



Prescription patterns and symptom relief of antitussives and expectorants in patients with cough: a nationwide study in Korea

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Background: Limited data are available on the prescription patterns and efficacy of antitussives and expectorants for patients with acute and chronic cough. This study examined the use and efficacy of these medications in a nationally representative sample of Korean patients.

Methods: We examined 4,206,016 individuals from the National Health Insurance Service (NHIS)-National Health Information Database (NHID) between 2015 and 2017. Among them, a sample of 10% (n=420,602) was retrieved for the diagnosis of respiratory diseases using the International Classification of Diseases, 10th edition (ICD-10; J00–J99), or the prescription of antitussives and expectorants for cough (ICD-10; R05). The acute cough group included those who were prescribed medications within 4 weeks of initial diagnosis (prescription within 14 days), whereas the chronic cough group included patients who were prescribed medications within 16 weeks of initial diagnosis (prescription within 56 days). If the prescription was discontinued or not changed to an alternative drug after the initial prescription, these cases were considered to have achieved symptom relief.

Results: This study included 288,460 patients (971,065 cases) with acute cough and 5,888 patients (15,399 cases) with chronic cough. ‘Expectorants, excluding combinations with cough suppressants’ had the highest prescription rates in both groups (acute cough, 63.8%; chronic cough, 61.7%), and showed the highest symptom relief regardless of the number of medications prescribed (acute cough, 84.3%; chronic cough, 70.4%).

Conclusions: ‘Expectorants, excluding combinations with cough suppressants’ were the most prescribed and effective medications for relieving cough symptoms in Korea patients. Further studies are needed to determine the optimal duration for using antitussives and expectorants in cough management.

Keywords: Cough; antitussives and expectorants; symptom relief

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Introduction

Cough is a common symptom for which medical advice is sought both in primary care and specialist practice (1,2). Acute cough is frequently observed subsequent to an upper respiratory tract infection and usually resolves spontaneously (3,4). Chronic cough is also prevalent in community populations, and it often manifests as the key symptom in many chronic respiratory diseases; however, it can also serve as the exclusive presenting feature of several extrapulmonary conditions (3,5). Despite the presence of a definitive diagnosis, managing cough can prove challenging and may result in an impaired quality of life (6-8).

It is important to investigate the cause of coughing and establish a treatment plan, particularly in patients with chronic cough (9). Nevertheless, in cases where the underlying cause of cough remains ambiguous, antitussives, expectorants, and mucolytic agents are often used as cough suppressants (10,11). For example, symptomatic relief may be achieved with antitussive preparations that are available as combinations of codeine or dextromethorphan with sedative antihistamines and expectorants (3,4).

Although it is likely that the use of antitussives and expectorants is substantial (12), there are few comprehensive data available regarding prescription patterns in nationwide database. Additionally, there are no studies on cough improvement effects or comparisons of these medications in patients with acute or chronic cough. Therefore, this study aimed to investigate the use of antitussives and expectorants and evaluate symptomatic relief from these medications in a nationally representative sample of Korean patients

with cough. We present this article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-1744/rc>).

Methods

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the National Health Insurance Service (NHIS) Institutional Review Board (IRB) (approval No. NHIS-2020-1-031) and Asan Medical Center (IRB No. 2019-1233). The IRB of the Asan Medical Center waived the requirement for informed consent because this study was conducted using the database provided by the NHIS.

Data source

We utilized data from the NHIS-National Health Information Database (NHID) provided by the NHIS. The NHIS-NHID dataset includes encrypted unique identification numbers (IDs), age, sex, primary and secondary diagnoses, admission status (inpatient or outpatient), medical institution IDs, and prescriptions. Diagnoses were coded based on the International Classification of Diseases, 10th edition (ICD-10) (13). The generic drug names were coded according to the Korean national code system.

Study population

The records of 4,206,016 individuals in the NHIS-NHID between January 1, 2015, and December 31, 2017 were examined, and approximately 10% (n=420,602) of the data were sampled for the diagnosis of respiratory diseases (ICD-10; J00-J99) or prescribed antitussives and expectorants for cough (ICD-10; R05) (*Figure 1*). Patients aged <18 years, those hospitalized for respiratory diseases, and those with incomplete records of prescription duration were excluded from the analysis.

