

# Recent trends in tablet subdivision and factors affecting subdivision in South Korea

## A cross-sectional study

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### Abstract

Tablet subdivision by physicians or patients frequently occurs in various clinical settings for multiple reasons, including dose adjustment, alleviation of swallowing difficulties, or cost savings. However, not all tablets are suitable for subdivision, and it might cause side effects. It is informative to know which medicines are regularly subdivided, which healthcare institutions prescribe subdivided medicines, and to whom the medicines are prescribed from the perspectives of quality of care and patient safety. In this study, we aimed to examine recent trends in tablet subdivision and to address factors associated with subdivision of tablets both at the patient and healthcare institution levels.

The yearly claims data in 2016 retrieved from the National Patients Sample provided by the Health Insurance Review and Assessment (HIRA-NPS). This study used descriptive statistics to examine characteristics of medicines that were frequently prescribed in subdivided forms, and retrieved information regarding the medicines to assess the appropriateness for tablet splitting. Then, we selected five medicines, and performed a multivariate logistic regression analysis to estimate the effect of the variables of interest on tablet subdivision.

We presented the top 25 medicines prescribed in subdivided forms in 2016, and confirmed these medicines could be relevantly halved according to their Summary of Product Characteristics. Of the 25 medicines, 14 (56%), 5 (20%), and 3 (12%) medicines belonged to the respiratory system (R), nervous system (N), and systemic hormonal preparations (H), according to the first category of Anatomical Therapeutic Chemical (ATC) classification system, respectively. Being female at the patient level and tertiary healthcare institutions and private owned institutions at the institution level were positively associated with subdivision of medicines.

Subdivision of tablets frequently occurred for vulnerable populations with various reasons. Female and geriatric patients are prescribed split medicines for clinical reasons, while low-income patients are prescribed nonsplit medicines for cost savings. It would be better if medicines were not so small, and if they had dividing lines on their surfaces to enable successful splitting of the tablet and to protect the health of vulnerable patients. Furthermore, avoid splitting those pharmacotherapies with a narrow therapeutic range, and provide a pharmacist assistance and a splitting device for unavoidable splitting.

**Abbreviations:** ATC = Anatomical Therapeutic Chemical, FDA = United States Food and Drug Administration, HIRA = Health Insurance Review and Assessment, SPC = Summary of Product Characteristics.

**Keywords:** dose adjustment, half tablet, South Korea, tablet splitting, tablet subdivision

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## 1. Introduction

Subdivision of tablets, sometimes called tablet splitting, by physicians or patients frequently occurs in various clinical settings for multiple reasons.<sup>[1–3]</sup> Tablet subdivision by physicians has numerous advantages, such as dose adjustment and alleviation of swallowing difficulties,<sup>[4–7]</sup> in addition to enabling provision of a proper dose in cases where dose tapering and dose titration are necessary, such as for antihypertensive or statin drugs. Geriatric and pediatric patients who cannot swallow tablets also benefit from tablet subdivision. Furthermore, tablet subdivision by patients can lead to cost savings.<sup>[5,6,8,9]</sup> For instance, prices do not increase proportionally with increasing dose strength, and sometimes the use of flat rate charges for medications and medication dispensing have occurred.

However, not all tablets are suitable for subdivision.<sup>[1,2,10–12]</sup> Subdivision of extended release formulations might induce unintended consequences regarding the safety of patients.<sup>[12–14]</sup> For instance, subdivision could result in toxicity from uncontrolled release of an active ingredient and sometimes active ingredients in enteric-coated formulations are destroyed when subdivided.

Given these unintended consequences, the United States Food and Drug Administration (FDA), American Medical Society, and American Pharmacists Association have advised that subdivision of modified or sustained release, co-formulated, film-coated, friable, or dose-critical tablets is not recommended.<sup>[15]</sup>

Tablet subdivision does not necessarily result in half tablets of uniform weight.<sup>[14,16–20]</sup> Not surprisingly, the accuracy of tablet subdivision is influenced by the size, shape, and hardness of the tablet and by the subdivision method.<sup>[18–20]</sup> Small and unusually shaped tablets have the greatest deviations in weight and harder tablets are likely to be crushed or fragmented, which might lead to drug loss. Additionally, dividing tablets into quarters results in a greater range of weight differences than dividing tablets into fewer pieces. These deviations may also result in incorrect dosing that affects clinical outcomes.

Thus, from the perspectives of quality of care and patient safety, it is informative to know which medicines are regularly subdivided, which healthcare institutions prescribe subdivided medicines, and to whom the medicines are prescribed. However, little is known about tablet splitting in South Korea. In this study, we aimed to examine recent trends in tablet subdivision and to address factors associated with subdivision of tablets both at the patient and healthcare institution levels.

