary analyses, we defined the nonusers as the participants who were not taking lithium regardless of whether they were taking valproic acid or not when we analyzed the effect of lithium on the risk of dementia, and as those who were not taking valproic acid regardless of whether they were taking lithium or not when we

analyzed the effect of valproic acid on the risk of dementia (Figure 2). In real world, a considerable portion of the bipolar disorder patients are taking both valproic acid and lithium in real world (29). The results from the main analyses were not changed when we applied these modified definitions of nonuser controls (Table 10).

Table 6. Dose-response relationship in the risk of dementia ascertained using the primary diagnosis code only regardless of the use of cognitive enhancers due to lithium and valproic acid use in the patients with bipolar disorder

	N(event)	Unadjusted*	P value	Adjusted*,†	P value
Lithium users	621 (65)	1.26 (0.94 - 1.69)	0.13	1.24 (0.92 - 1.67)	0.15
Valproic acid users	1164 (130)	1.59 (1.26 - 2.02)	< 0.01	1.56 (1.23 - 1.97)	< 0.01
Both users	621 (80)	1.62 (1.23 - 2.13)	< 0.01	1.62 (1.23 - 2.13)	< 0.01
Matched nonusers	2378(185)	Ref		Ref	
By defined daily dose					
Lithium					
T33 (<144)	206 (21)	1.34 (0.82 - 2.21)	0.24	1.31 (0.79 - 2.17)	0.29
T66 (140-665)	211 (24)	1.26 (0.79 - 2.01)	0.33	1.20 (0.75 - 1.93)	0.45
T100 (≥665)	204 (20)	1.10 (0.65 - 1.87)	0.72	1.12 (0.66 - 1.91)	0.67
Valproic acid					
T33 (<23)	383 (34)	1.31 (0.88 - 1.96)	0.18	1.25 (0.84 - 1.87)	0.28
T66 (23-107)	396 (44)	2.03 (1.40 - 2.95)	< 0.01	1.98 (1.34 - 2.89)	< 0.01
T100 (≥107)	385 (52)	1.62 (1.14 - 2.31)	< 0.01	1.59 (1.12 - 2.27)	< 0.01
By days of prescription					
Lithium					
T33 (<42)	203 (18)	1.19 (0.70 - 2.03)	0.51	1.14 (0.67 - 1.96)	0.63
T66 (42-183)	213 (23)	1.20 (0.75 - 1.92)	0.46	1.14 (0.71 - 1.85)	0.58

T100 (≥183)	205 (24)	1.31 (0.80 - 2.14)	0.28	1.33 (0.81 - 2.18)	0.26
Valproic acid					
T33 (<59)	380 (31)	1.21 (0.80 - 1.82)	0.37	1.15 (0.76 - 1.74)	0.52
T66 (59-244)	398 (46)	2.18 (1.50 - 3.15)	< 0.01	2.11 (1.45 - 3.07)	< 0.01
T100 (≥244)	386 (53)	1.63 (1.15 - 2.30)	< 0.01	1.60 (1.13 - 2.26)	< 0.01

*Hazard ratio with 95% confidence intervals compared to the nonusers (number = 2,378, event = 185)

†Adjusted for diabetes, alcohol related disorder, and use of antiepileptics,

Table 7. Dose-response relationship in the risk of dementia ascertained by the primary and secondary diagnosis code and the prescription of cognitive enhancers for 7 days or longer due to lithium and valproic acid use in the patients with bipolar disorder

	N(event)	Unadjusted*	P value	Adjusted*,†	P value
Lithium users	617 (69)	1.54 (1.15 - 2.06)	< 0.01	1.51 (1.12 - 2.03)	< 0.01
Valproic acid users	1,154 (134)	1.87 (1.47 - 2.37)	< 0.01	1.84 (1.45 - 2.34)	< 0.01
Both users	614 (86)	2.11 (1.61 - 2.77)	< 0.01	2.16 (1.64 - 2.83)	< 0.01
Matched nonusers	2366 (167)	Ref		Ref	
By defined daily dose					
Lithium					
T33 (<140)	205 (22)	1.58 (0.95 - 2.62)	< 0.01	1.53 (0.92 - 2.54)	0.10
T66 (140-722)	208 (26)	1.90 (1.20 - 3.01)	< 0.01	1.87 (1.17 - 2.98)	0.01
T100 (≥722)	204 (21)	1.18 (0.71 - 1.96)	0.53	1.19 (0.71 - 1.98)	0.51
Valproic acid					
T33 (<22)	379 (21)	1.60 (1.07 - 2.39)	0.02	1.51 (1.01 - 2.26)	0.05
T66 (22-103)	393 (40)	1.98 (1.34 - 2.91)	< 0.01	1.96 (1.33 - 2.89)	< 0.01
T100 (≥103)	382 (59)	2.07 (1.47 - 2.90)	< 0.01	2.08 (1.48 - 2.93)	< 0.01
By days of prescription					
Lithium					
T33 (<42)	203 (21)	1.82 (1.09 - 3.05)	0.02	1.75 (1.04 - 2.93)	0.10
T66 (42-205)	210 (25)	1.42 (0.89 - 2.26)	0.15	1.39 (0.87 - 2.24)	0.35

T100 (≥205)	204 (23)	1.44 (0.88 - 2.34)	0.15	1.44 (0.88 - 2.37)	0.05
Valproic acid					
T33 (<56)	377 (33)	1.66 (1.10 - 2.51)	0.02	1.55 (1.02 - 2.34)	0.04
T66 (56-226)	394 (41)	2.03 (1.39 - 2.97)	< 0.01	2.02 (1.38 - 2.97)	< 0.01
T100 (≥226)	383 (60)	1.96 (1.39 - 2.75)	< 0.01	1.97 (1.40 - 2.77)	< 0.01

*Hazard ratio with 95% confidence intervals compared to the nonusers (number = 2,366, event = 167)

†Adjusted for diabetes, alcohol related disorder, and use of antiepileptics,

Table 8. Dose-response relationship in the risk of dementia ascertained by the primary diagnosis code and the prescription of cognitive enhancers for 7 days or longer due to lithium and valproic acid use in the patients with bipolar disorder (censoring dementia event within 2 years from index date)

