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Trends in Prescribing of Antiseizure Medications in South Korea: Real-World Evidence for Treated Patients With Epilepsy

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Background and Purpose We investigated the trends in the prescribing of antiseizure medication (ASM) over a 9-year period, and provide real-world data regarding ASM prescriptions of patients with epilepsy in South Korea.

Methods This study used data in the Korean National Health Information Database for the period from 2009 to 2017. We included 18 oral ASMs, which were classified into older and newer ASMs based on them first becoming available on the market before or after 1991, respectively. The annual trends in ASM prescriptions were plotted over the 9-year study period, and changes in these trends were evaluated as average annual percentage changes (AAPCs) using Poisson regression. Age- and sex-stratified analyses were also conducted.

Results Overall, the proportion of prescriptions involving polytherapy with three or more ASMs increased from 10.08% in 2009 to 10.99% in 2017 (AAPC=0.9%, $p<0.001$) over the 9-year study period. Among monotherapies, although valproate (VPA) was the most frequently prescribed ASM, the prescription rate of levetiracetam (LEV) steadily increased regardless of age and sex over the study period. The monotherapy prescription trends differed depending on age and sex. In the five most frequently used ASM combination regimens, the prescription rates of VPA/LEV, LEV/oxcarbazepine, and LEV/lamotrigine regimens showed increasing tendencies. In contrast, prescription rates for all combined regimens of older ASMs declined over time in all age groups.

Conclusions This is the first epidemiological study of the changes in prescription trends for ASM in South Korea based on nationwide data from 2009 to 2017. We found progressive increases in the use of newer ASMs for both monotherapy and duotherapy, and for polytherapy with three or more ASMs over the 9-year study period.

Keywords epilepsy; antiseizure medication; antiepileptic drug; South Korea.

INTRODUCTION

Epilepsy is a neurological disorder that affects approximately 50 million individuals of all ages worldwide.[1] Epilepsy accounted for over 13 million disease disability-adjusted life years in 2016, and was responsible for 0.56% of the total global disease burden.[2] More than 5 million new cases of epilepsy are diagnosed annually. The increasing size of the older adult population (aged >65 years), which has the highest incidence of epilepsy among age groups, means that the number of individuals with newly diagnosed epilepsy is expected to increase.[1,3]

A survey performed in 2007 based on nationwide data in South Korea revealed that the incidence of epilepsy was the highest among older adults aged ≥60 years and adolescents.[4] Similar findings were obtained in a recent South Korean epidemiological study that ad-

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dressed the inherent limitations of using administrative health data by surveying medical records of a representative sample.[5] The ever-increasing number of older adults means that the burden of lifetime epilepsy in South Korea is likely to increase substantially, similar to global trends.[5]

Antiseizure medication (ASM) therapy is the current mainstay of treatment for patients with epilepsy (PWE), although other options such as surgery and nerve stimulation are also available. In general, the prescribing of ASMs is recommended alongside careful clinical assessments based on relevant guidelines.[6,7] However, in real-world clinical settings, physicians do not depend solely on evidence-based guidelines when selecting ASMs for treating epilepsy since each guideline might not encompass all factors that should be considered in the clinical management of PWE. For example, patterns of ASM prescription are affected by patient factors such as comorbid medical conditions, concurrent medications, and financial constraints.[7,8] Furthermore, discrepancies due to differences in cultural beliefs, unavailability of ASMs, and physicians' approaches to their patients have not been considered in current guidelines.[9,10]

The above-described situation indicates that pharmacoepidemiological studies are required to identify current patterns of ASM usage in real-world clinical settings. This will provide descriptive information for including newer ASMs in clinical practice and will help to inform clinical prescription policies. Several researchers have recently explored the utilization of ASMs in European countries including Germany,[11] the United Kingdom (UK),[12] Norway,[13] and Italy.[14] However, with the exception of several pediatric studies,[15-17] reports on ASM utilization based on large-scale data in Asia are lacking.[18]

We have therefore performed a nationwide analysis of data obtained in South Korea between 2009 and 2017, with the following aims: 1) to identify the trends of ASM utilization in PWE across the entire population during that period, 2) to determine changes in ASM prescription patterns such as monotherapy or combination treatment with regard to age and sex, and 3) to identify the preferred individual ASMs or combination ASM regimens in each year according to age and sex.

METHODS

Data sources

This study used nationwide data from the Korean National Health Information Database (NHID) provided by the Korean National Health Insurance Service (NHIS). South Korea has a unique obligatory health security system that incorporates insurance funds and is managed by a central organized system encompassing the entire population. Under this framework, the government exerts control at the primary level on medical services provided by the private sector, with the freedom to select service providers when those insured by the NHIS pay an insurance contribution and receive medical services.[19,20] The NHID comprises comprehensive big data that include diagnostic codes according to the International Classification of Diseases, Tenth Revision (ICD-10), laboratory examinations, hospitalization, socioeconomic profiles, and all prescriptions received by the entire South Korean population.

We used the NHID to evaluate nationwide prescription patterns and regimens of oral ASMs for PWE in South Korea from 2009 to 2017. This study was approved by the institutional review boards of Sungkyunkwan University (approval number: 2018-06-006) and of the NHIS for Bioethics Policy (NHIS-3208-1-342).

Study population and diagnostic codes

Anonymized PWE were identified using diagnostic codes and ASM prescription data from the NHID during the study period. PWE were categorized using the following ICD-10 diagnostic codes for epilepsy or seizures: G40 (epilepsy), G41 (status epilepticus), F803 (Landau-Kleffner syndrome), and R56 (convulsion). The ASMs included carbamazepine (CBZ), clobazam, ethosuximide, gabapentin (GBP), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), perampanel, phenobarbital (Pb), phenytoin (PHT), pregabalin (PGB), primidone, stripentol, topiramate (TPM), vigabatrin, valproate (VPA), zonisamide, and rufinamide. We excluded clonazepam from the analysis since this drug is also widely used to treat nonepileptic diseases such as movement disorders or psychiatric disorders. Patients who had at least two documented visits with diagnostic codes and had been prescribed ASMs for ≥180 days were considered PWE.

ASM classification

ASMs were classified as older or newer ASMs based on them first becoming available on the market before or after 1991, respectively.[14,21] Among the 18 ASMs included in our analysis, Pb, ethosuximide, PHT, VPA, CBZ, and primidone were classified as older ASMs, and the 12 remaining ASMs were classified as newer ASMs (i.e., vigabatrin, zonisamide, LTG, GBP, TPM, OXC, LEV, PGB, clobazam, stripentol, rufinamide, and perampanel).

Statistical analysis

Overall trends of individual ASM prescriptions and prescription patterns according to age and sex were described for the period from 2009 to 2017. Patients were classified into the following three age groups to evaluate the effects of age on the selection of prescription patterns and types of ASMs: 1) <20

years, 2) 20–59 years, and 3) ≥60 years. Each ASM duotherapy group was defined according to two individual ASMs contained; for example, a combination of VPA and CBZ would simultaneously classified as VPA combinations and CBZ combinations.

Changes in annual trends of ASM prescriptions in each age and sex group were assessed using a Poisson regression model. Values were expressed as average annual percentage changes (AAPCs), which quantify the estimated yearly percentage changes in prescription rates over a specified time interval.

Calculations were performed by exponentiating the coefficient of regression to obtain AAPC values. Data were ana-

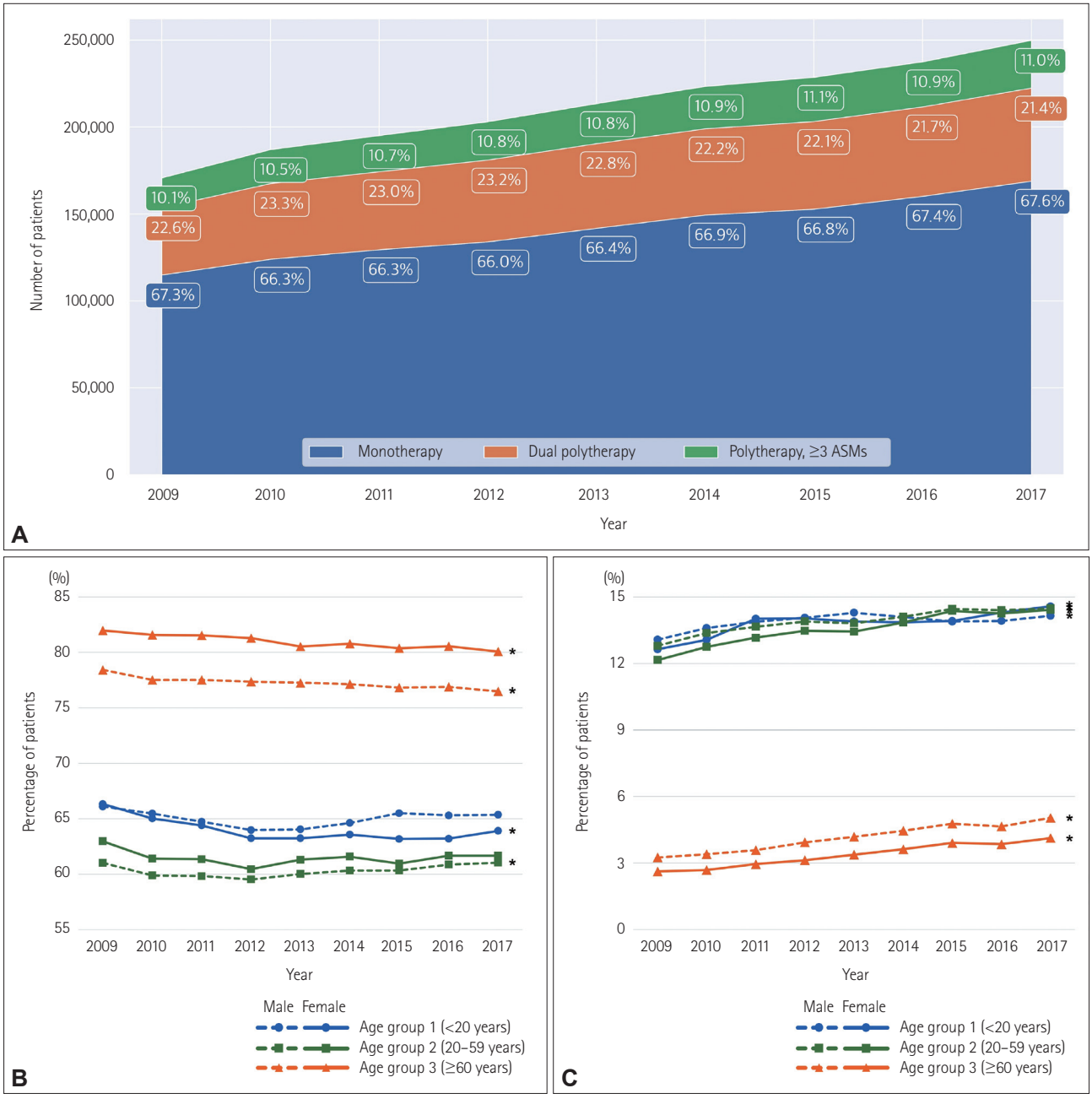

Fig. 1. ASM prescription patterns between 2009 and 2017 in South Korea. A: ASM prescription patterns according to prescribed number of ASMs. Blue, orange, and green colored areas indicate the absolute numbers of patients receiving ASM monotherapy, ASM duotherapy, and polytherapy with three or more ASMs, respectively. B, C: ASM prescription patterns according to age and sex groups. Asterisk indicates statistical significance (p<0.05). B: Vertical line indicates the proportion of single-ASM prescriptions in patients relative to the total number of PWE according to age group. C: Vertical line indicates the proportion of three or more ASMs being prescribed in patients relative to the total number of PWE according to age group: 1) <20 years, 2) 20–59 years, and 3) ≥60 years. ASM, antiseizure medication; PWE, patients with epilepsy.

lyzed using SPSS (version 26.0, IBM Corp., Armonk, NY, USA) and SAS Enterprise Guide (version 7.1 for Windows; SAS Institute, Cary, NC, USA). A p value<0.05 was considered statistically significant.