## 2. Methods

### 2.1. Subjects

This study was interested in the prescriptions for outpatients that required tablet subdivision. For this study, we defined a prescription with a decimal, such as 0.5 or 0.33, as a prescription requiring tablet subdivision. Thus, we excluded solutions, injections, and ointments. It should be noted that alternative dosage forms, including tablet powdering, are frequently performed for pediatric patients who cannot swallow tablets.<sup>[21]</sup> Given this, we excluded patients under the age of 15.

### 2.2. Data source

South Korea has a unique National Health Insurance program and all citizens, ~97% of the population, are covered under the program. The Health Insurance Review and Assessment (HIRA) reviews claims for reimbursement submitted by healthcare providers or healthcare institutions.<sup>[22–24]</sup> The HIRA also provides the National Patients Sample (HIRA-NPS) dataset by year. We used the 2016 HIRA-NPS dataset in this study to provide recent trends in tablet subdivision in South Korea.

The HIRA-NPS dataset is comprised of ~1.4 million individuals (~3% of the total population), randomly selected from among a population of 45 million, and their claims for reimbursement that were submitted to the HIRA.<sup>[24]</sup> It provides information on patients, health services that the patients utilized, outpatient prescriptions, and healthcare institutions. Specifically, the HIRA-NPS presents information on the sociodemographic characteristics of the patients, including sex, age grouped in 16 strata, and types of health insurance, and it provides information on healthcare institutions such as types of institutions, locations, and ownership.<sup>[24]</sup> The dataset also provides information on prescriptions for outpatients, including the active ingredients, dosage, and number of days prescribed.

### 2.3. Statistical analysis

This study used descriptive statistics to examine characteristics of medicines that were frequently prescribed in subdivided forms, and retrieved information regarding the medicines, including their shape and size, and the presence of a dividing line on the surface, from the website of the Korea Pharmaceutical Information Center (Available at <http://www.health.kr/main.asp>) to assess the appropriateness for tablet splitting. Then, we selected the five most frequently prescribed medicines in subdivided forms in the following categories of the Anatomical Therapeutic Chemical (ATC) classification system: respiratory system (R); systemic hormonal preparations, excluding sex hormones and insulins (H); nervous system (N); cardiovascular system (C); and co-formulated drug. For these five medicines, we used a chi-squared test to analyze differences in the variables of interest between two groups: a split and a nonsplit group. Furthermore, we performed a Cochran-Armitage test to examine the trends in subdivision of tablets according to the patients' ages and types of healthcare institutions.

We also performed a multivariate logistic regression analysis to estimate the effect of the variables of interest on tablet subdivision both at the patient and healthcare institution levels. At the patient level, we collected information on the sociodemographic characteristics of the patients, including sex, age, and types of health insurance. Types of health insurance included the National Health Insurance program for the total population and the Medical Aid program for low-income households.<sup>[25]</sup> At the healthcare institution level, we collected information on the location, type of institution, and ownership. First, we divided the location into several regions based on the administrative district. In the end, seven regions were created, including Seoul, Gyeonggi, Chungcheong, Gangwon, Gyeongnam, Gyeongbuk, and Jeonla. Second, we categorized the healthcare institutions by primary care, secondary care, and tertiary care<sup>[26]</sup>: primary care includes clinic-level institutions that provide healthcare services to outpatients, secondary care includes hospital-level institutions that provide services primarily to inpatients, and tertiary care includes superior general hospitals, designated by the Minister of Health and Welfare, that provide service requiring expertise for treating serious disease. Similarly, we categorized medical institutions by ownership, including public and private. Data management and analysis were conducted using R statistical software (version 3.4.3). Statistical significance is noted by *P*-values < .05.

### 2.4. Ethics

This study was approved by the Institutional Review Board of Ewha Women's University (IRB No. ewha-201812-0009-01).

## 3. Results

### 3.1. The top 25 medicines prescribed in subdivided forms

Table 1 presents the top 25 medicines prescribed in subdivided forms in 2016. Pseudoephedrine hydrochloride (60 mg), methylprednisolone (4 mg), and chlorpheniramine malate (2 mg) were the most frequently prescribed medicines in subdivided forms in South Korea. Interestingly, medicines belonging to the respiratory system were frequently prescribed in subdivided forms. Of the 25 medicines, 14 (56%), 5 (20%), and 3 (12%) medicines belonged to the respiratory system (R), nervous system (N), and systemic hormonal preparations, excluding sex hormones and