	N(event)	Unadjusted*	P value	Adjusted*,†	P value
Lithium users	621 (37)	1.43 (0.96 - 2.14)	0.08	1.40 (0.93 - 2.11)	0.11
Valproic acid users	1,164 (66)	1.70 (1.22 - 2.37)	< 0.01	1.66 (1.19 - 2.33)	< 0.01
Both users	621 (38)	1.51 (1.02 - 2.23)	0.04	1.58 (1.06 - 2.35)	0.02
Matched nonusers	2,378 (90)	Ref		Ref	
By defined daily dose					
Lithium					
T33 (<140)	206 (12)	1.57 (0.79 - 3.09)	0.19	1.45 (0.73 - 2.89)	0.29
T66 (140-722)	211 (14)	1.59 (0.85 - 2.96)	0.15	1.51 (0.79 - 2.89)	0.21
T100 (≥722)	204 (11)	1.17 (0.57 - 2.39)	0.68	1.26 (0.61 - 2.60)	0.54
Valproic acid					
T33 (<22)	383 (14)	1.15 (0.63 - 2.12)	0.65	1.02 (0.55 - 1.89)	0.96
T66 (22-103)	396 (22)	2.17 (1.27 - 3.70)	< 0.01	2.13 (1.24 - 3.66)	< 0.01
T100 (≥103)	385 (30)	1.82 (1.14 - 2.91)	< 0.01	1.88 (1.17 - 3.02)	< 0.01
By days of prescription					
Lithium					

T33 (<42)	203 (11)	1.59 (0.78 - 3.24)	0.20	1.43 (0.69 - 2.96)	0.33
T66 (42-205)	213 (13)	1.36 (0.72 - 2.58)	0.34	1.29 (0.66 - 2.48)	0.46
T100 (≥205)	205 (13)	1.39 (0.71 - 2.71)	0.34	1.50 (0.76 - 2.95)	0.25
Valproic acid					
T33 (<56)	380 (13)	1.10 (0.59 - 2.06)	0.77	0.95 (0.50 - 1.79)	0.86
T66 (56-226)	398 (22)	2.43 (1.42 - 4.16)	< 0.01	2.46 (1.43 - 4.23)	< 0.01
T100 (≥226)	386 (31)	1.72 (1.08 - 2.73)	0.02	1.77 (1.11 - 2.81)	0.02

*Hazard ratio with 95% confidence intervals compared to the nonusers (number = 2,378, event = 90)

†Adjusted for diabetes, alcohol related disorder, and use of antiepileptics,

Table 9. Dose-response relationship in the risk of dementia ascertained by the primary diagnosis code and the prescription of cognitive enhancers for 7 days or longer due to lithium and valproic acid use in the patients with bipolar disorder (censoring dementia event within 3 years from index date)

	N(event)	Unadjusted*	P value	Adjusted*,†	P value
Lithium users	621 (29)	1.38 (0.87 - 2.17)	0.17	1.34 (0.84 - 2.13)	0.22
Valproic acid users	1,164 (54)	1.72 (1.18 - 2.45)	< 0.01	1.69 (1.16 - 2.46)	< 0.01
Both users	621 (31)	1.52 (0.98 - 2.36)	0.06	1.62 (1.04 - 2.52)	0.03
Matched nonusers	2,378 (73)	Ref		Ref	
By defined daily dose					
Lithium					
T33 (<140)	206 (9)	1.34 (0.62 - 2.91)	0.46	1.14 (0.52 - 2.53)	0.74
T66 (140-722)	211 (10)	1.56 (0.75 - 3.26)	0.23	1.51 (0.70 - 3.26)	0.29
T100 (≥722)	204 (11)	1.21 (0.56 - 2.59)	0.63	1.29 (0.60 - 2.81)	0.52
Valproic acid					
T33 (<22)	383 (11)	1.14 (0.57 - 2.26)	0.71	0.95 (0.47 - 1.91)	0.88
T66 (22-103)	396 (14)	1.66 (0.87 - 3.16)	0.13	1.64 (0.85 - 3.17)	0.14
T100 (≥103)	385 (29)	2.15 (1.31 - 3.55)	< 0.01	2.28 (1.37 - 3.77)	< 0.01
By days of prescription					
Lithium					

T33 (<42)	203 (8)	1.29 (0.57 - 2.93)	0.54	1.10 (0.47 - 2.54)	0.83
T66 (42-205)	213 (10)	1.43 (0.69 - 2.96)	0.33	1.35 (0.64 - 2.88)	0.43
T100 (≥205)	205 (11)	1.34 (0.64 - 2.81)	0.43	1.46 (0.69 - 3.08)	0.33
Valproic acid					
T33 (<56)	380 (9)	0.95 (0.45 - 1.99)	0.88	0.77 (0.36 - 1.65)	0.50
T66 (56-226)	398 (16)	2.26 (1.21 - 4.22)	0.01	2.32 (1.22 - 4.39)	0.01
T100 (≥226)	386 (29)	1.93 (1.17 - 3.16)	< 0.01	2.01 (1.22 - 3.31)	< 0.01

*Hazard ratio with 95% confidence intervals compared to the nonusers (number = 2,378, event = 73)