RESULTS

Changes in prescription patterns in PWE

The total number of patients who were prescribed ASMs increased from 170,730 in 2009 to 249,878 in 2017. From 2009 to 2017, the absolute number of patients receiving ASM monotherapy increased (from 114,910 to 168,863), but the proportion remained statistically constant at about 67% (from 67.31% to 67.58%, p>0.05) (Fig. 1A). The proportion of PWE receiving ASM duotherapy decreased from 22.6% in 2009 to 21.4% in 2017 (AAPC=-1.0%, p<0.001), while the proportion receiving polytherapy with three or more ASMs increased from 10.08% in 2009 to 10.99% in 2017 (AAPC=0.9%, p<0.001).

Among age groups, males in age group 2 showed an increasing trend of ASM monotherapy prescriptions over time (AAPC=0.2%, p=0.011), while the other groups showed either a decreasing tendency or no significant changes (Fig. 1B). Age group 3 showed the highest prescription rate for ASM monotherapy throughout the study period, but at the same time showed a decreased proportion of ASM monotherapy over time (females: AAPC=-0.3%, p=0.001; males: AAPC=-0.2%, p=0.003). ASM monotherapy was more commonly prescribed for females than males in age groups 2 and 3. The proportion of PWE receiving polytherapy with three or more ASMs increased significantly in all age and sex groups (Table 1). The largest increase was observed in age group 3 (AAPC=5.76%, p<0.001), with a tendency to increase for females, although the prevalence was lower than that for males (Fig. 1C).

Prescriptions for individual ASMs in monotherapy in PWE

Of all ASMs used in monotherapy, a steady increase in the number and proportion of newer ASMs was noted over the study period: from 39,308 in 2009 to 83,441 in 2017 (34.21% and 49.41% of total ASM monotherapy use, respectively). The nine ASMs prescribed most commonly as monotherapy in 2017 are listed in Table 2, among which LEV and PGB showed a rapid increase in monotherapy prescription rates, and VPA, CBZ, PHT, OXC, TPM, and GBP showed decreasing trends. VPA was the most commonly prescribed ASM for both males and females from 2009 to 2017, more commonly for males than females in all age groups over the study period (Fig. 2). The proportion of prescriptions involving VPA exhibited different trends according to age group, showing significant increasing trends in males of age group 1 (AAPC=

Table 1. Annual trends in using three or more ASMs among PWE from 2009 to 2017 according to age and sex

Age group	Prevalence, *n* (%)									AAPC, %	p
	2009	2010	2011	2012	2013	2014	2015	2016	2017		
Age group 1 (<20 years)											
Total	3,484 (12.89)	3,604 (13.37)	3,715 (13.94)	3,721 (14.05)	3,722 (14.12)	3,638 (14.00)	3,524 (13.90)	3,465 (14.08)	3,494 (14.34)	1.01	<0.001
Females	1,481 (12.64)	1,522 (13.07)	1,617 (14.02)	1,616 (14.03)	1,592 (13.89)	1,573 (13.86)	1,546 (13.91)	1,542 (14.30)	1,561 (14.58)	1.31	<0.001
Males	2,003 (13.08)	2,082 (13.60)	2,098 (13.88)	2,105 (14.07)	2,130 (14.29)	2,065 (14.10)	1,978 (13.89)	1,923 (13.91)	1,933 (14.15)	0.70	0.023
Age group 2 (20–59 years)											
Total	12,397 (12.52)	14,415 (13.10)	15,296 (13.45)	16,203 (13.72)	16,833 (13.65)	17,836 (14.00)	18,644 (14.42)	19,001 (14.34)	19,909 (14.46)	1.61	<0.001
Females	5,159 (12.16)	6,008 (12.75)	6,366 (13.16)	6,717 (13.47)	7,004 (13.43)	7,484 (13.85)	7,836 (14.37)	7,947 (14.25)	8,345 (14.42)	2.02	<0.001
Males	7,238 (12.80)	8,407 (13.37)	8,930 (13.66)	9,486 (13.90)	9,829 (13.82)	10,352 (14.11)	10,808 (14.46)	11,054 (14.41)	11,564 (14.48)	1.41	<0.001
Age group 3 (≥60 years)											
Total	1,324 (2.96)	1,536 (3.07)	1,799 (3.29)	2,078 (3.55)	2,432 (3.81)	2,844 (4.07)	3,229 (4.37)	3,436 (4.27)	4,047 (4.61)	5.76	<0.001
Females	542 (2.63)	634 (2.69)	759 (2.95)	861 (3.13)	1,014 (3.38)	1,197 (3.62)	1,369 (3.91)	1,471 (3.85)	1,723 (4.13)	5.97	<0.001
Males	782 (3.25)	902 (3.41)	1,040 (3.58)	1,217 (3.93)	1,418 (4.19)	1,647 (4.46)	1,860 (4.78)	1,965 (4.65)	2,324 (5.04)	5.65	<0.001
Total population											
Total	17,205 (10.08)	19,555 (10.45)	20,810 (10.66)	22,002 (10.83)	22,987 (10.77)	24,318 (10.89)	25,397 (11.11)	25,902 (10.91)	27,450 (10.99)	0.90	<0.001
Females	7,182 (9.60)	8,164 (9.91)	8,742 (10.21)	9,194 (10.34)	9,610 (10.27)	10,254 (10.42)	10,751 (10.68)	10,960 (10.46)	11,629 (10.54)	1.01	<0.001
Males	10,023 (10.45)	11,391 (10.88)	12,068 (11.02)	12,808 (11.22)	13,377 (11.16)	14,064 (11.26)	14,646 (11.45)	14,942 (11.25)	15,821 (11.33)	0.80	<0.001

AAPC, average annual percentage change; ASMs, antiseizure medications; PWE, patients with epilepsy.

Table 2. Changes in trends in use of major ASMs as monotherapy according to age and sex in PWE