**Table 1**  
**The top 25 medicines prescribed in subdivided forms.**

Active Ingredient and strength	The ATC* code	Number of tablet splitted prescriptions	Numbers of available products <sup>†</sup>	Tablet characteristics				
				Shape	Size <sup>‡</sup>	Thickness <sup>‡</sup>	Dividing line present	Relevance on subdivision
Pseudoephedrine hydrochloride 60 mg	R	464,157	≥3	Circle	8–9	3–4	–, +, n/a	Available
Methylprednisolone 4 mg	H	226,897	≥3	Circle	7–8	2–3	+, n/a	Available
				Oval	7–8, 5–6	2–3	–, +, n/a	Available
Chlorpheniramine maleate 2 mg	R	141,506	1	Circle	6.5	2.4	n/a	Available
Diazepam 2 mg	N	139,044	≥3	Circle	7–8	2–3	–	Available
Levocetirizine dihydrochloride 5 mg	R	126,041	≥3	Circle	6–7	3–4	–	Available
				Oval	8–9, 4–5	3–4	n/a	Available
Prednisolone 5 mg	H	124,432	≥3	Circle	6–8	2–3	–, n/a	Available
Chlorpheniramine maleate 1.5 mg, Dihydrocodeine tartrate 5 mg, DL-methylephedrine hydrochloride 17.5 mg, Guaifenesin 50 mg	R	123,863	≥3	Circle	9–11	3–4	–, n/a	Available
Hydrochlorothiazide 25 mg	C	103,961	≥3	Circle	6–7	2–3	–	Available
Alprazolam 0.25 mg	N	69,798	≥3	Oval	9–10, 5–7	2–4	–	Available
Dimenhydrinate 50 mg	R	58,336	1	Circle	9	3.93	–	Available
Piprinhydrinate 3 mg	R	56,790	1	Circle	7	2	–	Available
Hydroxyzine hydrochloride 10 mg	N	47,488	1	Circle	7	2	–	Available
Mequitazine 5 mg	R	44,886	1	Circle	9	3	–	Available
Glimepiride 2 mg	A	41,233	≥3	Oval	9–11, 4–6	2–4	–	Available
Gurosemide 40 mg	C	39,312	≥3	Circle	8–9	2–3	–	Available
Azelastine hydrochloride 1 mg	R	36,397	≥3	Circle	6–7	3–4	n/a	Available
Cetirizine dihydrochloride 10 mg	R	35,536	≥3	Oval	7–11, 4–5	3–4	n/a	Available
Amitriptyline hydrochloride 10 mg,	N	29,839	≥3	Circle	6–8	2–4	n/a	Available
Caffeine anhydrous 10 mg,	R	28,786	≥3	Circle	6–10	3–5	–, n/a	Available
Chlorpheniramine maleate 1.5 mg, Dihydrocodeine tartrate 5 mg, DL-methylephedrine hydrochloride 17.5 mg								
Ebastine 10 mg	R	26,948	≥3	Oval	10–11, 4–5	3–4	–	Available
Olopatadine hydrochloride 5 mg	R	26,441	≥3	Circle	6–7	3–4	–, n/a	Available
Fenoterolhydrobromide 2.5 mg	R	25,151	≥3	Circle	6–7	2–3	–	Available
Acetaminophen 0.325 g, Tramadol hydrochloride 37.5 mg	N	24,739	≥3	Oval	15–16, 6–7	4–6	n/a	Available
Bepotastine 7.11 mg	R	23,946	≥3	Circle	7–8	2–3	–, n/a	Available
Levothyroxine sodium 50 µg	H	23,704	2	Circle	5.6	2.3	–	Available
				Oval	10.59, 5.76	3.76	–	Available

\* Anatomical therapeutic chemical classification: A (alimentary tract and metabolism); C (cardiovascular system); H (systemic hormonal preparations, excluding sex hormones and insulins); R (respiratory system); N (nervous system).

<sup>†</sup> ≥3 means that there are more than two products with the same active ingredient and the strength in the market.

<sup>‡</sup> If there is more than one product in the market, the value is provided as a range. Units of measurement is millimeters.

||– indicates half-scored tablet; + indicates quarter-scored tablet; n/a means no scored line on the tablet.

insulins (H), respectively, according to the category of the ATC classification system. Additionally, three co-formulated drugs were on the list.

We investigated the physical characteristics of the medicines, including the shape, size, and thickness, and the presence of a dividing line on the tablet surface. Note that the pharmaceutical market in South Korea is quite competitive.<sup>[27]</sup> Thus, several products with the same active ingredient and strength are available in the South Korean market. For these medicines, the value is provided as a range. All medicines on the list were circular or oval in shape, and their sizes were >6 mm in diameter, except for levothyroxine sodium (50 µg). We found several medicines without a dividing line on the surface. For instance, chlorpheniramine maleate (2 mg) with a 6.5 mm diameter does not have a dividing line on the surface. Finally, we retrieved information regarding the Summary of Product

Characteristics (SPC) from the website of the Korea Pharmaceutical Information Center to evaluate its relevance in subdivision. According to the SPC, the top 25 medicines on the list could be relevantly halved.