†Adjusted for diabetes, alcohol related disorder, and use of antiepileptics,

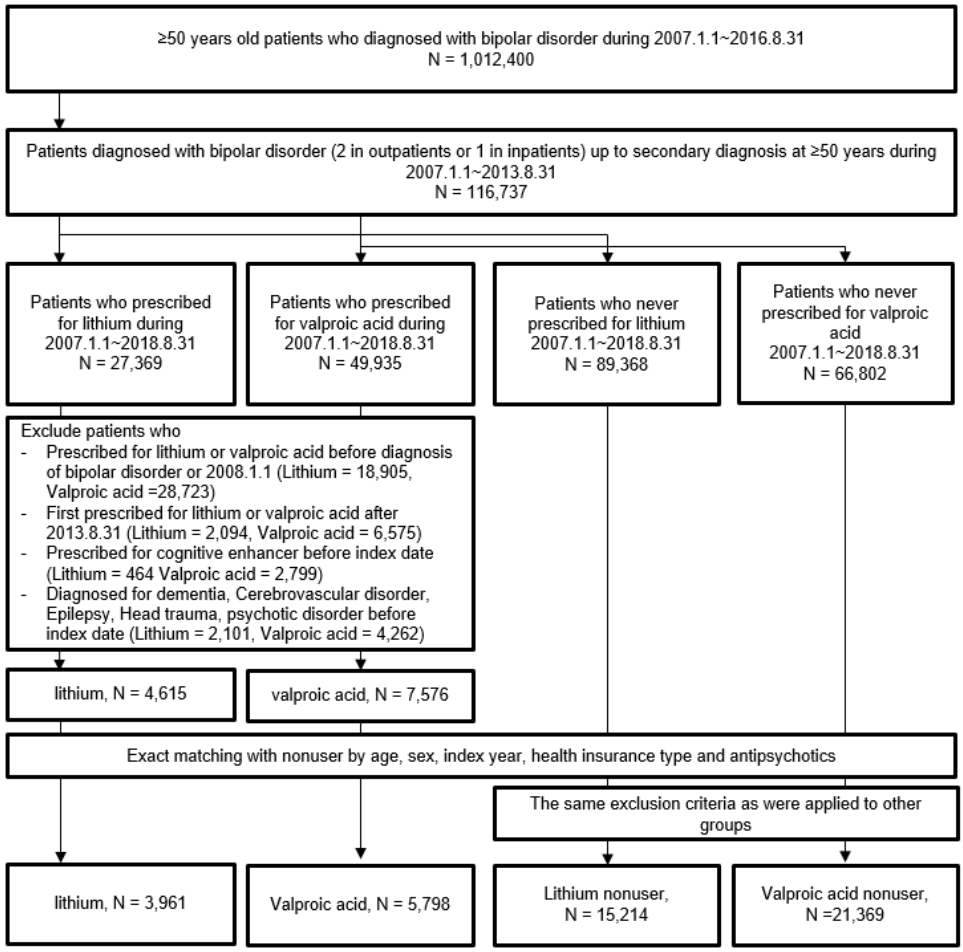


Figure 4. Assembly of study cohort for secondary analyses.

Table 10. Dose-response relationship in the risk of dementia due to lithium and valproic acid use compared to the nonusers of lithium and those of valproic acid respectively in the patients with bipolar disorder

	N(event)	Unadjusted*	P value	Adjusted*,†	P value
Lithium users	3,961 (338)	1.42 (1.24 - 1.63)	< 0.01	1.45 (1.26 - 1.66)	< 0.01
Matched nonusers	15,214 (921)	Ref		Ref	
Valproic acid users	5,798 (498)	1.49 (1.33 - 1.67)	< 0.01	1.46 (1.30 - 1.64)	< 0.01
Matched nonusers	21,639 (1370)	Ref		Ref	
By defined daily dose					
Lithium					
T33 (<144)	1,314 (107)	1.28 (1.01 - 1.62)	0.04	1.30 (1.21 - 1.65)	0.03
T66 (140-665)	1,341 (121)	1.88 (1.48 – 2.38)	< 0.01	1.91 (1.51 - 2.42)	< 0.01
T100 (≥664)	1,306 (110)	1.22 (0.97 – 1.54)	0.10	1.24 (0.98 – 1.57)	0.07
Valproic acid					
T33 (<23)	1,907 (134)	1.27 (1.03 - 1.58)	0.03	1.24 (1.00 - 1.54)	0.05
T66 (23-107)	1,978 (174)	1.70 (1.40 - 2.07)	< 0.01	1.64 (1.35 – 2.00)	< 0.01
T100 (≥107)	1,913 (190)	1.49 (1.23 - 1.80)	< 0.01	1.49 (1.23 - 1.81)	< 0.01
By days of prescription					
Lithium					
T33 (<42)	1,292 (99)	1.31 (1.03 - 1.67)	0.03	1.33 (1.04 - 1.70)	0.02
T66 (42-183)	1,358 (114)	1.69 (1.36 - 2.15)	< 0.01	1.72 (1.35 - 2.19)	< 0.01

T100 (≥205)	1,311 (125)	1.31 (1.05 - 1.64)	0.02	1.34 (1.07 - 1.68)	0.01
Valproic acid					
T33 (<59)	1,896 (127)	1.26 (1.02 - 1.57)	0.04	1.23 (0.99 - 1.54)	0.06
T66 (59-244)	1,986 (163)	1.69 (1.38 - 2.06)	< 0.01	1.63 (1.34 - 2.00)	< 0.01
T100 (≥244)	1,916 (208)	1.51 (1.26 - 1.81)	< 0.01	1.50 (1.25 - 1.80)	< 0.01

*Hazard ratio with 95% confidence intervals compared to the nonusers (number = 15,214, event = 921) in lithium group, Hazard ratio with 95% confidence intervals compared to the nonusers (number = 21,639, event = 1,370) in valproic acid group

†Adjusted for Charlson Comorbidities Index score, diabetes, hyperlipidemia, alcohol related disorders, use of anticholinergics in lithium group;
Adjusted for Charlson Comorbidities Index score, diabetes, alcohol related disorders, use of antiepileptic, use of antidiabetic agents in valproic acid group;

Discussion

Along with population aging, the number of OABD patients over 60 years old has increased, accounting for 25% of all bipolar disorder patients (1). In addition, epidemiological studies showed that bipolar I or II disorder affected 0.5-1.0% of elderly population (44, 45). In OABD patients, cognitive dysfunction is common reaching to one out of three (46). ISBD warned clinicians to aware cognitive dysfunction in overall treatments of OABD patients, and avoid medications that may negatively affect cognitive function (6). As lithium and valproic acid are most commonly prescribed mood stabilizers for old aged bipolar disorder patients (29, 47), it has become important to investigate the effects of these two medications on the cognitive function and/or the risk of dementia in OABD patients (6).

To the extent of the author's knowledge, this is the first study that directly comparing the risk of dementia between lithium only users, matched valproic acid only users, and matched both medication users with the common matched nonuser controls among older adults with bipolar disorder. This study found that the lithium and valproic acid increased the risk of dementia independently, and there was no significant difference between risk of dementia in lithium users, valproic acid users and the both users. The dose response relationship between risk of dementia and DDD or CPD of lithium was not prominent. However, in the valproic acid users, the risk of dementia became significant above the certain level of total prescription dose (22 defined daily dose) or prescription duration (56 days).