Definition and measurement

The patient population was divided into two groups to identify the prescription patterns of antitussive and expectorant components and determine the rate of symptom relief associated with each prescription pattern

Highlight box

Key findings

- 'Expectorants, excluding combinations with cough suppressants' were the most prescribed and effective medications for Korean patients with acute and chronic cough.

What is known and what is new?

- The prescription of antitussives, expectorants, and mucolytic agents are considerable in patients with cough. However, there is limited data about prescription patterns.
- The use and efficacy of antitussives and expectorants are evaluated in a nationally representative sample of Korean patients.

What is the implication, and what should change now?

- 'Expectorants, excluding combinations with cough suppressants' were effective for cough, but more information is needed regarding the optimal duration of use.

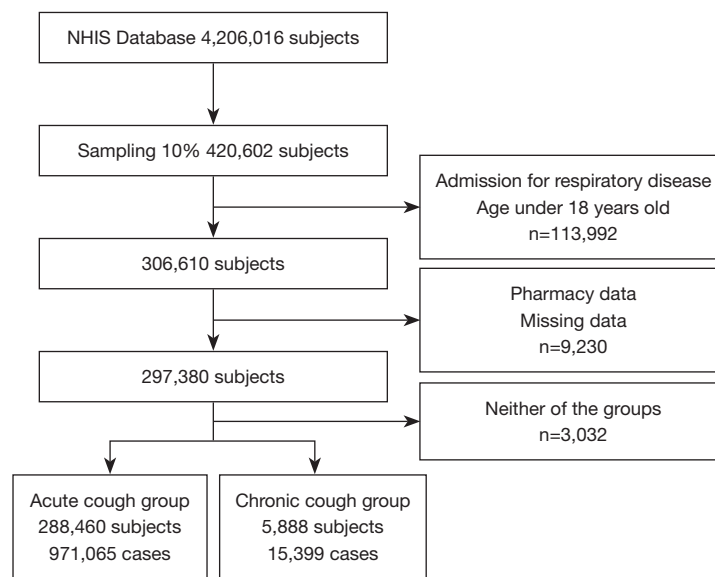


Figure 1 Flow chart of study population selection. NHIS, National Health Insurance Service.

in patients with acute and chronic cough. The acute cough group consisted of patients who prescribed medications within 4 weeks of the initial diagnosis, with a duration of no more than 14 days. The chronic cough group comprised patients who were prescribed medications within 16 weeks of the initial diagnosis, with a duration of no more than 8 weeks. Notably, patients who were defined as having both acute and chronic cough were classified as members of the chronic cough group. If the prescription was discontinued or not changed to an alternative drug during this period after the initial prescription, cases were considered to have achieved symptom relief. The major diseases in this study were respiratory diseases (J00–J99) and cough (R05). The main diagnoses include acute upper respiratory tract infections, pneumonia, chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), and interstitial lung diseases, but malignancies such as lung cancer are not included. The comorbidities of the patients were analyzed for the main diagnoses and sub-diagnoses presented in the NHIS-NHID database.

Antitussives and expectorants corresponding to the Ministry of Food and Drug Safety's drug class 222 were extracted, and their prescription frequency was analyzed by type according to the anatomical therapeutic chemical (ATC) codes ('adrenergics, inhalants', 'other drugs for obstructive airway diseases, inhalants', 'adrenergics for systemic use', 'other systemic drugs for obstructive airway

diseases', 'cough and cold preparations', 'expectorants, excl. combinations of cough suppressants and excl. combinations of expectorants', 'cough suppressants', 'expectorant combinations', and 'antihistamines for systemic use') (Table S1). Injectable and large-capacity syrup formulations were excluded. This study investigated the demographic characteristics of the patients, including age group (<20, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and ≥90 years), sex, and comorbidities.

The database provided by NHID has an identification factor that has already classified the institution, and it has been classified into general hospitals, secondary hospitals, and clinics. Others refer to health institutions, health centers, etc.

Statistical analysis

The frequency of drug prescription and drug components was analyzed in the acute and chronic cough groups. The frequencies of demographic characteristics were also analyzed. Furthermore, the main disease, comorbidities, prescription of antitussives and expectorants by the care institution, number of prescription days at the initial visit, total prescription days, and symptom relief rate by component were analyzed in both groups. All statistical analyses were performed using the SAS software (version 9.4; SAS Institute, Cary, NC, USA).