### 3.2. Characteristics of patients and healthcare institutions

We selected five medicines, including pseudoephedrine hydrochloride (60 mg), methylprednisolone (4 mg), diazepam (2 mg), hydrochlorothiazide (25 mg), and a co-formulated drug with guaifenesin (50 mg), in various categories of the ATC classification system to examine characteristics of patients and healthcare institutions as they related to subdivision of tablets. Then, we extracted patients who were prescribed the eligible medicines from the dataset, and categorized the patients into two groups: a split and a nonsplit group. The split group was defined as patients

**Table 2**  
**Characteristics of patients prescribed the selected medicines.**

	Pseudoephedrine hydrochloride 60 mg n=321,123			Methylprednisolone 4 mg n=282,313			Diazepam 2 mg n=81,930			Guaifenesin 50 mg + 3 others* n=339,830			Hydrochlorothiazide 25 mg n=29,953		
	Non-split	Split	P	Non-split	Split	P	Non-split	Split	P	Non-split	Split	P	Non-split	Split	P
Sex	97,585	223,538		169,969	112,344		28,128	53,802		269,627	70,203		9,360	20,593	
Male	46,594	91,266	<.0001	75,103	46,229	<.0001	10,864	18,188	<.0001	115,503	27,882	<.0001	3,574	7,225	<.0001
Female	50,991	132,272		94,866	66,115		17,264	35,614		154,124	42,321		5,786	13,368	
Age															
16–40	44,921	106,186	<.0001	69,068	44,552	<.0001	5,578	9,820	<.0001	102,161	26,406	.369	620	1,166	.001
41–65	41,006	92,585		77,274	50,303		13,800	25,571		118,998	31,075		3,988	9,067	
66–80	11,658	24,767		23,627	17,489		8,750	18,411		48,468	12,722		4,752	10,360	
Types of health insurance															
NHI program†	94,296	216,982	<.0001	164,878	108,711	<.0001	26,686	51,001	0.637	259,517	67,740	.003	8,662	19,276	.003
Medical aid program	3,289	6,556		5,091	3,633		1,442	2,801		10,110	2,463		689	1,326	

\* Chlorpheniramine maleate 1.5 mg, Dihydrocodeine tartrate 5 mg, DL-methylephedrine hydrochloride 17.5 mg.

† NHI=National Health Insurance.

who had been prescribed subdivided medicines at least one time during the study period.

Table 2 provides the descriptive statistics for patients prescribed the eligible medicines. We provide information on sex, age, and type of health insurance for the patients in the table. Significant differences between the split and nonsplit groups were consistently reported in the variable of sex. However, age and type of health insurance did not yield consistent results. For instance, 223,538 patients out of 321,123 patients (70%) were prescribed pseudoephedrine in a subdivided form, demonstrating that tablet subdivision is a routine practice in South Korea. Approximately 65% of males utilized pseudoephedrine in a subdivided form, while 72% of females utilized pseudoephedrine in a subdivided form. Additionally, a significant difference between the split and nonsplit groups was noted among age groups ( $P < .0001$ ). We also performed a Cochran-Armitage test

to investigate the trends between age groups and being prescribed the medication in a subdivided form, and found that the older the age group was, the lower the rate of being prescribed pseudoephedrine in a subdivided form ( $P < .0001$ ). Last, patients belonging to the Medical Aid program (67%) were less likely to be prescribed subdivided medicines compared to patients belonging to the National Health Insurance program (70%) ( $P < .0001$ ).

Table 3 presents the descriptive statistics for institutions prescribing the eligible medicines. The split group comprised institutions that had prescribed subdivided medicines at least one time during the study period. We provide information on the location, type of institution, and ownership of the healthcare institutions in the table. Significant differences between the split and nonsplit groups were consistently reported in the variables of location and type of institution for the five eligible medicines.

**Table 3**  
**Characteristics of healthcare institutions prescribing the selected medicines.**

	Pseudoephedrine hydrochloride 60 mg n=15,321			Methylprednisolone 4 mg n=12,346			Diazepam 2 mg n=10,165			Guaifenesin 50 mg + 3 others* n=15,543			Hydrochlorothiazide 25 mg n=9,392		
	Non-split	Split	P	Non-split	Split	P	Non-split	Split	P	Non-split	Split	P	Non-split	Split	P
Location	4,146	11,175		5,583	6,763		3,110	7,055		10,554	4,989		2,454	6,938	
Seoul	755	2,489	<.0001	1,197	1,548	<.0001	579	1,229	<.0001	2,155	1,061	.001	418	1,223	<.0001
Gyeonggi, Incheon	1,064	3,353		1,444	1,982		807	1,793		2,753	1,353		629	1,833	
Daejeon, Sejong, Chungcheong	474	1,197		498	623		341	931		1,176	593		331	794	
Gangwon	132	257		159	167		106	189		285	89		81	223	
Busan, Ulsan, Gyeongnam	612	1,633		932	1,007		504	998		1,644	786		307	1,107	
Daegu, Gyeongbuk	476	963		626	673		351	915		1,084	484		301	784	
Gwangju, Jeolla, Jeju	633	1,283		727	763		422	1,000		1,457	623		387	974	
Types of institutions															
Primary care	3,706	10,062	<.0001	5,279	6,398	<.0001	2,827	6,238	<.0001	9,279	4,621	<.0001	2,254	6,071	<.0001
Secondary care	410	831		239	191		264	510		1,123	277		187	554	
Tertiary care	30	282		65	174		19	307		152	91		13	313	
Ownership															
Public	212	184	<.0001	92	42	<.0001	41	77	0.377	461	40	<.0001	212	184	<.0001
Private	3,934	10,991		5,491	6,721		3,069	6,978		10,093	4,949		3,934	10,991	