Effect of lithium on the risk of dementia

This study found that lithium increased the risk of dementia in OABD patients, which is in line with previous clinical studies evaluating the effect of lithium on the cognitive function of affective disorder patients. According to a meta-analysis analyzing 11 clinical trials and 1 prospective cohort study to evaluate lithium's effect

on cognitive function, affective disorder patients taking lithium reported significant cognitive dysfunctions while healthy volunteers taking lithium did not (17). However, in a series of preclinical studies on mutated/normal mice or rats receiving lithium at subtherapeutic or minimally therapeutic range, lithium showed a protective effect on cognitive function (12-16). In RCTs on the patients with MCI (43, 48) or AD (49) without affective or other psychiatric disorders, administration of lithium for 1 – 2 years reduced phosphorylated tau and increased amyloid-beta peptide in CSF and improved the cognitive performance in MCI patients (43, 48) and delayed the decline of cognitive performance in AD patients (49). This differential effect of lithium on cognitive function between the patients with affective disorders and those with cognitive disorders but no affective disorder may be, at least in part, attributable to the difference in the mean administered doses of lithium between them. In the three RCTs on the patients with cognitive disorders but no affective disorders, lithium was prescribed to yield subtherapeutic concentrations (43, 48, 49), which is lower than the therapeutic dose prescribed for bipolar disorder patients (50). In contrast, lithium was prescribed to yield therapeutic concentrations in the clinical trials that reported the detrimental effect of lithium on cognitive function in the patients with affective disorder (17). In the current study, the average prescription dose was 638mg/day, which was in the therapeutic range. It is beyond the scope of this study to explain the underlying biological mechanism of the effect of different level of lithium on cognitive function and/or dementia onset. However, the outcome from this study suggest the needs for further research clarifying the relationship between levels of lithium exposure and cognitive function and/or risk of dementia.

Effect of valproic acid on the risk of dementia

This study also found that valproic acid increased the risk of dementia in older adults with bipolar disorder. From preclinical studies, while some in-vitro and animal study reported potential protective effect of valproic acid on neuronal cell via reduced

apoptosis and neuroinflammation (24, 25), reduction of cell proliferation and neutrophin in the hippocampus were suggested as major mechanism of cognitive dysfunction from valproic acid (26, 27). According to a recent review article that assessed clinical studies evaluating the impact of valproic acid on cognitive function of bipolar disorder patients, only 2 out of 10 studies reported positive effects of valproic acid while others presented negative effects on cognitive function (28). However, these two studies were cross-sectional studies including only 25 or 30 patients treated with valproic acid (51, 52). Indeed, majority of previous studies presented negative association between valproic acid and cognitive function in bipolar disorder patients. A clinical trial showed the poorer working memory in bipolar disorder patients treated with valproic acid compared to both healthy controls and patients treated with lithium (53). More clinical studies described cognitive impairment in bipolar disorder patients treated with mood stabilizers including valproic acid (54-56). Such negative effects of valproic acid on cognitive function naturally lead question whether it raises the risk of dementia or not. The effects of valproic acid on risk of dementia are evaluated in some claim data based studies, which reported the increasing risk of dementia associated with valproic acid in patients with bipolar disorder (31) or epilepsy (57). Our study finding is in line with results from such clinical studies.

Another notable finding from current study was dose response relationship of valproic acid on risk of dementia. In the patients with epilepsy (58, 59) or bipolar disorder (60), dose and/or serum level of valproic acid were negatively associated with cognitive function such as short term recall and working memory. However, there was no study that directly investigated the dose-response relationship between valproic acid and the risk of dementia in older adults with bipolar disorder. In current study, we found that valproic acid tend to present significantly high risk of dementia above the certain level of total prescription dose (22 defined daily dose) or prescription duration (56 days). Such findings warn clinicians to be more cautious in prescription of valproic acid for high dose or long term use in old age bipolar disorder

patients.

Effect of interaction between lithium and valproic acid on the risk of dementia

Another novel finding from this study was derived from the analysis of the dementia risk in both medication users. In author's knowledge, this is the first study that specifically analyzed the risk of incident dementia in bipolar disorder patients who prescribed for both lithium and valproic acid. The result showed that the hazard ratio for incident dementia of the both medication users was comparable to that of the lithium only users and the valproic acid only users. In addition, there was no significant interaction between lithium and valproic acid on the onset of dementia. Combination of lithium and valproic acid is often recommended for bipolar disorder patients who failed at monotherapy (38, 39), and clinical studies including RCT reported significantly lower relapse rate in combination therapy than monotherapy (61, 62). Researchers suggested addictive suppression of the protein myristoylated alanine-rich C kinase as potential synergy mechanism. In terms of adverse effect, combination of lithium and valproic acid seems relatively safe (63), and a study reported that administration of lithium or valproic acid did not significantly change the pharmacokinetics of each other (64). Our study result is in line with such findings, and adds novel insight as no study specifically evaluated dementia risk from of OABD patients who used the both medication. Unlike combination of lithium and valproic acid, synergistic cognitive side effects were found in patients who received other neuroleptics with lithium or valproic acid (63, 65, 66). Especially, administration of antipsychotics with lithium may accelerate cognitive dysfunction due to synergy between lithium's inhibition of presynaptic dopamine release and blockage of dopamine receptor by antipsychotics (67). In this context, our study finding helps clinicians in deciding medication for patients who failed at monotherapy of valproic acid or lithium. According to our result, lithium and

valproic acid combination therapy might be considerable before increasing the dose of valproic acid, especially for OABD patients who are at high risk of dementia.

Strength

Although the effects of lithium or valproic acid on dementia in OABD patients have been discussed for a long time, it is difficult to conduct RCT to answer this question due to insidious onset of dementia and the vulnerability of old age bipolar disorder patients. Instead, finding answers through the real-world claim data is the available choice. However, previous claim data based studies have several limitations (29-31). Thus, as described in Table 11, we tried to overcome such limitation of previous cohort studies in several aspects.

First, we used bipolar disorder patients who did not use the both lithium and valproic acid as common control for lithium user, valproic acid user, and both users, unlike previous studies in which other medication users are mixed in control. This design has two advantages; 1) It helps precise estimation of independent effect of each of lithium or valproic acid, 2) direct comparison of dementia risk between lithium users, valproic acid users, and both medication users is possible by using common nonuser control.

Second, in order to minimize the residual confounding in claims data, we rigorously excluded comorbidities (cerebrovascular disorders, epilepsy, traumatic head injury, psychotic disorder and Parkinson disorders) related to onset of dementia at screening phase from both patients and control group, and adjusted risk factors associated with incident dementia extensively.

Third, unlike previous studies, we censored dementia case which developed within one year from the index date to avoid protopathic bias caused by undiagnosed or prodromal stage dementia. In sensitivity analyses, we tested different lag times (2 year, and 3 year) and found consistent result.