Age group	Sex	ASM	Prevalence, *n* (%)									AAPC, %	*p*
			2009	2010	2011	2012	2013	2014	2015	2016	2017		
Age group 1 (<20 years)	Total	VPA	5,963(33.31)	5,931(33.71)	5,819 (33.80)	5,643 (33.48)	5,597 (33.33)	5,783 (34.68)	5,584 (34.15)	5,310 (33.52)	5,305 (33.64)	0.10	0.424
		CBZ	1,768 (9.88)	1,418 (8.06)	1,134 (6.59)	896 (5.32)	836 (4.98)	764 (4.58)	613 (3.75)	508 (3.21)	378 (2.40)	-14.96	<0.001
		PHT	103 (0.58)	85 (0.48)	89 (0.52)	82 (0.49)	92 (0.55)	80 (0.48)	68 (0.42)	71 (0.45)	68 (0.43)	-2.96	<0.001
		LEV	116 (0.65)	319 (1.81)	557 (3.23)	856 (5.08)	1,129 (6.72)	1,360 (8.15)	1,825 (11.16)	2,293 (14.47)	2,729 (17.30)	35.66	<0.001
		LTG	1,884 (10.53)	2,255 (12.82)	2,213 (12.85)	2,190 (12.99)	2,113 (12.58)	2,065 (12.38)	1,880 (11.50)	1,708 (10.78)	1,544 (9.79)	-1.59	<0.001
		OXC	3,950 (22.07)	4,105 (23.33)	4,386 (25.47)	4,467 (26.50)	4,369 (26.01)	4,288 (25.71)	4,223 (25.83)	3,992 (25.20)	3,809 (24.15)	1.01	<0.001
		TPM	2,012 (11.24)	1,899 (10.79)	1,847 (10.73)	1,734 (10.29)	1,615 (9.62)	1,348 (8.08)	1,213 (7.42)	1,062 (6.70)	910 (5.77)	-7.69	<0.001
		GBP	10 (0.06)	18 (0.10)	15 (0.09)	9 (0.05)	8 (0.05)	6 (0.04)	2 (0.01)	5 (0.03)	9 (0.06)	-11.22	0.007
		PGB	3 (0.02)	1 (0.01)	3 (0.02)	5 (0.03)	4 (0.02)	6 (0.04)	4 (0.02)	3 (0.02)	2 (0.01)	4.08	0.568
	Males	VPA	3,549 (35.04)	3,603 (35.95)	3,539 (36.16)	3,472 (36.26)	3,491 (36.57)	3,619 (38.25)	3,549 (38.04)	3,378 (37.43)	3,449 (38.63)	1.11	<0.001
		CBZ	1,049 (10.36)	830 (8.28)	675 (6.90)	533 (5.57)	519 (5.44)	479 (5.06)	385 (4.13)	326 (3.61)	242 (2.71)	-14.01	<0.001
		PHT	62 (0.61)	51 (0.51)	57 (0.58)	56 (0.58)	60 (0.63)	42 (0.44)	35 (0.38)	41 (0.45)	39 (0.44)	-4.5	0.013
		LEV	67 (0.66)	162 (1.62)	298 (3.04)	459 (4.79)	574 (6.01)	714 (7.55)	999 (10.71)	1,219 (13.51)	1,407 (15.76)	35.39	<0.001
		LTG	917 (9.06)	1,072 (10.7)	1,052 (10.75)	1,031 (10.77)	925 (9.69)	905 (9.56)	808 (8.66)	741 (8.21)	674 (7.55)	-3.15	<0.001
		OXC	2,282 (22.53)	2,355 (23.50)	2,504 (25.58)	2,526 (26.38)	2,782 (26.00)	2,437 (25.76)	2,437 (26.12)	2,290 (25.37)	2,157 (24.16)	0.9	0.001
		TPM	1,101 (10.87)	1,098 (10.96)	1,036 (10.58)	945 (9.87)	902 (9.48)	735 (7.77)	640 (6.86)	579 (6.42)	487 (5.45)	-8.24	<0.001
		GBP	5 (0.05)	10 (0.1)	4 (0.04)	3 (0.03)	2 (0.02)	5 (0.05)	2 (0.02)	4 (0.04)	7 (0.08)	-2.76	0.646
		PGB	0 (0.00)	0 (0.00)	1 (0.01)	3 (0.03)	4 (0.04)	4 (0.04)	1 (0.01)	0 (0.00)	1 (0.01)	7.14	0.506
	Females	VPA	2,414 (31.06)	2,328 (30.74)	2,280 (30.69)	2,171 (29.81)	2,106 (29.05)	2,164 (29.99)	2,035 (28.99)	1,932 (28.34)	1,856 (27.12)	-1.49	<0.001
		CBZ	719 (9.25)	588 (7.77)	459 (6.18)	363 (4.98)	317 (4.37)	285 (3.95)	228 (3.25)	182 (2.67)	136 (1.99)	-16.56	<0.001
		PHT	41 (0.53)	34 (0.45)	32 (0.43)	26 (0.36)	32 (0.44)	38 (0.53)	33 (0.47)	30 (0.44)	29 (0.42)	-0.8	0.737
		LEV	49 (0.63)	157 (2.07)	259 (3.49)	397 (5.45)	555 (7.66)	646 (8.95)	826 (11.77)	1,074 (15.75)	1,322 (19.32)	35.8	<0.001
		LTG	967 (12.44)	1,183(15.62)	1,161 (15.63)	1,159 (15.91)	1,188 (16.39)	1,160 (16.08)	1,072 (15.27)	967 (14.19)	870 (12.71)	-0.3	0.460
		OXC	1,668 (21.46)	1,750 (23.11)	1,882 (25.33)	1,941 (26.65)	1,887 (26.03)	1,851 (25.65)	1,786 (25.44)	1,702 (24.97)	1,652 (24.14)	1.11	<0.001
		TPM	911 (11.72)	801 (10.58)	811 (10.92)	789 (10.83)	710 (9.79)	613 (8.50)	573 (8.16)	483 (7.09)	423 (6.18)	-6.95	<0.001
		GBP	5 (0.06)	8 (0.11)	11 (0.15)	6 (0.08)	6 (0.08)	1 (0.01)	0 (0.00)	1 (0.01)	2 (0.03)	-20.23	0.001
		PGB	3 (0.04)	1 (0.01)	2 (0.03)	2 (0.03)	0 (0.00)	2 (0.03)	3 (0.04)	3 (0.04)	1 (0.01)	1.61	0.866
Age group 2 (20–59 years)	Total	VPA	21,938 (35.82)	24,050 (36.11)	24,573 (35.71)	24,966 (35.27)	26,527 (35.52)	28,275 (36.46)	28,511 (36.38)	29,374 (36.22)	30,761 (36.43)	0.3	0.001
		CBZ	16,317 (26.64)	16,786 (25.20)	16,083 (23.37)	15,401 (21.76)	15,187 (20.34)	14,554 (18.77)	13,658 (17.43)	12,848 (15.84)	12,261 (14.52)	-7.32	<0.001
		PHT	3,739 (6.11)	3,856 (5.79)	3,688 (5.36)	3,346 (4.73)	3,132 (4.19)	2,802 (3.61)	2,518 (3.21)	2,574 (3.17)	2,371 (2.81)	-9.79	<0.001
		LEV	429 (0.70)	1,111 (1.67)	2,095 (3.04)	3,384 (4.78)	5,358 (7.17)	7,423 (9.57)	10,351 (13.21)	13,490 (16.64)	15,857 (18.78)	36.75	<0.001
		LTG	4,194 (6.85)	4,901 (7.36)	5,498 (7.99)	5,737 (8.10)	6,136 (8.22)	6,586 (8.49)	6,668 (8.51)	6,818 (8.41)	7,099 (8.41)	2.12	<0.001
		OXC	4,035 (6.59)	4,609 (6.92)	5,133 (7.46)	5,481 (7.74)	5,746 (7.69)	5,696 (7.34)	5,717 (7.30)	5,688 (7.01)	5,772 (6.84)	0	0.817
		TPM	5,909 (9.65)	6,423 (9.64)	6,845 (9.95)	7,612 (10.75)	7,500 (10.04)	7,044 (9.08)	6,180 (7.89)	5,750 (7.09)	5,570 (6.60)	-4.97	<0.001
		GBP	2,482 (4.05)	2,388 (3.59)	2,383 (3.46)	2,351 (3.32)	2,362 (3.16)	2,199 (2.84)	2,070 (2.64)	1,970 (2.43)	1,980 (2.34)	-6.48	<0.001
		PGB	296 (0.48)	518 (0.78)	657 (0.95)	723 (1.02)	922 (1.23)	1,116 (1.44)	1,024 (1.31)	1,017 (1.25)	1,057 (1.25)	8.55	<0.001
	Males	VPA	13,554 (39.26)	14,875 (39.49)	15,458 (39.50)	15,935 (39.21)	16,842 (39.43)	17,947 (40.54)	18,128 (40.19)	18,771 (40.20)	19,795 (40.61)	0.40	<0.001
		CBZ	9,306 (26.96)	9,661 (25.65)	9,243 (23.62)	8,857 (21.79)	8,726 (20.43)	8,360 (18.88)	7,974 (17.68)	7,471 (16.00)	7,144 (14.66)	-7.32	<0.001

Table 2. Changes in trends in use of major ASMs as monotherapy according to age and sex in PWE (continued)

Age group	Sex	ASM	Prevalence, *n* (%)									AAPC, %	*p*
			2009	2010	2011	2012	2013	2014	2015	2016	2017		
		PHT	2,382 (6.90)	2,429 (6.45)	2,295 (5.86)	2,108 (5.19)	1,970 (4.61)	1,757 (3.97)	1,585 (3.51)	1,601 (3.43)	1,471 (3.02)	-10.24	<0.001
		LEV	211 (0.61)	511 (1.36)	1,016 (2.60)	1,780 (4.38)	2,974 (6.96)	4,055 (9.16)	5,828 (12.92)	7,683 (16.45)	9,034 (18.53)	38.68	<0.001
		LTG	1,631 (4.72)	1,888 (5.01)	2,169 (5.54)	2,286 (5.62)	2,396 (5.61)	2,574 (5.81)	2,611 (5.79)	2,628 (5.63)	2,734 (5.61)	1.71	<0.001
		OXC	2,281 (6.61)	2,572 (6.83)	2,966 (7.58)	3,224 (7.93)	3,373 (7.90)	3,427 (7.74)	3,458 (7.67)	3,458 (7.41)	3,480 (7.14)	0.70	0.004
		TPM	2,431 (7.04)	2,938 (7.80)	3,192 (8.16)	3,679 (9.05)	3,567 (8.35)	3,241 (7.32)	2,830 (6.27)	2,537 (5.43)	2,430 (4.98)	-5.16	<0.001
		GBP	1,500 (4.35)	1,448 (3.84)	1,444 (3.69)	1,405 (3.46)	1,369 (3.21)	1,282 (2.90)	1,193 (2.64)	1,120 (2.40)	1,097 (2.25)	-7.78	<0.001
		PGB	184 (0.53)	283 (0.75)	357 (0.91)	403 (0.99)	498 (1.17)	631 (1.43)	610 (1.35)	582 (1.25)	623 (1.28)	8.98	<0.001
Age group 2 (20–59 years)	Females	VPA	8,384 (31.38)	9,175 (31.71)	9,115 (30.71)	9,031 (29.96)	9,685 (30.30)	10,328 (31.03)	10,383 (31.22)	10,603 (30.83)	10,966 (30.72)	-0.1	0.255
		CBZ	7,011 (26.24)	7,125 (24.63)	6,840 (23.05)	6,544 (21.71)	6,461 (20.21)	6,194 (18.61)	5,684 (17.09)	5,377 (15.63)	5,117 (14.34)	-7.23	<0.001
		PHT	1,357 (5.08)	1,427 (4.93)	1,393 (4.69)	1,238 (4.11)	1,162 (3.63)	1,045 (3.14)	933 (2.81)	973 (2.83)	900 (2.52)	-9.15	<0.001
		LEV	218 (0.82)	600 (2.07)	1,079 (3.64)	1,604 (5.32)	2,384 (7.46)	3,368 (10.12)	4,523 (13.60)	5,807 (16.88)	6,823 (19.12)	34.58	<0.001
		LTG	2,563 (9.59)	3,013 (10.41)	3,329 (11.22)	3,451 (11.45)	3,740 (11.70)	4,012 (12.06)	4,057 (12.20)	4,190 (12.18)	4,365 (12.23)	2.63	<0.001
		OXC	1,754 (6.56)	2,037 (7.04)	2,167 (7.30)	2,257 (7.49)	2,373 (7.42)	2,269 (6.82)	2,259 (6.79)	2,230 (6.48)	2,292 (6.42)	-1.09	<0.001
		TPM	3,478 (13.02)	3,485 (12.04)	3,653 (12.31)	3,933 (13.05)	3,933 (12.30)	3,803 (11.43)	3,350 (10.07)	3,213 (9.34)	3,140 (8.80)	-4.59	<0.001
		GBP	982 (3.68)	940 (3.25)	939 (3.16)	946 (3.14)	993 (3.11)	917 (2.76)	877 (2.64)	850 (2.47)	883 (2.47)	-4.69	<0.001
		PGB	112 (0.42)	235 (0.81)	300 (1.01)	320 (1.06)	424 (1.33)	485 (1.46)	414 (1.24)	435 (1.26)	434 (1.22)	8.11	<0.001
	Total	VPA	12,278 (34.33)	13,303 (33.44)	14,422 (33.20)	14,882 (32.13)	15,985 (31.78)	17,759 (32.19)	17,943 (30.90)	19,593 (30.98)	20,948 (30.51)	-1.39	<0.001
		CBZ	7,525 (21.04)	8,063 (20.27)	8,290 (19.09)	7,927 (17.11)	8,040 (15.99)	8,032 (14.56)	7,969 (13.73)	8,042 (12.72)	8,098 (11.80)	-7.32	<0.001
		PHT	3,056 (8.54)	3,068 (7.71)	3,010 (6.93)	2,933 (6.33)	2,845 (5.66)	2,808 (5.09)	2,725 (4.69)	2,916 (4.61)	3,024 (4.40)	-8.33	<0.001
		LEV	107 (0.30)	459 (1.15)	1,059 (2.44)	2,059 (4.45)	3,828 (7.61)	6,038 (10.95)	9,237 (15.91)	12,441 (19.67)	15,244 (22.20)	41.62	<0.001
		LTG	974 (2.72)	1,201 (3.02)	1,536 (3.54)	1,716 (3.70)	1,917 (3.81)	2,097 (3.80)	2,164 (3.73)	2,300 (3.64)	2,527 (3.68)	2.53	<0.001
		OXC	1,744 (4.88)	2,304 (5.79)	2,620 (6.03)	2,939 (6.35)	3,125 (6.21)	3,057 (5.54)	3,053 (5.26)	3,235 (5.12)	3,359 (4.89)	-1.78	<0.001
		TPM	3,127 (8.74)	3,791 (9.53)	4,379 (10.08)	5,187 (11.20)	5,030 (10.00)	4,765 (8.64)	4,025 (6.93)	3,718 (5.88)	3,464 (5.05)	-7.6	<0.001
		GBP	5,225 (14.61)	5,334 (13.41)	5,550 (12.78)	5,748 (12.41)	6,209 (12.35)	6,439 (11.67)	6,356 (10.95)	6,187 (9.78)	6,451 (9.40)	-5.07	<0.001
		PGB	589 (1.65)	895 (2.25)	1,134 (2.61)	1,413 (3.05)	1,833 (3.64)	2,466 (4.47)	2,685 (4.62)	2,744 (4.34)	3,164 (4.61)	11.29	<0.001
Age group 3 (≥60 years)	Males	VPA	6,904 (36.63)	7,246 (35.29)	7,912 (35.19)	8,184 (34.20)	8,849 (33.83)	9,719 (34.12)	9,719 (32.49)	10,532 (32.44)	11,279 (32.00)	-1.59	<0.001
		CBZ	3,898 (20.68)	4,065 (19.80)	4,135 (18.39)	3,955 (16.53)	4,081 (15.60)	4,077 (14.31)	3,957 (13.23)	4,032 (12.42)	4,062 (11.53)	-7.32	<0.001
		PHT	1,764 (9.36)	1,699 (8.28)	1,690 (7.52)	1,646 (6.88)	1,591 (6.08)	1,537 (5.40)	1,480 (4.95)	1,542 (4.75)	1,595 (4.53)	-8.97	<0.001
		LEV	53 (0.28)	242 (1.18)	575 (2.56)	1,083 (4.53)	2,005 (7.66)	3,194 (11.21)	4,917 (16.44)	6,532 (20.12)	8,076 (22.92)	41.91	<0.001
		LTG	471 (2.50)	568 (2.77)	720 (3.20)	799 (3.34)	888 (3.39)	924 (3.24)	981 (3.28)	1,043 (3.21)	1,145 (3.25)	1.92	<0.001
		OXC	967 (5.13)	1,270 (6.19)	1,371 (6.10)	1,555 (6.50)	1,672 (6.39)	1,607 (5.64)	1,609 (5.38)	1,720 (5.30)	1,762 (5.00)	-2.08	<0.001
		TPM	1,354 (7.18)	1,776 (8.65)	2,107 (9.37)	2,527 (10.56)	2,477 (9.47)	2,321 (8.15)	1,931 (6.46)	1,733 (5.34)	1,549 (4.40)	-7.32	<0.001
		GBP	2,560 (13.58)	2,577 (12.55)	2,719 (12.09)	2,779 (11.61)	2,952 (11.28)	3,052 (10.72)	3,009 (10.06)	2,939 (9.05)	3,022 (8.57)	-5.35	<0.001
		PGB	287 (1.52)	435 (2.12)	580 (2.58)	723 (3.02)	966 (3.69)	1,249 (4.39)	1,387 (4.64)	1,409 (4.34)	1,671 (4.74)	12.19	<0.001
	Females	VPA	5,374 (31.76)	6,057 (31.46)	6,510 (31.07)	6,698 (29.92)	7,136 (29.57)	8,040 (30.13)	8,224 (29.21)	9,061 (29.45)	9,669 (28.94)	-1.09	<0.001
		CBZ	3,627 (21.43)	3998 (20.77)	4,155 (19.83)	3,972 (17.74)	3,959 (16.40)	3,955 (14.82)	4,012 (14.25)	4,010 (13.03)	4,036 (12.08)	-7.32	<0.001