\* Chlorpheniramine maleate 1.5 mg, Dihydrocodeine tartrate 5 mg, DL-methylephedrine hydrochloride 17.5 mg.

However, the variable of ownership did not yield consistent results. Specifically, 11,175 institutions out of 15,321 institutions (73%) prescribed pseudoephedrine in a subdivided form, demonstrating that tablet subdivision is a routine practice among healthcare providers in South Korea. A significant difference between the split and nonsplit groups was noted in the variables of location ( $P < .0001$ ), type of healthcare institution ( $P < .0001$ ), and ownership ( $P < .0001$ ).

### 3.3. Logistic regression analysis

We performed a multivariate logistic regression analysis to estimate the effect of the variables of interest on tablet subdivision both at the patient and healthcare institution levels. Table 4 shows that females (reference\_males) were positively associated with being prescribed subdivided medicines for all eligible medicines at the patient level. However, ages above 65 years old (reference\_16–40 years old) did not present consistent results. Elderly individuals were less likely to be prescribed pseudoephedrine in a subdivided form, but more likely to be prescribed subdivided methylprednisolone, diazepam, and hydrochlorothiazide than younger individuals. Table 5 also indicates that tertiary care (reference\_primary care) and privately owned institutions (reference\_public owned) and were positively correlated with prescribing subdivided medicines at the healthcare institution level.

## 4. Discussion

Physicians frequently prescribe tablets in subdivided forms for various reasons, and patients consider subdivided tablets a

normal oral drug therapy.<sup>[1]</sup> However, not all tablets are suitable for splitting.<sup>[2,10–12]</sup> Tablet subdivision might cause unintended consequences, including deviations in dose that affect clinical outcomes and patient safety.<sup>[12,14,20]</sup> Thus, tablet subdivision is an important research area from the perspectives of quality of care and patient safety. However, this issue has been neglected in South Korea. Specifically, which medicines are regularly subdivided, which healthcare institutions prescribe subdivided medicines, and to whom the medicines are prescribed remain gray areas. This study was conducted to examine recent trends in tablet subdivision and to address factors affecting subdivision in South Korea.

### 4.1. Summary of findings

Similar to other countries, tablet subdivision is a routine practice among physicians in South Korea.<sup>[1,19]</sup> In this study, we reported the most frequently prescribed medicines in subdivided forms in 2016, and confirmed that these medicines could be relevantly halved. Interestingly, the majority of these medicines belonged to the respiratory system in ATC classification system. Specifically, physicians prescribed medicines to treat nasal disease, cough, or other respiratory conditions for a short period of time in South Korea. Thus, subdivision of medicines belonging to the respiratory system category is not deemed dangerous in most cases.

However, a few medicines, which should be used with caution, are also frequently prescribed in subdivided forms. For instance, diazepam is designated as a psychotropic drug in South Korea,<sup>[28]</sup> and 70% of patients were prescribed diazepam in a subdivided

**Table 4**  
Factors affecting subdivision of tablet at the patient level.

	Pseudoephedrine hydrochloride 60 mg			Methylprednisolone 4 mg			Diazepam 2 mg			Guaifenesin 50 mg + 3 others*			Hydrochlorothiazide 25 mg		
	Estimate	Std. error	P	Estimate	Std. error	P	Estimate	Std. error	P	Estimate	Std. error	P	Estimate	Std. error	P
Sex_Female (vs Male)	0.28	0.007	<.0001	0.12	0.007	<.0001	0.20	0.015	<.0001	0.13	0.008	<.0001	0.14	0.025	<.0001
Age_(41–65) (vs 16–40) (Above 65)	–0.05	0.008	<.0001	0.01	0.008	.293	0.04	0.019	.041	0.01	0.009	.299	0.19	0.053	<.0001
Insurance_Medical Aid (vs NHI)	–0.11	0.012	<.0001	0.13	0.011	<.0001	0.17	0.021	<.0001	0.02	0.012	.204	0.15	0.052	.005
	–0.13	0.021	<.0001	0.05	0.022	.037	–0.02	0.033	.535	–0.08	0.023	.001	–0.15	0.048	.002

\* Chlorpheniramine maleate 1.5 mg, Dihydrocodeine tartrate 5 mg, DL-methylephedrine hydrochloride 17.5 mg.