Results

Study population

The final study population consisted of 288,460 patients (971,065 cases) with acute cough and 5,888 patients (15,399 cases) with chronic cough (Figure 1). Table 1 presents the patients' demographic characteristics. Females comprised 59.2% and 50.1% of patients in the acute and chronic cough groups, respectively. Regarding age, cases involving patients aged 30–39 years (n=200,289, 20.6%), 40–49 years (n=187,324, 19.3%), and 50–59 years (n=183,117, 18.9%) accounted for 58.8% of all cases in the acute cough group, whereas cases involving patients aged 70–79 years (n=4,787, 31.1%) and 60–69 years (n=3,813, 24.8%) constituted 59.9% of all cases in the chronic cough group. The most common comorbidities in the acute and chronic cough groups were gastritis and duodenitis with prevalence rates of 10.8% and 9.4%, respectively.

Prescription patterns of antitussives and expectorants

The most common major diagnoses at the time of prescription in the acute and chronic cough groups were 'vasomotor and allergic rhinitis' (n=1,334,865, 16.3% and n=110,357, 12.6%, respectively), and 'acute bronchitis' (n=1,254,603, 15.4% and n=96,525, 11.1%, respectively) (Table 2). Moreover, 'asthma' (n=54,980, 6.3%), 'chronic sinusitis' (n=14,109, 1.6%), and 'other COPD' (n=13,974, 1.6%) were observed consecutively in the chronic cough group. However, these diagnoses were not made in the acute cough group.

The drug component of antitussives and expectorants with the highest prescription rates were 'expectorants, excl. combinations with cough suppressants' in both the acute (63.8%) and chronic (61.7%) cough groups (Figure 2). The second most commonly prescribed drug components were 'cough suppressants and expectorants, combinations' in acute cough (41.0%), and 'other systemic drugs for obstructive airway diseases' for the chronic cough group (31.3%). The most commonly prescribed drug components across all institutions were 'expectorants, excl. combinations with cough suppressants', with percentages ranging from 44.1% to 45.0% in the acute cough group and 30.5% to 41.0% in the chronic cough group (Table S2).

The mean initial prescription duration for the acute cough group was 1.1±2.2 days, with a total prescription duration was 5.0±2.7 days. The chronic cough group had a mean initial prescription duration of 2.4±8.7 days and a

total prescription duration of 99.5±37.2 days (Table 3).

Symptom relief rate according to number of drug components

The drug components that provided the highest symptom relief rates were 'expectorants, excl. combinations with cough suppressants' in the acute (84.3%) and chronic (70.4%) cough groups (Table 4). The top 30 drug components for symptom relief in patients with acute and chronic cough are presented in Tables S3,S4, respectively.

When only one drug component was initially prescribed in patients with acute cough, the following order of effectiveness was observed: 'expectorants, excl. combinations with cough suppressants' (48.4%), 'cough suppressants and expectorants, combinations' (28.8%), 'cough suppressants, excl. combinations with expectorants' (13.7%) and 'cough and cold preparations' (5.0%) (Figure 3A). This same pattern was observed in the chronic cough group as well, with the percentages for each category being: 'expectorants, excl. combinations with cough suppressants' (55.9%), 'cough suppressants and expectorants, combinations' (5.4%), 'cough suppressants, excluding combinations with expectorants' (3.1%), and 'cough and cold preparations' (0.8%) (Figure 3B). These patterns remained consistent, even when two or more drug components were prescribed to both groups. As the number of drug components increased, the symptom relief rate decreased in both groups. In the acute cough group, the symptom relief rates were 100%, 93.0%, and 51.1% for components 1, 2, and ≥3, respectively (Figure 3A). The symptom relief rates in the chronic cough group were 100%, 96.1%, and 66.0% for components 1, 2, and ≥3, respectively (Figure 3B).

Symptom relief rates based on the initial prescription days for the acute and chronic cough groups are shown in Figure S1. Regardless of the number of prescribed days, 'expectorants, excl. combinations with cough suppressants' were the most effective drug component in both the acute (62.8%) and chronic (58.0%) cough groups.