Table 2. Changes in trends in use of major ASMs as monotherapy according to age and sex in PWE (continued)

Age group	Sex	ASM	Prevalence, *n* (%)									AAPC, %	*p*
			2009	2010	2011	2012	2013	2014	2015	2016	2017		
Age group 3 (≥60 years)		PHT	1,292 (7.63)	1,369 (7.11)	1,320 (6.30)	1,287 (5.75)	1,254 (5.20)	1,271 (4.76)	1,245 (4.42)	1,374 (4.47)	1,429 (4.28)	-7.32	<0.001
		LEV	54 (0.32)	217 (1.13)	484 (2.31)	976 (4.36)	1,823 (7.55)	2,844 (10.66)	4,320 (15.35)	5,909 (19.20)	7,168 (21.46)	41.34	<0.001
		LTG	503 (2.97)	633 (3.29)	816 (3.89)	917 (4.10)	1,029 (4.26)	1,173 (4.40)	1,183 (4.20)	1,257 (4.09)	1,382 (4.14)	2.84	<0.001
		OXC	777 (4.59)	1,034 (5.37)	1,249 (5.96)	1,384 (6.18)	1,453 (6.02)	1,450 (5.43)	1,444 (5.13)	1,515 (4.92)	1,597 (4.78)	-1.49	<0.001
		TPM	1,773 (10.48)	2,015 (10.47)	2,272 (10.84)	2,660 (11.88)	2,553 (10.58)	2,444 (9.16)	2,094 (7.44)	1,985 (6.45)	1,915 (5.73)	-7.87	<0.001
		GBP	2,665 (15.75)	2,757 (14.32)	2,831 (13.51)	2,969 (13.26)	3,257 (13.50)	3,387 (12.69)	3,347 (11.89)	3,248 (10.56)	3,429 (10.26)	-4.78	<0.001
		PGB	302 (1.78)	460 (2.39)	554 (2.64)	690 (3.08)	867 (3.59)	1,217 (4.56)	1298 (4.61)	1,335 (4.34)	1,493 (4.47)	10.41	<0.001
Total population	Total	VPA	40,179 (34.97)	43,284 (34.91)	44,814 (34.62)	45,491 (33.96)	48,109 (33.94)	51,817 (34.69)	52,038 (34.06)	54,277 (33.89)	57,014 (33.76)	-0.4	<0.001
		CBZ	25,610 (22.29)	26,267 (21.19)	25,507 (19.70)	24,224 (18.08)	24,063 (16.97)	23,350 (15.63)	22,240 (14.56)	21,398 (13.36)	20,737 (12.28)	-7.23	<0.001
		PHT	6,898 (6.00)	7,009 (5.65)	6,787 (5.24)	6,361 (4.75)	6,069 (4.28)	5,690 (3.81)	5,311 (3.48)	5,561 (3.47)	5,463 (3.24)	-7.96	<0.001
		LEV	652 (0.57)	1,889 (1.52)	3,711 (2.87)	6,299 (4.70)	10,315 (7.28)	14,821 (9.92)	21,413 (14.02)	28,224 (17.62)	33,830 (20.03)	38.82	<0.001
		LTG	7,052 (6.14)	8,357 (6.74)	9,247 (7.14)	9,643 (7.20)	10,166 (7.17)	10,748 (7.19)	10,712 (7.01)	10,826 (6.76)	11,170 (6.61)	0.2	0.095
		OXC	9,729 (8.47)	11,018 (8.89)	12,139 (9.38)	12,887 (9.62)	13,240 (9.34)	13,041 (8.73)	12,993 (8.50)	12,915 (8.06)	12,940 (7.66)	-1.78	<0.001
		TPM	11,048 (9.61)	12,113 (9.77)	13,071 (10.10)	14,533 (10.85)	14,145 (9.98)	13,157 (8.81)	11,418 (7.47)	10,530 (6.57)	9,944 (5.89)	-6.29	<0.001
		GBP	7,717 (6.72)	7,740 (6.24)	7,948 (6.14)	8,108 (6.05)	8,579 (6.05)	8,644 (5.79)	8,428 (5.52)	8,162 (5.10)	8,440 (5.00)	-3.34	<0.001
		PGB	888 (0.77)	1,414 (1.14)	1,794 (1.39)	2,141 (1.60)	2,759 (1.95)	3,588 (2.40)	3,713 (2.43)	3,764 (2.35)	4,223 (2.50)	12.64	<0.001
	Male	VPA	24,007 (37.81)	25,724 (37.71)	26,909 (37.69)	27,591 (37.21)	29,182 (37.21)	31,285 (38.05)	31,396 (37.22)	32,681 (37.06)	34,523 (37.15)	-0.2	0.006
		CBZ	14,253 (22.45)	14,556 (21.34)	14,053 (19.68)	13,345 (18.00)	13,326 (16.99)	12,916 (15.71)	12,316 (14.60)	11,829 (13.41)	11,448 (12.32)	-7.23	<0.001
		PHT	4,208 (6.63)	4,179 (6.13)	4,042 (5.66)	3,810 (5.14)	3,621 (4.62)	3,336 (4.06)	3,100 (3.68)	3,184 (3.61)	3,105 (3.34)	-8.7	<0.001
		LEV	331 (0.52)	915 (1.34)	1,889 (2.65)	3,322 (4.48)	5,553 (7.08)	7,963 (9.69)	11,744 (13.92)	15,434 (17.50)	18,517 (19.93)	39.93	<0.001
		LTG	3,019 (4.75)	3,528 (5.17)	3,941 (5.52)	4,116 (5.55)	4,209 (5.37)	4,403 (5.36)	4,400 (5.22)	4,412 (5.00)	4,553 (4.90)	-0.4	0.04
		OXC	5,530 (8.71)	6,197 (9.08)	6,841 (9.58)	7,305 (9.85)	7,527 (9.60)	7,471 (9.09)	7,504 (8.90)	7,468 (8.47)	7,399 (7.96)	-1.49	<0.001
		TPM	4,886 (7.70)	5,812 (8.52)	6,335 (8.87)	7,151 (9.64)	6,949 (8.86)	6,297 (7.66)	5,401 (6.40)	4,849 (5.50)	4,466 (4.81)	-6.48	<0.001
		GBP	4,065 (6.40)	4,035 (5.91)	4,167 (5.84)	4,187 (5.65)	4,323 (5.51)	4,339 (5.28)	4,204 (4.98)	4,063 (4.61)	4,126 (4.44)	-4.21	<0.001
		PGB	471 (0.74)	718 (1.05)	938 (1.31)	1,129 (1.52)	1,468 (1.87)	1,884 (2.29)	1,998 (2.37)	1,991 (2.26)	2,295 (2.47)	13.2	<0.001
	Female	VPA	16,172 (31.45)	17,560 (31.49)	17,905 (30.84)	17,900 (29.93)	18,927 (29.88)	20,532 (30.56)	20,642 (30.17)	21,596 (30.00)	22,491 (29.61)	-0.7	<0.001
		CBZ	11,357 (22.09)	11,711 (21.00)	11,454 (19.73)	10,879 (18.19)	10,737 (16.95)	10,434 (15.53)	9,924 (14.50)	9,569 (13.29)	9,289 (12.23)	-7.23	<0.001
		PHT	2,690 (5.23)	2,830 (5.08)	2,745 (4.73)	2,551 (4.27)	2,448 (3.86)	2,354 (3.50)	2,211 (3.23)	2,377 (3.30)	2,358 (3.10)	-7.04	<0.001
		LEV	321 (0.62)	974 (1.75)	1,822 (3.14)	2,977 (4.98)	4,762 (7.52)	6,858 (10.21)	9,669 (14.13)	12,790 (17.77)	15,313 (20.16)	37.44	<0.001
		LTG	4,033 (7.84)	4,829 (8.66)	5,306 (9.14)	5,527 (9.24)	5,957 (9.40)	6,345 (9.44)	6,312 (9.22)	6,414 (8.91)	6,617 (8.71)	0.7	<0.001
		OXC	4,199 (8.17)	4,821 (8.65)	5,298 (9.13)	5,582 (9.33)	5,713 (9.02)	5,570 (8.29)	5,489 (8.02)	5,447 (7.57)	5,541 (7.30)	-2.18	<0.001
		TPM	6,162 (11.98)	6,301 (11.30)	6,736 (11.60)	7,382 (12.34)	7,196 (11.36)	6,860 (10.21)	6,017 (8.79)	5,681 (7.89)	5,478 (7.21)	-6.11	<0.001
		GBP	3,652 (7.10)	3,705 (6.64)	3,781 (6.51)	3,921 (6.56)	4,256 (6.72)	4,305 (6.41)	4,224 (6.17)	4,099 (5.69)	4,314 (5.68)	-2.47	<0.001
		PGB	417 (0.81)	696 (1.25)	856 (1.47)	1,012 (1.69)	1,291 (2.04)	1,704 (2.54)	1,715 (2.51)	1,773 (2.46)	1,928 (2.54)	11.96	<0.001