**Table 5**  
Factors affecting subdivision of tablet at the healthcare institution level.

	Pseudoephedrine hydrochloride 60 mg			Methylprednisolone 4 mg			Diazepam 2 mg			Guaifenesin 50 mg + 3 others*			Hydrochlorothiazide 25 mg		
	Estimate	Std. error	P	Estimate	Std. error	P	Estimate	Std. error	P	Estimate	Std. error	P	Estimate	Std. error	P
Region (vs Seoul)															
Gyeonggi, Incheon	–0.31	0.054	.567	0.06	0.051	.219	0.05	0.066	.479	0.03	0.050	.600	0.01	0.073	.942
Daejeon, Sejong, Chungcheong	–0.23	0.068	.001	–0.03	0.071	.718	0.26	0.081	.001	0.08	0.063	.196	–0.18	0.087	.041
Gangwon	–0.49	0.116	<.0001	–0.19	0.118	.111	–0.20	0.132	.142	–0.40	0.128	.002	–0.06	0.142	.694
Busan, Ulsan, Gyeongnam	–0.18	0.063	<.0001	–0.17	0.059	.004	–0.08	0.075	.315	0.04	0.057	.458	0.20	0.086	.018
Daegu, Gyeongbuk	–0.45	0.070	.004	–0.16	0.067	.016	0.22	0.081	.006	–0.03	0.066	.679	–0.10	0.088	.259
Gwangju, Jeonla, Sejong	–0.43	0.064	<.0001	–0.19	0.065	.004	0.11	0.077	.166	–0.05	0.061	.461	–0.15	0.083	.065
Types of institutions (vs Primary care)															
Secondary care	–0.25	0.064	<.0001	–0.36	0.099	<.0001	–0.10	0.080	.203	–0.71	0.069	<.0001	0.08	0.088	.381
Tertiary care	1.48	0.197	<.0001	0.99	0.153	<.0001	2.11	0.241	<.0001	0.32	0.137	.018	2.22	0.284	<.0001
Ownership (vs Public)															
Private	1.20	0.106	<.0001	1.17	0.197	<.0001	0.67	0.213	.002	1.75	0.166	<.0001	0.33	0.105	.002

\* Chlorpheniramine maleate 1.5 mg, Dihydrocodeine tartrate 5 mg, DL-methylephedrine hydrochloride 17.5 mg.



form. Similarly, methylprednisolone, which is a synthetic glucocorticoid, is used primarily as an anti-inflammatory or immunosuppressant agent,<sup>[29]</sup> and 54% of patients were prescribed methylprednisolone in a subdivided form. Glucocorticoid therapy can cause significant morbidity and adverse events, including weight gain, skin thinning, and neuropsychiatric disorder, and these unintended consequences appeared to be dose- and duration-dependent.<sup>[30]</sup> Thus, physicians consciously attempted to decrease unnecessary glucocorticoid exposure via sparing, tapering, and subdivision.<sup>[31]</sup>

#### 4.2. Factors affecting subdivision of tablet

Tablet subdivision as recommended by physicians has the advantage of allowing for dose adjustment and aiding patients with swallowing difficulties. To this end, physicians are more likely to prescribe medicines in subdivided forms for female and geriatric patients.

In our study, we confirmed that female sex was positively associated with being prescribed subdivided medicines for the five eligible medicines, which included medicines belonging to respiratory system, systemic hormonal system, nervous system, and cardiovascular system classifications, and a combination drug for the respiratory system. However, our analysis did not yield consistent results for geriatric patients. For instance, physicians were less likely to prescribe pseudoephedrine in a subdivided form for geriatric patients, whereas physicians were more likely to prescribe methylprednisolone, diazepam, and hydrochlorothiazide in subdivided forms for geriatric patients.

The characteristics of the eligible drugs are noteworthy for understanding these interesting results. Pseudoephedrine is used as a nasal/sinus decongestant for short periods of time.<sup>[32]</sup> Similarly, combination drugs including guaifenesin are prescribed to treat a similar disease for a short period. Given the characteristics of these drugs belonging to respiratory system, it is not surprising that geriatric patients are less likely to be prescribed subdivided medicines. However, the other remaining medicines should be prescribed with caution. For instance, methylprednisolone is used to decrease inflammation or sometimes to suppress the immune system,<sup>[33]</sup> hydrochlorothiazide is prescribed to treat high blood pressure and swelling due to fluid build-up, and diazepam is used to treat a range of conditions, including anxiety.<sup>[34]</sup> Furthermore, these medicines are prescribed for long periods of time compared to the drugs belonging to the respiratory system. Thus, it is realistic to interpret the results as indicating that physicians are more likely to prescribe potent medicines in subdivided forms for geriatric patients. In the same vein, we found that tertiary-level healthcare institutions were more likely to prescribe medicines in subdivided forms. For instance, tertiary care institutions, designated by the Minister of Health and Welfare, provide medical services requiring a high level of expertise for treating serious diseases.<sup>[25]</sup> Thus, physicians at the tertiary care institutions were more likely to prescribe medicines with subdivided forms for debilitated patients.