Discussion

Using a nationally representative sample of NHIS-NHID data, this study described the usage and prescription patterns of antitussives and expectorants and their symptom relief rates in a nationwide database of patients with acute and chronic cough in Korea. The drug component with the highest prescription and symptom relief rates was

Table 1 Demographic characteristics of the study population

Demographic characteristics	Acute cough (n=971,065)		Chronic cough (n=15,399)	
	N	%	N	%
Sex				
Male	396,188	40.8	7,678	49.9
Female	574,877	59.2	7,721	50.1
Age (years)				
0–19	29,593	3.0	32	0.2
20–29	135,097	13.9	212	1.4
30–39	200,289	20.6	500	3.3
40–49	187,324	19.3	1,052	6.8
50–59	183,117	18.9	2,474	16.1
60–69	131,365	13.5	3,813	24.8
70–79	81,823	8.4	4,787	31.1
80–89	21,026	2.2	2,336	15.2
≥90	1,431	0.1	193	1.3
Comorbid diagnoses				
Gastritis and duodenitis	882,389	10.8	82,001	9.4
Other soft tissue disorders, NEC	277,432	3.4	19,413	2.2
Gastro-oesophageal reflux disease	146,248	1.8	29,001	3.3
Functional dyspepsia	116,073	1.4	11,092	1.3
Essential (primary) hypertension	88,244	1.1	25,136	2.9
Dorsalgia	63,383	0.8	10,951	1.3
Disorders of lipoprotein metabolism and other lipidaemias	53,045	0.6	12,605	1.4
Headache	52,242	0.6	3,512	0.4
Heartburn	45,469	0.6	3,960	0.5
Type 2 diabetes mellitus	39,689	0.5	11,028	1.3
Urticaria	37,897	0.5	3,629	0.4
Otitis externa	31,997	0.4	3,601	0.4
Gastric ulcer	28,838	0.4	5,471	0.6
Peptic ulcer, site unspecified	28,346	0.3	3,483	0.4
Other arthritis	26,177	0.3	5,581	0.6

Acute cough was calculated as the percentage of the number of comorbid diagnoses for 8,174,311 cases and chronic cough was calculated for 872,351 cases. NEC, not elsewhere classified.

‘expectorants, excl. combinations with cough suppressants’ in both acute (63.8% prescription rate, 84.3% symptom relief rate) and chronic cough groups (61.7% prescription rate, 70.4% symptom relief rate).

Moreover, the prescription patterns and major diagnoses differed between the acute and chronic cough groups in the present study. Although we found a substantial proportion of expectorants prescriptions in both groups,

Table 2 Top 10 major diagnoses at the time of prescription

Diseases	N	%
Acute cough (n=971,065)		
Vasomotor and allergic rhinitis	1,334,865	16.3
Acute bronchitis	1,254,603	15.3
Acute laryngitis and tracheitis	385,057	4.7
Acute upper respiratory infections of multiple and unspecified sites	379,132	4.6
Acute tonsillitis	321,651	3.9
Acute pharyngitis	256,317	3.1
Acute sinusitis	254,125	3.1
Asthma	173,269	2.1
Acute nasopharyngitis (common cold)	155,543	1.9
Bronchitis, not specified as acute or chronic	155,020	1.9
Chronic cough (n=15,399)		
Vasomotor and allergic rhinitis	110,357	12.7
Acute bronchitis	96,525	11.1
Asthma	54,980	6.3
Acute laryngitis and tracheitis	25,517	2.9
Acute upper respiratory infections of multiple and unspecified sites	24,566	2.8
Bronchitis, not specified as acute or chronic	18,724	2.1
Acute sinusitis	16,587	1.9
Acute tonsillitis	15,085	1.7
Chronic sinusitis	14,109	1.6
Other COPD	13,974	1.6

Acute cough was calculated as the percentage of the number of comorbid diagnoses for 8,174,311 cases and chronic cough was calculated for 872,351 cases. COPD, chronic obstructive pulmonary disease.