Long follow-up period (average 7 years, max 10 years) is another strength of the current study. Considering the gradual onset of dementia, sufficient follow-up period is critical for evaluation of the long-term effect of lithium or valproic acid. However, in US study, the follow-up period was shorter than 3 years. Although Danish and Taiwan studies have similar follow-up period with current study, their study

populations were too young to capture the onset of dementia (aged 40 years or older in Danish study, 20 years or older in Taiwan study) even with long follow-up period.

Table 11. Comparison of study design with previous cohort studies

	This study	Danish study (29)	US study (30)	Taiwan study (31)
Patients	Lithium only users, Valproic acid only users, both medication users	Lithium users, Anticonvulsant users, Anti-depressant users, Anti-psychotics users	Lithium users, Anticonvulsant users	Valproic acid users
Control group	Common control for all medication users, Patients who prescribed for none of the lithium or valproic acid	Separated control for each medication users, patients who did not prescribed for lithium (or anti-convulsant , anti-depressant, or anti-psychotics)	Separated control for each medication users, patient who did not prescribed for lithium (or anticonvulsant)	Patients who did not prescribed for valproic acid
Wash out of lithium or valproic acid exposure	1-6 years before index date	Not applied	Not applied	Not applied
Exclusion criteria	Diagnosed or treated for dementia,	Diagnosed for dementia or schizophrenia	Diagnosed or treated for dementia,	Diagnosed for dementia

	diagnosed for cerebrovascular disorder, epilepsy, head trauma, psychotic disorder		Diagnosed for schizophrenia or psychoses	
Age of participants	≥50 years old	≥40 years old	≥50 years old	≥20 years old
Follow-up duration	Average ~7 years (max 10 years)	Max 10 years	Max 3 years	Max 11 years
Dementia definition	Diagnosis code and prescription of cognitive enhancer with 1 year lag time	Diagnosis code only without lag time	Diagnosis code only without lag time	Diagnosis code only (lag time in sensitivity analyses)

Limitation

Despite the efforts to overcome the intrinsic problem of claim data, some limitations were remained in current study. First, there were residual confounding factors which did not exist in HIRA data, such as level of education. This is common intrinsic problem in claim data based studies. Indeed, none of the previous claim data based studies with bipolar disorder patients could adjust level of education (29-31). To minimize confounding by such unknown social factors, we matched type of insurance which is closely related to socioeconomic status.

Second, as we used medication nonuser as control, cofounding by indication should be considered. To avoid such confounding effect, we matched use of antipsychotics between users and nonusers as antipsychotics is most commonly prescribed for bipolar disorder along with lithium or valproic acid. The characteristics of nonusers also lessens the concern for over-estimation of dementia risk in user group. In current study, nonusers tend to have more medical comorbidities and use more medications. (Table 3). As polypharmacy and multiple comorbidities are related to higher risk of dementia (68), the high risk of dementia in lithium or valproic acids users compared to nonuser from this study seems conservative estimation. Still, potential unknown features of nonuser control should be carefully considered in interpretation of the study results.

Third, identification of case was depending on claim data only. Therefore, we tested several operational definitions of dementia. In particular, the definition of the new dementia case in main analyses was determined not only by diagnosis code but also by prescription of cognitive enhancer, unlike previous studies in which outcome was identified only by diagnosis code.

Lastly, as this study used a limited dataset from 2007 to 2018, prescription of lithium or valproic acid before 2007 in nonusers could not be evaluated. This is intrinsic limitation of claim data, but we tried to minimize effect from unknown exposure by applying minimum 1 year wash-out period (from 2007.1.1 to index date) for all

participants. In contrast, prior studies did not consider such wash-out period.

Implication

Even with limitations described above, our study finding is meaningful as the first cohort study that evaluated and compared risk of dementia in lithium only user, valproic acid only users and both medication users compared to nonusers among OABD patients. In addition, as we used the entire population data of Korea, current study has high generalizability.

Most of all, our study results provided findings that support choice of medication for elderly bipolar disorder patients. Recently, clinicians tend to favor valproic acid over lithium in elderly bipolar disorder patients without unclear benefits of valproic acid (21, 22). While meta-analyses support distinctive effect of lithium on bipolar disorder recurrence prevention (69, 70), one of the major reason hindering prescription of lithium is the belief that lithium use can result in cognitive dysfunction (71). However, according to this study, there was no difference in risk of dementia between lithium users and valproic acid users.

From current study, we found the tendency of increasing risk of dementia with longer CPD or higher DDD, particularly in valproic acid users. In contrast, combination of lithium and valproic acid did not show the higher risk of dementia compared to single medication users. In this regard, for elderly bipolar disorder patients who has limited response to valproic acid monotherapy, a combination with lithium might be considerable before using high dose of valproic acid or combination with other medications such as antipsychotics, at least in respects of the dementia risk. More future studies including larger scale cohort studies or RCTs are required to verify this hypothesis.

Conclusion

From this retrospective cohort study using national insurance claim data, we found that the lithium and valproic acid independently increased the risk of dementia compared to nonuser controls, and there was no significant difference between risk of dementia in lithium users, valproic acid users and both users. Although dose response relationship was not prominent in lithium users, the risk of dementia became significant above the mid-range total prescription dose (22 defined daily dose) or prescription duration (56 days). Therefore, clinicians should pay more attention to risk of dementia in OABD patients using lithium or valproic acid. In addition, for OABD patients who are resistant to valproic acid monotherapy, combination of lithium and valproic acid is considerable in respects of dementia risk.

Potential Conflicts of Interest

Nothing to report.