Finally, tablet splitting by patients could lead to cost savings because the price of the drug does not increase proportionally with increasing dose strength.<sup>[6,9]</sup> In this case, physicians do not prescribe medicines in subdivided forms, and pharmacists do not need to split the medications. Instead, patients subdivided the medications on their own. In our analysis, several medicines, including pseudoephedrine, hydrochlorothiazide, and combination drugs, including

guaifenesin, were less likely to be prescribed in subdivided forms for low-income patients in the Medical Aid program.

#### 4.3. A way forward to improve patient safety

The top 25 medicines on the list could be relevantly halved. However, the size and shape of a tablet, and the presence of a dividing line on a tablet could affect weight variation when splitting the tablet.<sup>[4,18,19,35]</sup> For instance, medicines without a dividing line are less accurately split than scored tablets.<sup>[19]</sup> Furthermore, splitting a smaller size tablet is more challenging than splitting a larger size tablet.<sup>[4,35]</sup> Given this information, we assessed the appropriateness of tablet splitting for the 25 most frequently prescribed medicines. Generally, the shape of these medicines was round, their size and thickness were above 6 mm and above 2 mm, respectively, and they had dividing lines on their surfaces. However, few medicines are very small, with 5.6-mm diameters, and a few medicines do not have dividing lines on their surfaces. It would be better if these medicines were not small, and if they had dividing lines on their surfaces so that the tablet could be split successfully. In this vein, we suggest that manufacturers market low-dose medicines for the safety of vulnerable patients. Furthermore, minimizing the number of splitting and avoiding splitting pharmacotherapies with a narrow therapeutic range for vulnerable patients is essential. Pharmacists also provide assistance and a splitting device with a razor blade for unavoidable splitting.

#### 4.4. Study limitations

This study has several limitations. First, we used country-level HIRA-NPS data that do not contain information on clinical data of patients. This means that we could not assess prescription patterns by disease severity. In the same vein, this study noted subdivision of tablets by physicians or patients in various clinical settings. Subdivision by physicians is medically advised or recommended, indicating that subdivision is outside of the control of the patient or physicians, while subdivision by patients is made at the discretion of the patient for various reasons. Thus, further information on clinical data of patients are needed to determine whether tablets are subdivided by physicians or patients. Finally, this study was a cross-sectional study that provided a snapshot of tablet subdivision in 2016, indicating that it is necessary to expand the study period to fully understand trends in tablet subdivision in South Korea.

### 5. Conclusions

This study was conducted to examine recent trends in tablet subdivision and to address factors associated with subdivision both at the patient and institution levels. In this study, we reported the most frequently prescribed medicines in subdivided forms in 2016 and confirmed that these medicines could be relevantly halved. However, it would be better if medicines were not so small, and if they had dividing lines on their surfaces to enable successful splitting of the tablet and to protect the health of vulnerable patients. We also found that vulnerable populations, including females and geriatric patients, were more likely to be prescribed split medicines, while low-income patients participating in the Medical Aid program were less likely to be prescribed split medicines. This means that tablet splitting in South Korea occurs for various reasons. Female and geriatric patients are

prescribed split medicines for clinical reasons, while low-income patients are prescribed nonsplit medicines for cost savings.