ASMs, antiseizure medications; CBZ, carbamazepine; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; PHT, phenytoin; PWE, patients with epilepsy; TPM, topiramate; VPA, valproate;.

1.11, $p<0.001$) and 2 (AAPC=0.40, $p<0.001$) but not in other groups. The largest decrease in the VPA prescription rate was observed for males (AAPC=-1.59, $p<0.001$) and females (AAPC=-1.09, $p<0.001$) in age group 3.

The second most commonly prescribed ASMs in all groups were CBZ in 2009 and LEV in 2017 with the exception of age group 1, for which OXC was the second most commonly prescribed ASM in both years (Table 2). The use of LEV, the most frequently prescribed newer ASM in 2017, increased in all age and sex groups. Age group 3 demonstrated the largest increase in the LEV prescription rate from 2009 to 2017 (AAPC=41.62, $p<0.001$) and highest prescription proportion for LEV among age groups in 2017. The prescription rate for LTG was higher for females than for males throughout the study period (Fig. 2) and showed an increasing trend over the study period except in age group 1 (Table 2).

TPM was prescribed more often for females than for males (Fig. 2). The TPM prescription rate for females in age group 2 remained the highest among age groups throughout the study period, with a decreasing tendency in all age groups over time (Table 2). The GBP prescription rate declined over time for both males and females (Fig. 2) and was more commonly prescribed for both males and females in age group 3 (Table 2). Also, the PGB prescription rate exhibited the largest increase in age group 3 over time (AAPC=11.29, $p<0.001$).

Duotherapy prescriptions in PWE

Fig. 3 presents the data on prescriptions for ASM duotherapy, including the five most frequently used combinations yearly from 2009 to 2017 in PWE. The most frequent combination in 2009 was VPA/CBZ duotherapy (12.97% and 16.28% of total duotherapy use in females and males, respectively) (Fig. 3D). In contrast to patients in other age groups, in the age group 1, the most commonly prescribed combination for both males and females was the VPA/LTG combination in 2009 (14.16% and 13.70% of total duotherapy use in females and males, respectively), although this was the only age group exhibiting a tendency for a decline in VPA/LTG duotherapy use from 2009 to 2017 (females: AAPC=-3.54, $p<0.001$; males: AAPC=-4.59, $p<0.001$) (Fig. 3A).

In 2017, the most frequent combinations of ASMs differed between age groups. VPA/CBZ duotherapy was the most frequently prescribed combination for the entire cohort. In age group 1, the most frequently used combinations of ASMs were LEV/OXC (12.29% of total duotherapy use) for females and VPA/LEV (13.11% of total duotherapy use) for males (Fig. 3A). VPA/CBZ duotherapy was the most frequently prescribed combination for age group 2 (10.86% for females and 15.52% for males) (Fig. 3B). Among age group 3, VPA/LEV duotherapy was the most commonly prescribed combination for both males (11.34%) and females (9.02%) (Fig. 3C).

The prescription rates for all combined regimens of older ASMs, such as VPA/CBZ, VPA/PHT, and Pb/PHT, generally declined over time for all age groups (Fig. 3). Substantial decreases over time were observed in the utilization of combination regimens that included older ASMs such as VPA, CBZ, and PHT for all age groups (Table 3). The most common duotherapy regimens in 2017 included VPA, except for females in age group 1. However, of VPA combinations, the only proportion of VPA/LEV use increased steadily from

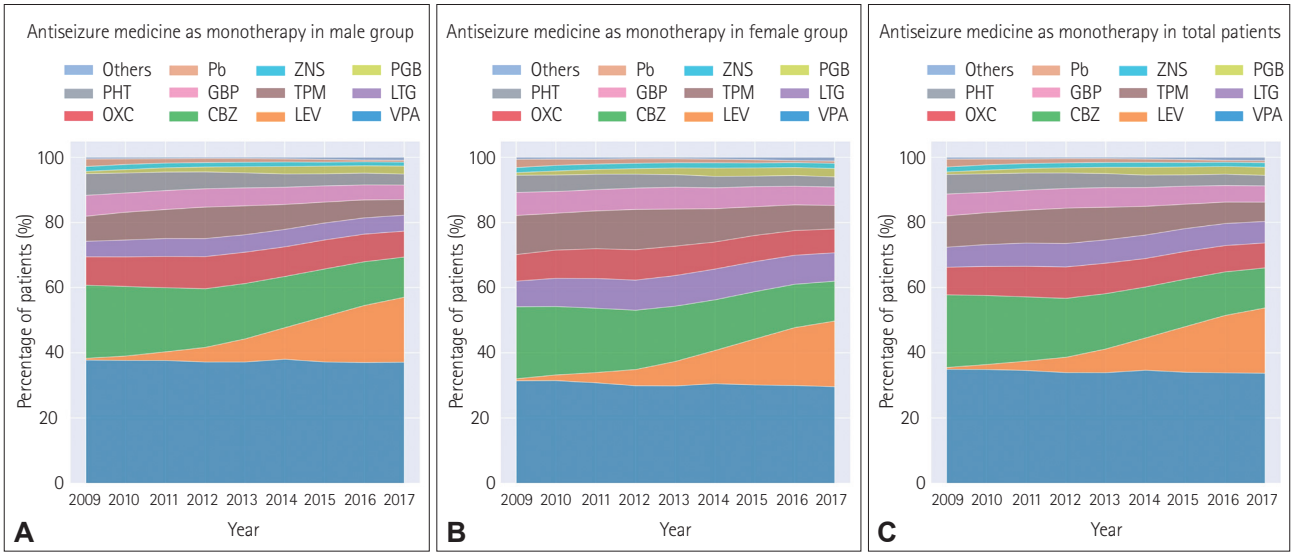

Fig. 2. Proportions of antiseizure medication monotherapy prescriptions between 2009 and 2017 in South Korea in (A) males, (B) females, and (C) the total population. CBZ, carbamazepine; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; Pb, phenobarbital; PGB, pregabalin; PHT, phenytoin; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