References

1. Sajatovic M, Gyulai L, Calabrese JR, Thompson TR, Wilson BG, White R, Evoniuk G. Maintenance treatment outcomes in older patients with bipolar I disorder. Am J Geriatr Psychiatry. 2005;13:305-311.
2. Solé B, Jiménez E, Torrent C, Reinares M, Bonnin CDM, Torres I, Varo C, Grande I, Valls E, Salagre E, Sanchez-Moreno J, Martinez-Aran A, Carvalho AF, Vieta E. Cognitive Impairment in Bipolar Disorder: Treatment and Prevention Strategies. Int J Neuropsychopharmacol. 2017;20:670-680.
3. Bharadwaj R. Cognitive impairment in euthymic patients with bipolar disorder. Br J Psychiatry. 2006;189:468-469; author reply 469.
4. Martinez-Aran A, Vieta E, Colom F, Torrent C, Sanchez-Moreno J, Reinares M, Benabarre A, Goikolea JM, Brugue E, Daban C, Salamero M. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. Bipolar Disord. 2004;6:224-232.
5. Woo YS, Bahk WM, Lee JG, Jeong JH, Kim MD, Sohn I, Shim SH, Jon DI, Seo JS, Min KJ, Kim W, Song HR, Yoon BH. Korean Medication Algorithm Project for Bipolar Disorder 2018 (KMAP-BP 2018): Fourth Revision. Clinical psychopharmacology and neuroscience : the official scientific journal of the Korean College of Neuropsychopharmacology. 2018;16:434-448.
6. Sajatovic M, Strejilevich SA, Gildengers AG, Dols A, Al Jurdi RK, Forester BP, Kessing LV, Beyer J, Manes F, Rej S, Rosa AR, Schouws SN, Tsai SY, Young RC, Shulman KI. A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. Bipolar Disord. 2015;17:689-704.
7. Chuang DM, Wang Z, Chiu CT. GSK-3 as a Target for Lithium-Induced Neuroprotection Against Excitotoxicity in Neuronal Cultures and Animal Models of Ischemic Stroke. Front Mol Neurosci. 2011;4.
8. Quiroz JA, Machado-Vieira R, Zarate CA, Jr., Manji HK. Novel insights into lithium's mechanism of action: neurotrophic and neuroprotective effects. Neuropsychobiology. 2010;62:50-60.
9. Rybakowski JK, Suwalska A. Excellent lithium responders have normal cognitive functions and plasma BDNF levels. Int J Neuropsychopharmacol. 2010;13:617-622.
10. Yazlovitskaya EM, Edwards E, Thotala D, Fu A, Osusky KL, Whetsell WO, Jr., Boone B, Shinohara ET, Hallahan DE. Lithium treatment prevents neurocognitive deficit resulting from cranial irradiation. Cancer Res. 2006;66:11179-11186.
11. Fiorentini A, Rosi MC, Grossi C, Luccarini I, Casamenti F. Lithium improves hippocampal neurogenesis, neuropathology and cognitive functions in APP mutant mice. PLoS One. 2010;5:e14382.
12. Nocjar C, Hammonds MD, Shim SS. Chronic lithium treatment magnifies learning in rats. Neuroscience. 2007;150:774-788.
13. Watase K, Gatchel JR, Sun Y, Emamian E, Atkinson R, Richman R, Mizusawa H, Orr HT, Shaw C, Zoghbi HY. Lithium therapy improves

neurological function and hippocampal dendritic arborization in a spinocerebellar ataxia type 1 mouse model. PLoS Med. 2007;4:e182.
14. King MK, Jope RS. Lithium treatment alleviates impaired cognition in a mouse model of fragile X syndrome. Genes Brain Behav. 2013;12:723-731.
15. Harada H, Sugiyama T, Suketa Y. Characterization of inhibition by chronic treatment with lithium ion on nerve growth factor-induced neuronal differentiation of rat PC12 pheochromocytoma cells. J Toxicol Environ Health. 1996;49:197-206.
16. Licht RW, Smith D, Braendgaard H. The effect of chronic lithium treatment on the calibre of axons and nerve fibres in the rat sural nerve. Eur Neuropsychopharmacol. 1997;7:95-98.
17. Wingo AP, Wingo TS, Harvey PD, Baldessarini RJ. Effects of lithium on cognitive performance: a meta-analysis. J Clin Psychiatry. 2009;70:1588-1597.
18. Lopez-Jaramillo C, Lopera-Vasquez J, Ospina-Duque J, Garcia J, Gallo A, Cortez V, Palacio C, Torrent C, Martinez-Aran A, Vieta E. Lithium treatment effects on the neuropsychological functioning of patients with bipolar I disorder. J Clin Psychiatry. 2010;71:1055-1060.
19. Karanti A, Kardell M, Lundberg U, Landen M. Changes in mood stabilizer prescription patterns in bipolar disorder. J Affect Disord. 2016;195:50-56.
20. Smith LA, Cornelius VR, Azorin JM, Perugi G, Vieta E, Young AH, Bowden CL. Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis. J Affect Disord. 2010;122:1-9.
21. Shulman KI, Rochon P, Sykora K, Anderson G, Mamdani M, Bronskill S, Tran CT. Changing prescription patterns for lithium and valproic acid in old age: shifting practice without evidence. BMJ. 2003;326:960-961.
22. Post RM. The New News about Lithium: An Underutilized Treatment in the United States. Neuropsychopharmacology. 2018;43:1174-1179.
23. Zhang XZ, Li XJ, Zhang HY. Valproic acid as a promising agent to combat Alzheimer's disease. Brain Res Bull. 2010;81:3-6.
24. Liu Q, Li H, Yang J, Niu X, Zhao C, Zhao L, Wang Z. Valproic acid attenuates inflammation of optic nerve and apoptosis of retinal ganglion cells in a rat model of optic neuritis. Biomed Pharmacother. 2017;96:1363-1370.
25. Zhao L, Zhu L, Guo X. Valproic acid attenuates Abeta25-35-induced neurotoxicity in PC12 cells through suppression of mitochondria-mediated apoptotic pathway. Biomed Pharmacother. 2018;106:77-82.
26. Welbat JU, Sangrich P, Sirichoat A, Chaisawang P, Chaijaroonkhanarak W, Prachaney P, Pannangrong W, Wigmore P. Fluoxetine prevents the memory deficits and reduction in hippocampal cell proliferation caused by valproic acid. J Chem Neuroanat. 2016;78:112-118.
27. Chaudhary S, Parvez S. An in vitro approach to assess the neurotoxicity of valproic acid-induced oxidative stress in cerebellum and cerebral cortex of young rats. Neuroscience. 2012;225:258-268.
28. Pigoni A, Mandolini GM, Delvecchio G, Bressi C, Soares JC, Brambilla P. A focus on valproate and cognitive deficits in Bipolar Disorders: A mini-review: Special Section on "Translational and Neuroscience Studies in