### Author contributions

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### References

- Quinzler R, Gasse C, Schneider A, et al. The frequency of inappropriate tablet splitting in primary care. *Eur J Clin Pharmacol* 2006;62:1065–73.
- Chou CL, Hsu CC, Chou CY, et al. Tablet splitting of narrow therapeutic index drugs: a nationwide survey in Taiwan. *Int J Clin Pharm* 2015; 37:1235–41.
- Rodenhuis N, De Smet PA, Barends DM. The rationale of scored tablets as dosage form. *Eur J Pharm Sci* 2004;21:305–8.
- van Santen E, Barends DM, Frijlink HW. Breaking of scored tablets: a review. *Eur J Pharm Biopharm* 2002;53:139–45.
- Miller DP, Furberg CD, Small RH, et al. Controlling prescription drug expenditures: a report of success. *Am J Manag Care* 2007;13:473.
- Choe HM, Stevenson JG, Streetman DS, et al. Impact of patient financial incentives on participation and outcomes in a statin pill-splitting program. *Am J Manag Care* 2007;13:298–305.
- van Riet-Nales DA, Doeve ME, Nicia AE, et al. The accuracy, precision and sustainability of different techniques for tablet subdivision: breaking by hand and the use of tablet splitters or a kitchen knife. *Int J Pharm* 2014;466:44–51.
- Bachynsky J, Wiens C, Melnychuk K. The practice of splitting tablets. *Pharmacoeconomics* 2002;20:339–46.
- Cohen CI, Cohen SI. Potential cost savings from pill splitting of newer psychotropic medications. *Psychiatr Serv* 2000;51:527–9.
- Blix HS, Viktil KK, Moger TA, et al. Drugs with narrow therapeutic index as indicators in the risk management of hospitalised patients. *Pharm Pract* 2010;8:50–5.
- Helmy SA. Tablet splitting: is it worthwhile? Analysis of drug content and weight uniformity for half tablets of 16 commonly used medications in the outpatient setting. *J Manag Care Spec Pharm* 2015;21:76–88.
- Teixeira MT, Sa-Barreto LCL, Gratieri T, et al. Key technical aspects influencing the accuracy of tablet subdivision. *AAPS PharmSciTech* 2017;18:1393–401.
- Somogyi O, Zelko R. Pharmaceutical counseling of non-conventional dosage forms concerning the health-literacy and the patient adherence in public medication dispensing-Questionnaire surveys in Hungarian community pharmacies. *Acta Pharm Hung* 2016;86:113–27.
- Temer AC, Teixeira MT, Sa-Barreto LL, et al. Subdivision of tablets containing modified delivery technology: the case of orally disintegrating tablets. *J Pharm Innov* 2018;13:261–9.
- Food and Drug Administration. Best Practices for Tablet Splitting. 2013.
- Arnet I, von Moos M, Hersberger KE. Wrongly prescribed half tablets in a Swiss University Hospital. *Int J Clin Med* 2012;3:637.
- Quinzler R, Schmitt SP, Pritsch M, et al. Substantial reduction of inappropriate tablet splitting with computerised decision support: a prospective intervention study assessing potential benefit and harm. *BMC Med Inform Decis Making* 2009;9:30.
- Ciavarella AB, Khan MA, Gupta A, et al. Dose uniformity of scored and unscored tablets: application of the FDA tablet scoring guidance for industry. *PDA J Pharm Sci Technol* 2016;70:523–32.
- Elliott I, Mayxay M, Yeuchaixong S, et al. The practice and clinical implications of tablet splitting in international health. *Trop Med Int Health* 2014;19:754–60.
- Somogyi O, Mesk? A, Csorba L, et al. Pharmaceutical counselling about different types of tablet-splitting methods based on the results of weighing tests and mechanical development of splitting devices. *Eur J Pharm Sci* 2017;106:262–73.
- Andersson AC, Lindemalm S, Eksborg S. Dividing the tablets for children-good or bad? *Pharm Methods* 2016;7(1.):
- Kim L, Sakong J, Kim Y, et al. Developing the inpatient sample for the National Health Insurance claims data. *Health Policy Manag* 2013; 23:152–61.
- Bae SR, Seong J-M, Kim LY, et al. The epidemiology of reno-ureteral stone disease in Koreans: a nationwide population-based study. *Urolithiasis* 2014;42:109–14.
- Kim L, Kim J-A, Kim S. A guide for the utilization of health insurance review and assessment service national patient samples. *Epidemiol Health* 2014;36.
- Song YJ. The South Korean health care system. *JMAJ* 2009;52:206–9.
- Medical Services Act. Article 3 (Medical Institutions).
- Son K-B. Generic atorvastatin and rosuvastatin in the South Korean market: time of introduction in relation to manufacturer characteristics. *Expert Rev Pharmacoecon Outcomes Res* 2019;1–8. doi: 10.1080/14737167.2019.1664291.
- Systematic review of the benzodiazepines. Guidelines for data sheets on diazepam, chlordiazepoxide, medazepam, clorazepate, lorazepam, oxazepam, temazepam, triazolam, nitrazepam, and flurazepam. Committee on the Review of Medicines. *Br Med J*. 1980;280(6218):910–912. doi:10.1136/bmj.280.6218.910
- McDonough AK, Curtis JR, Saag KG. The epidemiology of glucocorticoid-associated adverse events. *Curr Opin Rheumatol* 2008;20:131–7.
- Curtis JR, Westfall AO, Allison J, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis Care Res* 2006;55:420–6.
- Carville SF, Arendt-Nielsen S, Bliddal H, et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis* 2008;67:536–41.
- Werler MM. Teratogen update: pseudoephedrine. *Birth Defects Res A Clin Mol Teratol* 2006;76:445–52.
- Behrend EN, Kemppainen RJ. Glucocorticoid therapy: pharmacology, indications, and complications. *Vet Clin Small Anim Pract* 1997;27:187–213.
- Klockhoff I, Lindblom U. Meni?e’s disease and hydrochlorothiazide (Dichlotride®)—a critical analysis of symptoms and therapeutic effects. *Acta Otolaryngol* 1967;63:347–65.
- Shah RB, Collier JS, Sayeed VA, et al. Tablet splitting of a narrow therapeutic index drug: a case with levothyroxine sodium. *AAPS PharmSciTech* 2010;11:1359–67.