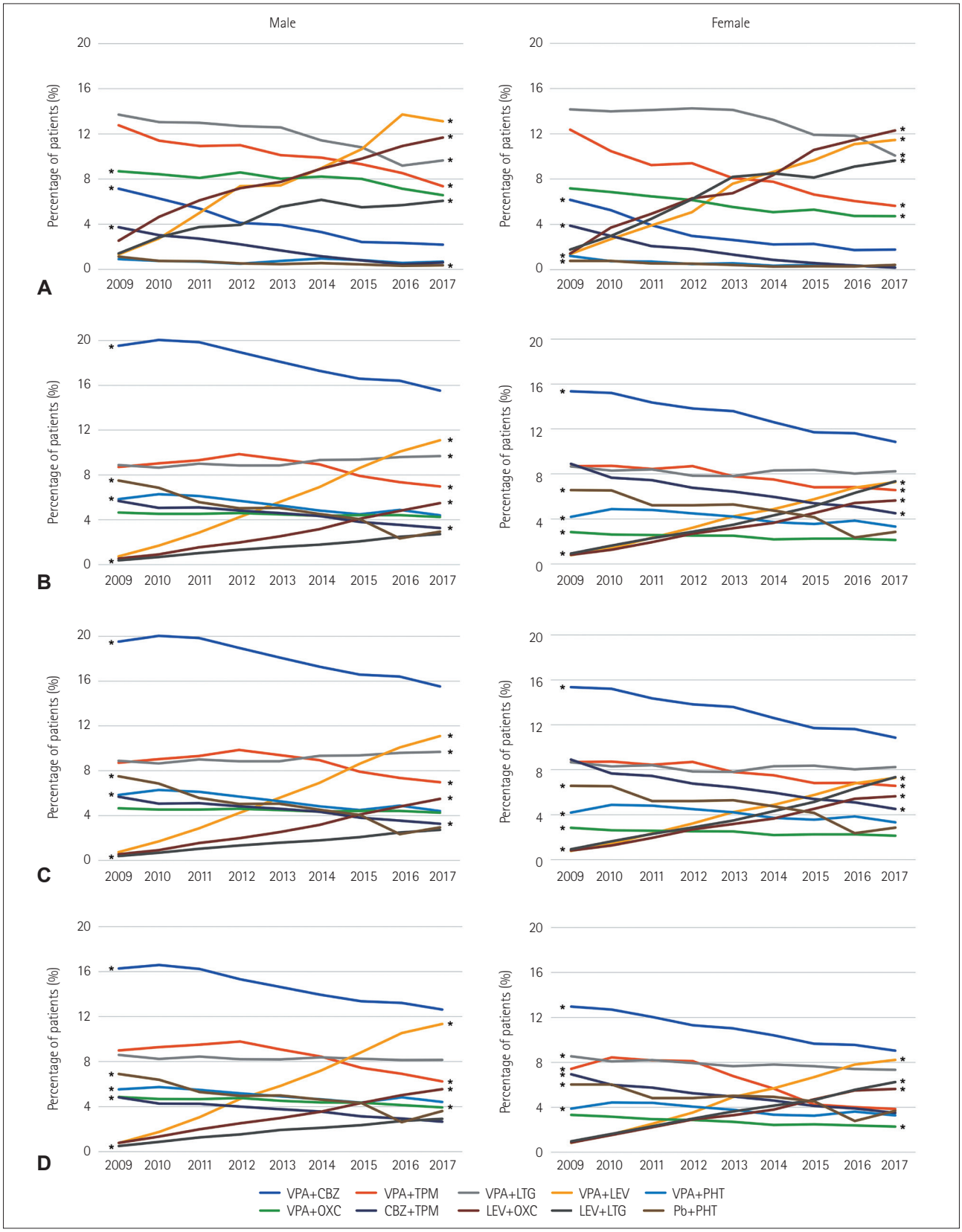

Fig. 3. Annual changes in prescription trends of the five most frequently prescribed antiseiaure medication duotherapy regimens yearly in (A) age group 1, (B) age group 2, (C) age group 3, and (D) the total population. Asterisk indicates statistical significance ($p<0.05$). CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; Pb, phenobarbital; PHT, phenytoin; VPA, valproate.

Table 3. Changes in trends in use of major ASMs in duotherapy regimens according to age group and sex in PWE

Age group	Sex	ASM	Prevalence of prescription, *n* (%)									AAPC, %	*p*
			2009	2010	2011	2012	2013	2014	2015	2016	2017		
	Total	VPA combinations	3,049 (53.93)	2,965 (51.51)	2,822 (49.31)	2,888 (48.92)	2,797 (47.80)	2,653 (46.74)	2,511 (45.82)	2,434 (45.94)	2,254 (44.17)	-2.27	<0.001
		CBZ combinations	891 (15.76)	781 (13.57)	639 (11.17)	555 (9.40)	453 (7.74)	375 (6.61)	306 (5.58)	243 (4.59)	223 (4.37)	-15.72	<0.001
		PHT combinations	201 (3.56)	167 (2.90)	151 (2.64)	116 (1.97)	134 (2.29)	130 (2.29)	139 (2.54)	110 (2.08)	114 (2.23)	-5.07	<0.001
		LEV combinations	399 (7.06)	811 (14.09)	1,143 (19.97)	1,508 (25.55)	1,741 (29.76)	1,943 (34.23)	2,113 (38.56)	2,250 (42.47)	2,280 (44.68)	18.77	<0.001
		LTG combinations	1,649 (29.17)	1,705 (29.62)	1,744 (30.47)	1,749 (29.63)	1,785 (30.51)	1,669 (29.40)	1,529 (27.90)	1,413 (26.67)	1,337 (26.20)	-1.49	<0.001
		OXC combinations	1,480 (26.18)	1,566 (27.21)	1,602 (27.99)	1,661 (28.14)	1,597 (27.29)	1,594 (28.08)	1,575 (28.74)	1,512 (28.54)	1,442 (28.26)	0.8	<0.001
	Males	VPA combinations	1,761 (55.22)	1,703 (53.14)	1,662 (51.41)	1,693 (51.54)	1,611 (49.88)	1,533 (49.21)	1,430 (48.72)	1,395 (48.57)	1,315 (46.96)	-1.78	<0.001
		CBZ combinations	504 (15.80)	448 (13.98)	386 (11.94)	328 (9.98)	272 (8.42)	225 (7.22)	164 (5.59)	138 (4.81)	131 (4.68)	-15.21	<0.001
Age group 1		PHT combinations	121 (3.79)	95 (2.96)	84 (2.60)	61 (1.86)	76 (2.35)	85 (2.73)	75 (2.56)	65 (2.26)	74 (2.64)	-3.82	0.008
<20 years		LEV combinations	233 (7.31)	452 (14.1)	652 (20.17)	830 (25.27)	911 (28.20)	1,016 (32.62)	1,062 (36.18)	1,184 (41.23)	1,201 (42.89)	18.06	<0.001
		LTG combinations	887 (27.81)	889 (27.74)	905 (27.99)	870 (26.48)	886 (27.43)	817 (26.23)	745 (25.38)	666 (23.19)	659 (23.54)	-2.27	<0.001
		OXC combinations	849 (26.62)	894 (27.89)	916 (28.33)	955 (29.07)	923 (28.58)	926 (29.73)	880 (29.98)	831 (28.93)	810 (28.93)	1.01	0.027
	Females	VPA combinations	1,288 (52.25)	1,262 (49.47)	1,160 (46.59)	1,195 (45.65)	1,186 (45.25)	1,120 (43.73)	1,081 (42.48)	1,039 (42.83)	939 (40.77)	-2.76	<0.001
		CBZ combinations	387 (15.70)	333 (13.05)	253 (10.16)	227 (8.67)	181 (6.91)	150 (5.86)	142 (5.58)	105 (4.33)	92 (3.99)	-16.39	<0.001
		PHT combinations	80 (3.25)	72 (2.82)	67 (2.69)	55 (2.10)	58 (2.21)	45 (1.76)	64 (2.51)	45 (1.85)	40 (1.74)	-6.67	<0.001
		LEV combinations	166 (6.73)	359 (14.07)	491 (19.72)	678 (25.90)	830 (31.67)	927 (36.20)	1,051 (41.30)	1,066 (43.94)	1,079 (46.85)	19.60	<0.001
		LTG combinations	762 (30.91)	816 (31.99)	839 (33.69)	879 (33.58)	899 (34.30)	752 (33.27)	784 (30.81)	747 (30.79)	678 (29.44)	-0.80	0.089
		OXC combinations	631 (25.60)	672 (26.34)	686 (27.55)	706 (26.97)	674 (25.72)	668 (26.08)	695 (27.31)	681 (28.07)	632 (27.44)	0.70	0.171
	Total	VPA combinations	13,695 (53.99)	15,789 (54.47)	16,119 (54.36(	16,735 (53.76)	16,871 (53.10)	16,753 (52.32)	16,573 (51.33)	16,756 (51.74)	16,891 (50.64)	-0.9	<0.001
		CBZ combinations	10,252 (40.42)	11,473 (39.58)	11,315 (38.16)	11,279 (36.24)	11,151 (35.10)	10,623 (33.18)	10,250 (31.75)	10,058 (31.06)	9,681 (29.03)	-4.11	<0.001
		PHT combinations	4,817 (18.99)	5,580 (19.25)	5,207 (17.56)	5,066 (16.28)	4,427 (13.93)	4,535 (14.16)	4,181 (12.95)	3,412 (10.54)	3,828 (11.48)	-7.32	<0.001
		LEV combinations	1,014 (4.00)	2,005 (6.92)	3,076 (10.37)	4,383 (14.08)	5,546 (17.46)	6,784 (21.19)	8,289 (25.67)	9,667 (29.85)	10,845 (32.52)	23.74	<0.001
		LTG combinations	4,228 (16.67)	4,700 (16.21)	5,103 (17.21)	5,408 (17.37)	5,637 (17.74)	5,971 (18.65)	6,225 (19.28)	6,349 (19.61)	6,754 (20.25)	2.84	<0.001
		OXC combinations	2,692 (10.61)	3,119 (10.76)	3,445 (11.62)	3,822 (12.28)	3,950 (12.43)	4,039 (12.61)	4,331 (13.41)	4,523 (13.97)	4,788 (14.36)	3.87	<0.001
	Males	VPA combinations	8,607 (58.12)	9,888 (58.81)	10,299 (59.43)	10,724 (59.14)	10,861 (58.37)	10,883 (58.07)	10,780 (57.24)	10,965 (57.82)	11,074 (56.71)	-0.40	0.001
		CBZ combinations	5,973 (40.34)	6,691 (39.80)	6,671 (38.50)	6,671 (36.79)	6,584 (35.38)	6,323 (33.74)	6,107 (32.43)	5,999 (31.64)	5,809 (29.75)	-3.82	<0.001
Age group 2		PHT combinations	3,058 (20.65)	3,434 (20.42)	3,213 (18.54)	3,105 (17.12)	3,081 (16.56)	2,819 (15.04)	2,586 (13.73)	2,436 (12.85)	2,452 (12.56)	-6.67	<0.001
20–59 years		LEV combinations	483 (3.26)	1,020 (6.07)	1,572 (9.07)	2,321 (12.80)	2,976 (15.99)	3,696 (19.72)	4,562 (24.22)	5,360 (28.27)	6,074 (31.10)	25.23	<0.001
		LTG combinations	2,128 (14.37)	2,338 (13.91)	2,554 (14.74)	2,709 (14.94)	2,856 (15.35)	2,978 (15.89)	3,064 (16.27)	3,164 (16.69)	3,290 (16.85)	2.43	<0.001
		OXC combinations	1,565 (10.57)	1,832 (10.90)	2,027 (11.70)	2,229 (12.29)	2,336 (12.55)	2,403 (12.82)	2,564 (13.61)	2,675 (14.11)	2,849 (14.59)	4.08	<0.001
	Females	VPA combinations	5,088 (48.2)	5,901 (48.46)	5,820 (47.22)	6,011 (46.26)	6,010 (45.65)	5,870 (44.22)	5,793 (43.06)	5,791 (43.15)	5,817 (42.08)	-1.88	<0.001
		CBZ combinations	4,279 (40.54)	4,782 (39.27)	4,644 (37.68)	4,608 (35.46)	4,567 (34.69)	4,300 (32.39)	4,143 (30.80)	4,059 (30.25)	3,872 (28.01)	-4.50	<0.001
		PHT combinations	1,759 (16.66)	2,146 (17.62)	1,994 (16.18)	1,961 (15.09)	1,346 (10.22)	1,716 (12.93)	1,595 (11.86)	976 (7.27)	1,376 (9.95)	-8.52	<0.001
		LEV combinations	531 (5.03)	985 (8.09)	1,504 (12.20)	2,062 (15.87)	2,570 (19.52)	3,088 (23.26)	3,727 (27.70)	4,307 (32.09)	4,771 (34.51)	22.02	<0.001
		LTG combinations	2,100 (19.89)	2,362 (19.40)	2,549 (20.68)	2,699 (20.77)	2,781 (21.13)	2,993 (22.54)	3,161 (23.50)	3,185 (23.73)	3,464 (25.06)	3.25	<0.001
		OXC combinations	1,127 (10.68)	1,287 (10.57)	1,418 (11.50)	1,593 (12.26)	1,614 (12.26)	1,636 (12.32)	1,767 (13.13)	1,848 (13.77)	1,939 (14.03)	3.67	<0.001