Affective Disorders" Section Editor, Maria Nobile MD, PhD. J Affect Disord. 2020;261:277-281.
29. Kessing LV, Forman JL, Andersen PK. Does lithium protect against dementia? Bipolar disorders. 2010;12:87-94.
30. Gerhard T, Devanand DP, Huang C, Crystal S, Olfson M. Lithium treatment and risk for dementia in adults with bipolar disorder: population-based cohort study. Brit J Psychiat. 2015;207:46-51.
31. Tsai PS, Liu IC, Chiu CH, Huang CJ, Wang MY. Effect of valproic acid on dementia onset in patients with bipolar disorder. J Affect Disorders. 2016;201:131-136.
32. Cheol Seong S, Kim YY, Khang YH, Heon Park J, Kang HJ, Lee H, Do CH, Song JS, Hyon Bang J, Ha S, Lee EJ, Ae Shin S. Data Resource Profile: The National Health Information Database of the National Health Insurance Service in South Korea. Int J Epidemiol. 2017;46:799-800.
33. Bramer GR. International statistical classification of diseases and related health problems. Tenth revision. World Health Stat Q. 1988;41:32-36.
34. Sajatovic M, Strejilevich SA, Gildengers AG, Dols A, Al Jurdi RK, Forester BP, Kessing LV, Beyer J, Manes F, Rej S, Rosa AR, Schouws SNTM, Tsai SY, Young RC, Shulman KI. A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. Bipolar Disord. 2015;17:689-704.
35. Cho MJ, Chang SM, Lee YM, Bae A, Ahn JH, Son J, Hong JP, Bae JN, Lee DW, Cho SJ, Park JI, Lee JY, Kim JY, Jeon HJ, Sohn JH, Kim BS. Prevalence of DSM-IV major mental disorders among Korean adults: A 2006 National Epidemiologic Survey (KECA-R). Asian J Psychiatr. 2010;3:26-30.
36. McElroy SL, Altshuler LL, Suppes T, Keck PE, Jr., Frye MA, Denicoff KD, Nolen WA, Kupka RW, Leverich GS, Rochussen JR, Rush AJ, Post RM. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry. 2001;158:420-426.
37. Perlis RH. Treatment of bipolar disorder: the evolving role of atypical antipsychotics. Am J Manag Care. 2007;13:S178-188.
38. Practice guideline for the treatment of patients with bipolar disorder. American Psychiatric Association. Am J Psychiatry. 1994;151:1-36.
39. Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP. The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder 2000. Postgrad Med. 2000;Spec No:1-104.
40. Reilly JL, Harris MS, Keshavan MS, Sweeney JA. Adverse effects of risperidone on spatial working memory in first-episode schizophrenia. Arch Gen Psychiatry. 2006;63:1189-1197.
41. Harris MS, Wiseman CL, Reilly JL, Keshavan MS, Sweeney JA. Effects of risperidone on procedural learning in antipsychotic-naive first-episode schizophrenia. Neuropsychopharmacology. 2009;34:468-476.
42. Soyka M, Winter C, Kagerer S, Brunnauer M, Laux G, Moller HJ. Effects of haloperidol and risperidone on psychomotor performance relevant to driving ability in schizophrenic patients compared to healthy controls. J

Psychiatr Res. 2005;39:101-108.
43. Forlenza OV, Diniz BS, Radanovic M, Santos FS, Talib LL, Gattaz WF. Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. Br J Psychiatry. 2011;198:351-356.
44. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:593-602.
45. Dols A, Kupka RW, van Lammeren A, Beekman AT, Sajatovic M, Stek ML. The prevalence of late-life mania: a review. Bipolar Disord. 2014;16:113-118.
46. Tsai SY, Lee HC, Chen CC, Huang YL. Cognitive impairment in later life in patients with early-onset bipolar disorder. Bipolar Disord. 2007;9:868-875.
47. De Fazio P, Gaetano R, Caroleo M, Pavia M, De Sarro G, Fagiolini A, Segura-Garcia C. Lithium in late-life mania: a systematic review. Neuropsychiatr Dis Treat. 2017;13:755-766.
48. Forlenza OV, Radanovic M, Talib LL, Gattaz WF. Clinical and biological effects of long-term lithium treatment in older adults with amnestic mild cognitive impairment: randomised clinical trial. Br J Psychiatry. 2019:1-7.
49. Nunes MA, Viel TA, Buck HS. Microdose Lithium Treatment Stabilized Cognitive Impairment in Patients with Alzheimer's Disease. Curr Alzheimer Res. 2013;10:104-107.
50. Tredget J, Kirov A, Kirov G. Effects of chronic lithium treatment on renal function. J Affect Disord. 2010;126:436-440.
51. Tournikioti K, Ferentinos P, Michopoulos I, Alevizaki M, Soldatos CR, Dikeos D, Douzenis A. Clinical and treatment-related predictors of cognition in bipolar disorder: focus on visual paired associative learning. Eur Arch Psychiatry Clin Neurosci. 2017;267:661-669.
52. Kozicky JM, Torres IJ, Silveira LE, Bond DJ, Lam RW, Yatham LN. Cognitive change in the year after a first manic episode: association between clinical outcome and cognitive performance early in the course of bipolar I disorder. J Clin Psychiatry. 2014;75:e587-593.
53. Muralidharan K, Kozicky JM, Bucker J, Silveira LE, Torres IJ, Yatham LN. Are cognitive deficits similar in remitted early bipolar I disorder patients treated with lithium or valproate? Data from the STOP-EM study. Eur Neuropsychopharmacol. 2015;25:223-230.
54. Senturk V, Goker C, Bilgic A, Olmez S, Tugcu H, Oncu B, Atbasoglu EC. Impaired verbal memory and otherwise spared cognition in remitted bipolar patients on monotherapy with lithium or valproate. Bipolar Disord. 2007;9 Suppl 1:136-144.
55. Holmes MK, Erickson K, Luckenbaugh DA, Drevets WC, Bain EE, Cannon DM, Snow J, Sahakian BJ, Manji HK, Zarate CA, Jr. A comparison of cognitive functioning in medicated and unmedicated subjects with bipolar depression. Bipolar Disord. 2008;10:806-815.
56. Senturk Cankorur V, Demirel H, Atbasoglu C. Cognitive Functioning in Euthymic Bipolar Patients on Monotherapy with Novel Antipsychotics or