Table 3. Changes in trends in use of major ASMs in duotherapy regimens according to age group and sex in PWE (continued)

Age group	Sex	ASM	Prevalence of prescription, *n* (%)									AAPC, %	*p*
			2009	2010	2011	2012	2013	2014	2015	2016	2017		
Age group 3 ≥60 years	Total	VPA combinations	3,394 (44.68)	3,955 (45.07)	4,216 (44.50)	4,461 (44.24)	4,711 (42.40)	5,064 (42.37)	5,245 (41.37)	5,837 (42.43)	6,226 (41.21)	-1.09	<0.001
		CBZ combinations	3,022 (39.78)	3,219 (36.68)	3,479 (36.72)	3,453 (34.24)	3,691 (33.22)	3,793 (31.74)	3,761 (29.66)	4,017 (29.20)	4,161 (27.54)	-4.3	<0.001
		PHT combinations	1,957 (25.76)	2,158 (24.59)	2,130 (22.48)	2,223 (22.04)	2,393 (21.54)	2,483 (20.77)	2,564 (20.22)	2,576 (18.72)	3,027 (20.03)	-3.34	<0.001
		LEV combinations	173 (2.28)	420 (4.79)	774 (8.17)	1,257 (12.47)	1,885 (16.97)	2,404 (20.11)	3,210 (25.32)	4,113 (29.90)	4,751 (31.44)	26.74	<0.001
		LTG combinations	616 (8.11)	737 (8.40)	865 (9.13)	932 (9.24)	1,050 (9.45)	1,157 (9.68)	1,314 (10.36)	1,468 (10.67)	1,622 (10.74)	3.56	<0.001
		OXC combinations	655 (8.62)	913 (10.40)	1,014 (10.70)	1,116 (11.07)	1,209 (10.88)	1,171 (9.80)	1,340 (10.57)	1,526 (11.09)	1,679 (11.11)	1.51	0.037
	Males	VPA combinations	2,116 (47.92)	2,428 (48.01)	2,594 (47.28)	2,738 (47.28)	2,851 (45.37)	3,110 (45.76)	3,212 (44.80)	3,578 (45.88)	3,777 (44.35)	-1.00	<0.001
		CBZ combinations	1,675 (37.93)	1,788 (35.36)	1,913 (34.87)	1,877 (32.41)	1,991 (31.68)	2,020 (29.72)	2,004 (27.95)	2,175 (27.89)	2,277 (26.74)	-4.30	<0.001
		PHT combinations	1,198 (27.13)	1,271 (25.13)	1, 268 (23.11)	1,331 (22.98)	1,420 (22.60)	1,444 (21.25)	1,471 (20.52)	1,477 (18.94)	1,728 (20.29)	-3.73	<0.001
		LEV combinations	84 (1.90)	218 (4.31)	427 (7.78)	733 (12.66)	1,050 (16.71)	1,371 (20.17)	1,827 (25.48)	2,364 (30.32)	2,749 (32.28)	28.02	<0.001
		LTG combinations	342 (7.74)	425 (8.40)	484 (8.82)	479 (8.27)	570 (9.07)	635 (9.34)	712 (9.93)	782 (10.03)	825 (9.69)	2.84	<0.001
		OXC combinations	379 (8.58)	529 (10.46)	601 (10.96)	667 (11.52)	714 (11.36)	709 (10.43)	804 (11.21)	872 (11.18)	968 (11.37)	1.71	0.001
	Females	VPA combinations	1,278 (40.18)	1,527 (41.06)	1,622 (40.66)	1,723 (40.14)	1,860 (38.58)	1,954 (37.90)	2,033 (36.90)	2,259 (37.90)	2,449 (37.15)	-1.29	<0.001
		CBZ combinations	1,347 (42.35)	1,431 (38.48)	1,566 (39.26)	1,576 (36.71)	1,700 (35.22)	1,773 (34.39)	1,757 (31.89)	1,842 (30.91)	1,884 (28.58)	-4.40	<0.001
		PHT combinations	759 (23.86)	887 (23.85)	862 (21.61)	892 (20.78)	973 (20.16)	1,039 (20.15)	1,093 (19.84)	1,099 (18.44)	1,299 (19.70)	-2.76	<0.001
		LEV combinations	89 (2.80)	202 (5.43)	347 (8.70)	524 (12.21)	835 (17.30)	1,033 (20.03)	1,383 (25.10)	1,749 (29.35)	2,002 (30.37)	24.98	<0.001
		LTG combinations	274 (8.61)	312 (8.39)	381 (9.55)	453 (10.55)	480 (9.94)	522 (10.12)	602 (10.93)	686 (11.51)	797 (12.09)	4.29	<0.001
		OXC combinations	276 (8.68)	384 (10.33)	413 (10.35)	449 (10.46)	495 (10.25)	462 (8.96)	536 (9.73)	654 (10.97)	711 (10.78)	1.21	0.037
Total population	Total	VPA combinations	20,138 (52.15)	22,709 (52.18)	23,157 (51.63)	24,084 (51.12)	24,379 (50.03)	24,470 (49.29)	24,329 (48.23)	25,027 (48.65)	25,371 (47.36)	-1.29	<0.001
		CBZ combinations	14,165 (36.68)	15,473 (35.55)	15,433 (34.41)	15,287 (32.45)	15,295 (31.39)	14,791 (29.79)	14,317 (28.38)	14,318 (27.83)	14,065 (26.26)	-4.11	<0.001
		PHT combinations	6,975 (18.06)	7,905 (18.16)	7,488 (16.69)	7,405 (15.72)	6,954 (14.27)	7,148 (14.40)	6,884 (13.65)	6,098 (11.85)	6,969 (13.01)	-4.97	<0.001
		LEV combinations	1,586 (4.11)	3,236 (7.44)	4,993 (11.13)	7,148 (15.17)	9,172 (18.82)	11,131 (22.42)	13,612 (26.98)	16,030 (31.16)	17,876 (33.37)	22.88	<0.001
		LTG combinations	6,493 (16.81)	7,142 (16.41)	7,712 (17.19)	8,089 (17.17)	8,472 (17.38)	8,797 (17.72)	9,068 (17.98)	9,230 (17.94)	9,713 (18.13)	1.11	<0.001
		OXC combinations	4,827 (12.50)	5,598 (12.86)	6,061 (13.51)	6,599 (14.01)	6,756 (13.86)	6,804 (13.71)	7,246 (14.36)	7,561 (14.70)	7,909 (14.77)	1.92	<0.001
	Male	VPA combinations	12,484 (55.70)	14,019 (55.91)	14,555 (55.88)	15,155 (55.70)	15,323 (54.49)	15,526 (54.19)	15,422 (53.29)	15,938 (53.78)	16,166 (52.41)	-0.8	0.001
		CBZ combinations	8,152 (36.37)	8,927 (35.60)	8,970 (34.44)	8,876 (32.62)	8,847 (31.46)	8,568 (29.90)	8,275 (28.60)	8,312 (28.05)	8,217 (26.64)	-3.92	<0.001
		PHT combinations	4,377 (19.53)	4,800 (19.14)	4,565 (17.53)	4,497 (16.53)	4,577 (16.28)	4,348 (15.17)	4,132 (14.28)	3,978 (13.42)	4,254 (13.79)	-4.78	<0.001
		LEV combinations	800 (3.57)	1,690 (6.74)	2,651 (10.18)	3,884 (14.28)	4,937 (17.56)	6,083 (21.23)	7,451 (25.75)	8,908 (30.06)	10,024 (32.50)	24.11	<0.001
		LTG combinations	3,357 (14.98)	3,652 (14.56)	3,943 (15.14)	4,058 (14.91)	4,312 (15.33)	4,430 (15.46)	4,521 (15.62)	4,612 (15.56)	4,774 (15.48)	0.7	<0.001
		OXC combinations	2,793 (12.46)	3,255 (12.98)	3,544 (13.61)	3,851 (14.15)	3,973 (14.13)	4,038 (14.09)	4,248 (14.68)	4,378 (14.77)	4,627 (15.00)	2.12	<0.001
	Female	VPA combinations	7,654 (47.24)	8,690 (47.11)	8,602 (45.74)	8,929 (44.86)	9,056 (43.94)	8,944 (42.60)	8,907 (41.41)	9,089 (41.68)	9,205 (40.51)	-2.08	<0.001
		CBZ combinations	6,013 (37.11)	6,546 (35.49)	6,463 (34.37)	6,411 (32.21)	6,448 (31.28)	6,223 (29.64)	6,042 (28.09)	6,006 (27.54)	5,848 (25.74)	-4.4	<0.001
		PHT combinations	2,598 (16.04)	3,105 (16.83)	2,923 (15.54)	2,908 (14.61)	2,377 (11.53)	2,800 (13.34)	2,752 (12.80)	2,120 (9.72)	2,715 (11.95)	-5.35	<0.001
		LEV combinations	786 (4.85)	1,546 (8.38)	2,342 (12.45)	3,264 (16.40)	4,235 (20.55)	5,048 (24.05)	6,161 (28.65)	7,122 (32.66)	7,852 (34.56)	21.53	<0.001
		LTG combinations	3,136 (19.36)	3,490 (18.92)	3,769 (20.04)	4,031 (20.25)	4,160 (20.18)	4,367 (20.80)	4,547 (21.14)	4,618 (21.18)	4,939 (21.74)	1.61	<0.001
		OXC combinations	2,034 (12.55)	2,343 (12.70)	2,517 (13.38)	2,748 (13.80)	2,783 (13.50)	2,766 (13.18)	2,998 (13.94)	3,183 (14.60)	3,282 (14.45)	1.71	<0.001

ASM, antiseizure medication; CBZ, carbamazepine; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; PHT, phenytoin; PWE, patients with epilepsy; TPM, topiramate; VPA, valproate.

2009 to 2017 among all age groups. Prescription rates for duotherapy, including VPA, were higher for males than females in all age groups throughout the 9-year study period.

In contrast, the prescription rates for newer ASM combinations such as LEV/OXC and LEV/LTG in all age groups tended to increase over time (Fig. 3). Prescription rates for duotherapy containing newer ASMs, such as LEV, LTG, and OXC, increased significantly over time except for age group 1 (Table 3). In particular, the prescription rates for LEV and OXC combinations increased in all age groups from 2009 to 2017. In 2017, LEV combinations constituted the first or second most commonly prescribed duotherapy regimens.

DISCUSSION

This study analyzed changes in the trends of ASM prescriptions over a 9-year period from 2009 to 2017 using real-world data for South Korea. We observed distinct differences in the trends of ASM utilization between sex and age groups. An increasing trend in ASM prescriptions over time was revealed in this study. As a previous study has also shown, this finding may be due to the increasing incidence and prevalence of epilepsy in South Korea from 2009 to 2017 attributable to improvements in the survival rates of elderly people and patients with chronic central nervous system illness, which is associated with a higher risk of developing epilepsy.[22] Moreover, the treatment gap, which has been reported to decrease over time in many countries, may also have contributed to our results.[23]

However, the use of monotherapy in PWE in South Korea remained relatively stable compared with polytherapy use comprising three or more ASMs. Our results are consistent with previous reports on monotherapy use based on nationwide data in other countries (46.6% in 2013 in Germany[11] and 72.6% in 2008 in the UK[12]), which fell within the previously reported range according to national or regional pediatric databases (58%–94%).[15,24] The frequency of ASM monotherapy prescriptions over the analysis period was the highest in age group 3 in the present study (Fig. 1B). This may be due to medical comorbidities and drug interactions with other medications in this age group.[25] Another potential reason for the highest frequency of monotherapy use and lowest frequency of polytherapy use with three ASMs or more in this age group is the prevalence of drug-resistant epilepsy (DRE) being lower than those in other age groups.[26,27] The International League Against Epilepsy (ILAE) defines DRE as seizures that cannot be controlled by at least two tolerated and appropriate ASMs according to relevant schedules.[28] Our observation of the prevalence of monotherapy use being highest in age group 3 is at least partly explained by this definition. A retrospective analysis of data from a single tertiary referral hospital revealed that the DRE prevalence increased from 20% in those aged 20–29 years to the highest value of 25.8% in those aged 40–49 years.[26] Similarly, in our study, age group 2 (20–59 years) exhibited the lowest frequency of monotherapy use (Fig. 1B).

In our study, females preferred monotherapy more than males from 2009 to 2017 in only age groups 2 and 3 (Fig. 1B). This result could be at least partly attributed to hormonal changes that occur during puberty. Despite inconsistencies in previous reports, the risk of epilepsy is generally in males than in females, whereas the prevalence of idiopathic generalized epilepsy is higher in females.[4,18,29-31] Further work is required to elucidate the exact mechanisms underlying these differences, although sex hormones probably play a role.[31] Similarly, the preexisting seizure frequency in young females may increase at menarche.[29,32] This may encourage physicians to prescribe ASM polytherapy for controlling seizures in adolescent females. Recent expert opinions recommend avoiding VPA for young females with epilepsy; indeed, females aged <20 years received the fewest VPA prescriptions throughout the period analyzed in the present study (Table 2). The avoidance of VPA may worsen the seizure outcomes of patients with idiopathic generalized epilepsy[33] and promote the use of combination ASMs in this group.

We noted patterns of an increasing prescription frequency for newer ASMs and a decreasing prescription frequency for older ASMs in monotherapy over the study period, which is similar to previous findings.[10,11,15,16,30] In particular, the linear trends of increasing and decreasing prescription frequencies for LEV and CBZ, respectively, were similar in the two sexes from 2009 to 2017 (Fig. 2 and Supplementary Fig. 1 in the online-only Data Supplement). Nevertheless, the proportion of VPA prescriptions (an older ASM) was the highest in monotherapy prescriptions and did not change significantly in either sex over time, although it was generally higher in males than in females due to growing concerns about the potential detrimental effects of VPA in female patients (Fig. 2 and Supplementary Fig. 1 in the online-only Data Supplement).[33] These findings could be due to the high efficacy of VPA in treating various seizure types.[33] Indeed, no other broad-spectrum ASMs have proven as effective as VPA for treating generalized seizures.[34]

Despite the superior effectiveness of VPA, caution is necessary when prescribing this drug in specific groups, including females of childbearing age and older adult patients. Particularly for older adults, VPA use may reduce the bone density and increase the occurrence of Parkinsonism.[35] In our study, the frequency of VPA prescriptions for adults aged ≥60 years was lower than that for those aged 20–59 years, with

the largest decrease in the prescription frequency observed in males aged ≥60 years (AAPC=-1.59, p<0.001) (Table 2). Among age groups, LEV and LTG prescription frequencies exhibited the largest increase in both sexes among adults aged ≥60 years, although the LTG prescription frequency in 2017 was lower than in other age groups. These findings are comparable to a recent report from a survey of 42 epileptologists in South Korea evaluating preferences for ASMs among older adults.[36]

LEV was the drug of choice for various seizure types in a recent South Korean survey.[36] This is supported by the proportion of LEV prescriptions exhibiting the largest increase over time in all age groups in the present study, with LEV being the second most commonly used drug after VPA in patients aged ≥20 years in 2017. However, in age group 1 (<20 years), OXC was the second most commonly prescribed ASM throughout the study period. The OXC prescription frequency increased significantly in both sexes. Nevertheless, the National Institute for Health and Care Excellence guideline recommends CBZ or LTG as first-line treatment for partial-onset seizures, and VPA or LTG as first-line treatment for generalized tonic–clonic seizures in children with epilepsy.[37] Our finding that OXC was preferred over LEV and LTG for children and adolescents is similar to previous reports from South Korea and China.[4,15,16] In contrast, previous studies from Western countries have produced opposing findings.[24,30,38] In a retrospective cohort analysis based on the UK Clinical Practice Research Datalink, the frequency of LEV and LTG prescriptions was higher than that of OXC up to the third ASM attempts in children aged <16 years.[30] A meta-analysis of the global ASM utilization frequency in children revealed that LTG was the most frequently prescribed newer ASM in Europe.[24] Multiple factors including clinical characteristics and race may underlie the discrepancies between the findings of Asian and European studies. LTG, which is used to treat pediatric patients in other countries,[24,30] may result in adverse skin reactions, as found in a retrospective analysis of the Korea Institute of Drug Safety and Risk Management-Korea Adverse Event Reporting System database between 2008 and 2017.[39]

OXC is a causative ASM of drug eruptions, although the proportion of severe adverse skin reactions was found to be more than twofold lower than for LTG.[39] OXC is the only ASM with Class I evidence for initial monotherapy in children with partial-onset seizures according to the ILAE guidelines,[6] and is not subject to age restrictions in South Korea. Additionally, OXC is available in various forms including as an oral solution, and has been approved by the Ministry of Korean Food and Drug Safety for monotherapy in children with epilepsy aged >4 years for longer than has LEV.

While this is evidence for the efficacy of TPM in adults with partial-onset seizures[6] and for its additional beneficial effects on migraine and obesity, this drug exhibited the largest decrease among newer ASMs in our study (AAPC=-6.29, p<0.001) (Table 2). Especially, both age groups 1 and 3—in which cognitive performance is a particularly important consideration when choosing ASM—showed a prominent decreasing trend (AAPC<-7%, p<0.001). We speculated that the adverse cognitive effects of TPM resulted in the decreasing prescription rate in South Korea during the study period, which is supported by a recent study using functional MRI finding decreased activations in cognitive frontal and parietal lobe networks in patients taking TPM.[40]

From 2009 to 2017, prescriptions for duotherapy regimens differed according to age and sex, although a decreasing frequency of older ASM prescriptions and increasing frequency of newer ASM prescriptions were confirmed in all groups. The decrease in the prescription frequency of regimens including VPA and CBZ was the largest in age group 1 (Table 3). The order of ASM combination frequencies in children aged <20 years in 2017 was consistent with that found in a study of Chinese children from 2013 to 2018: the most frequently used combination was LEV/OXC, followed by LEV/VPA and LTG/VPA.[15] The higher prescription frequencies of OXC in monotherapy and duotherapy regimens, including LEV, in this age group may have affected the composition of selected duotherapy (Fig. 3).

Despite the lack of guidelines for polytherapy, practical strategies for this have been proposed.[7,41] For example, the probability of eliciting synergistic effects might be higher for combinations of ASMs with different mechanisms of action, with LEV/OXC and VPA/LTG being notable examples.[7] Newer ASMs that operate via multiple mechanisms may also be suitable for rational polytherapy.

We also found that the increased convenience of prescribing polytherapy using newer ASMs seems to have led to an increase in the prevalence of polytherapy with three or more ASMs to control DRE. A longitudinal cohort study found that the overall seizure-freedom rate remained constant over a 30-year period, but the proportion of patients that achieved seizure freedom on ASM polytherapy progressively increased from the baseline of 3.0% to 6.4% at the first follow-up and 8.4% at the second follow-up.[42,43] Furthermore, an Italian multicenter study conducted in the era of newer ASMs showed that the burden of adverse events is likely to be related more to individual responsiveness, type of ASM combination chosen, and physical treatment skills than to the number of coprescribed ASMs or the ASM load.[44] Our results reflect the new approach to patients with DRE in the era of newer ASMs.

This study had some limitations. First, we did not analyze information on epilepsy classification and severity due to the

inherent limitations of the NHID, and so we were unable to identify changes in the ASM prescription patterns according to epilepsy type. Second, misclassification bias may exist when identifying PWE in the NHID.[21] For example, the diagnostic codes used to define epilepsy in our study may also have been entered for some patients without epilepsy in order to receive reimbursement. However, given epilepsy-related stigma, we believe that the number of such false registrations was negligible.

This was the first epidemiological study of the changes in prescription trends for ASM monotherapy and duotherapy in South Korea based on nationwide real-world evidence from 2009 to 2017. Over the 9-year study period there were major changes in treatment patterns, including an increased frequencies of newer ASM prescriptions for both monotherapy and duotherapy and of polytherapy with three or more ASMs. Further studies relevant to the domestic circumstances in South Korea should investigate the trends in ASM prescriptions over time for specific types of epilepsy.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.2.179.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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