Mood Stabilizers. Noro Psikiyatr Ars. 2017;54:244-250.
57. Jacob L, Bohlken J, Kostev K. Is There an Association Between Antiepileptic Drug Use and Dementia Risk? A Case-Control Study. J Alzheimers Dis. 2019;68:97-103.
58. Jakovljevic MB, Jankovic SM, Jankovic SV, Todorovic N. Inverse correlation of valproic acid serum concentrations and quality of life in adolescents with epilepsy. Epilepsy Res. 2008;80:180-183.
59. Prevey ML, Delaney RC, Cramer JA, Cattanach L, Collins JF, Mattson RH. Effect of valproate on cognitive functioning. Comparison with carbamazepine. The Department of Veterans Affairs Epilepsy Cooperative Study 264 Group. Arch Neurol. 1996;53:1008-1016.
60. Steen NE, Aas M, Simonsen C, Dieset I, Tesli M, Nerhus M, Gardsjord E, Morch R, Agartz I, Melle I, Vaskinn A, Spigset O, Andreassen OA. Serum concentrations of mood stabilizers are associated with memory, but not other cognitive domains in psychosis spectrum disorders; explorative analyses in a naturalistic setting. Int J Bipolar Disord. 2016;4:24.
61. Solomon DA, Ryan CE, Keitner GI, Miller IW, Shea MT, Kazim A, Keller MB. A pilot study of lithium carbonate plus divalproex sodium for the continuation and maintenance treatment of patients with bipolar I disorder. J Clin Psychiatry. 1997;58:95-99.
62. investigators B, collaborators, Geddes JR, Goodwin GM, Rendell J, Azorin JM, Cipriani A, Ostacher MJ, Morriss R, Alder N, Juszczak E. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet. 2010;375:385-395.
63. Freeman MP, Stoll AL. Mood stabilizer combinations: a review of safety and efficacy. Am J Psychiatry. 1998;155:12-21.
64. Granneman GR, Schneck DW, Cavanaugh JH, Witt GF. Pharmacokinetic interactions and side effects resulting from concomitant administration of lithium and divalproex sodium. J Clin Psychiatry. 1996;57:204-206.
65. Emilien G, Maloteaux JM. Lithium neurotoxicity at low therapeutic doses Hypotheses for causes and mechanism of action following a retrospective analysis of published case reports. Acta Neurol Belg. 1996;96:281-293.
66. Hsu CW, Lee Y, Lee CY, Lin PY. Neurotoxicity and nephrotoxicity caused by combined use of lithium and risperidone: a case report and literature review. BMC Pharmacol Toxicol. 2016;17:59.
67. Boeker HS, A; Schopper, C. Neurotoxicitiy related to combined treatment with lithium, antidepressants and atpyical neuroleptics: a series of cases. Schweizer Archiv für Neurologie und Psychiatrie. 2011:72-76.
68. Park HY, Park JW, Song HJ, Sohn HS, Kwon JW. The Association between Polypharmacy and Dementia: A Nested Case-Control Study Based on a 12-Year Longitudinal Cohort Database in South Korea. PLoS One. 2017;12:e0169463.
69. Severus E, Taylor MJ, Sauer C, Pfennig A, Ritter P, Bauer M, Geddes JR. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. Int J Bipolar Disord. 2014;2:15.
70. Nivoli AM, Murru A, Vieta E. Lithium: still a cornerstone in the long-

term treatment in bipolar disorder? Neuropsychobiology. 2010;62:27-35.
71. Rybakowski JK, Permoda-Osip A, Borkowska A. Response to prophylactic lithium in bipolar disorder may be associated with a preservation of executive cognitive functions. Eur Neuropsychopharmacol. 2009;19:791-795.

초 록

배경 및 목적: 국내외 노인 양극성 장애 환자가 점점 증가하는 가운데, 노인에서 리튬과 발프로산의 복용이 치매에 미치는 영향에 대한 임상 데이터 기반 연구는 제한적이다. 미국 및 덴마크의 보험 청구 자료를 활용한 선행 코호트 연구가 있으나, 연구 설계상 리튬과 발프로산 각각의 위험성의 평가하는 데 있어, 서로의 영향을 배제하지 못하는 등 여러 한계점이 있다.

방법: 본 연구는 한국의 국가건강보험 심사평가원 청구 자료를 활용하여, 50세 이상 양극성 장애 환자에서 리튬 및 발프로산 복용이 치매 발생에 미치는 영향을 매칭 변수를 층화한 Cox-proportional hazard model을 통해 분석하였다. 리튬과 발프로산 각각의 독립적인 영향을 정확히 평가하기 위해, 리튬 단독 처방군, 발프로산 단독 처방군, 두 가지 약물 모두를 처방 받은 환자군에서의 치매 발생 위험도를 두 가지 약물 모두를 처방 받지 않은 환자군을 대조군으로 매칭하여 분석하였으며. 분석 시 치매 발생에 영향을 주는 질환 및 약물 복용자는 사전에 배제 혹은 보정하였다.

결과: 매칭 및 배제기준 적용 후 선정된 4,784 명의 고령 양극성 장애 환자들을 평균 7년간 관찰 결과, 269명에서 치매가 발생하였다. 교란요인들을 보정한 분석 결과, 치매 발생의 위험도는, 리튬 단독 처방군 (HR, 1.59; 95% CI, 1.10 - 2.31), 발프로산 단독 처방군 (HR, 1.76; 95% CI, 1.29 - 2.41), 두 가지 약물 처방군 (HR, 1.81; 95% CI, 1.26 - 2.59) 모두에서 매칭된 리튬 및 발프로산 미 처방군에 비해서 유의미하게

높았으며, 리튬과 발프로산의 상호작용은 통계적 유의성을 보이지 않았다 (p = 0.07). 용량-반응 분석 결과, 리튬군에서는 용량 반응 관계가 뚜렷하지 않으나, 발프로산 군에서는 특정 수준 이상의 총 처방량 (≥22 DDD)이나 총 처방 기간(≥56일)에서 치매 위험성이 유의미하게 높아지는 경향을 보였다.

결론: 본 연구의 결과는 노인 양극성 장애 환자에서 리튬 및 발프로산 사용 시 치매 발생 위험을 고려할 필요가 있음을 시사한다. 또한, 발프로산 단독치료에 저항을 보이는 노인 양극성 장애 환자에서, 적어도 치매 위험성 측면에서는 고용량 발프로산 치료 이전에 리튬 병용 투여를 고래해 볼 여지를 제언한다.

주요어: 리튬, 발프로산, 양극성장애, 치매, 인지기능장애, 빅데이터, 보험청구용데이터, 한국국가보험데이터

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