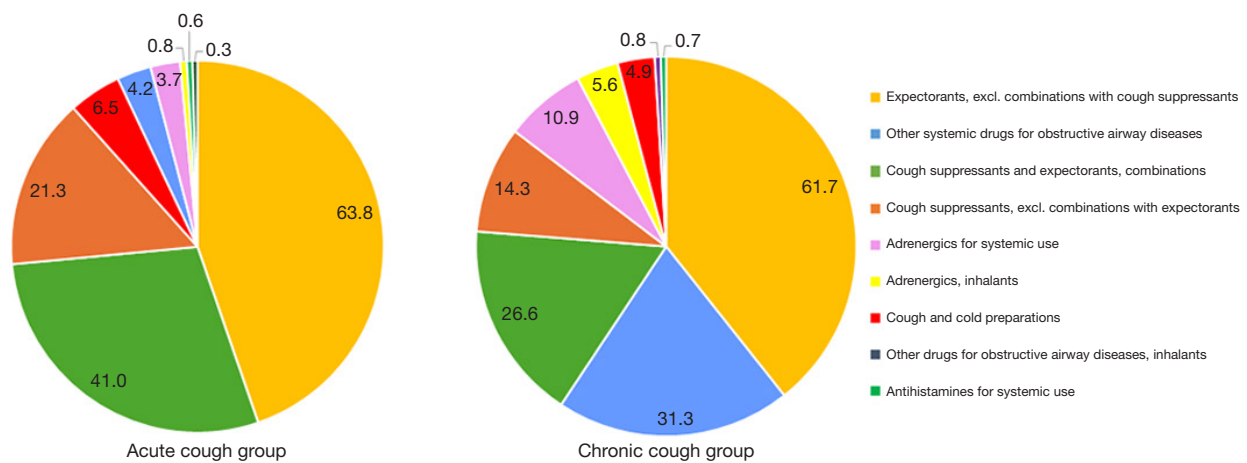


Figure 2 Prescription rate according to drug components in the acute and chronic cough groups. Excl., excluding.

Table 3 Initial and total prescription days of antitussives and expectorants

Initial and total prescription days	Acute cough (n=971,065)	Chronic cough (n=15,399)
Initial prescription (days)		
Mean ± SD	1.1±2.2	2.4±8.7
Median [min, max]	1 [0, 720]	1 [0, 180]
Total prescription (days)		
Mean ± SD	5.0±2.7	99.5±37.2
Median [min, max]	4 [1, 13]	90 [56, 392]

SD, standard deviation.

Table 4 Symptom relief rates according to antitussives and expectorants

Drug components	Acute cough (n=971,065)		Chronic cough (n=15,399)	
	Symptom relief, n/total	Symptom relief rate (%)	Symptom relief, n/total	Symptom relief rate (%)
Expectorants, excl. combinations with cough suppressants	522,042/619,267	84.3	6,693/9,507	70.4
Cough suppressants and expectorants, combinations	330,004/398,556	82.8	2,537/4,099	61.9
Cough and cold preparations	51,436/63,345	81.2	504/760	66.3
Cough suppressants, excl. combinations with expectorants	164,001/206,291	79.5	1,284/2,199	58.4

Excl., excluding.

the prescription patterns showed relatively different characteristics. Patients with an acute cough were prescribed medications primarily aimed at cough suppression, such as antitussives and expectorants. However, patients with chronic cough were prescribed 'other systemic drugs for obstructive airway diseases' drugs, such as theophylline and doxophylline, for chronic airway diseases. The variation in prescription patterns reflects the potential differences in the underlying causes between patients with acute and chronic cough.

Many common cold medications contain expectorants due to a low occurrence of side effects long-term and its affordable price (14). Most of the drug known as expectorants are mucolytics (15), and this study included ivy-leaf dried extract, acetylcysteine, bromhexine, ambroxol, and erdosteine. Although there are geographical differences in prescription, it seems that expectorants are widely used as cough-related medicines, including in Korea, where they constitute over 60% of prescriptions. For example, in Germany, over-the-counter (OTC) mucolytics such as ambroxol and N-acetylcysteine dominate the common cold OTC market, accounting for an impressive market share of up to 47.4% (16). Expectorants play a crucial role in

alleviating respiratory discomfort caused by the presence of sticky mucus in patients by liquefying the mucus and facilitating its expulsion from the airways (15). However, the evidence supporting drug therapy for patients with cough is lacking (16). Expectorants and mucolytic drugs have not been proven effective in treatment of cough in acute bronchitis (17). Some expectorants have been reported to have anti-inflammatory (18), antioxidant (19), or antitussive activity in challenge studies (20). Therefore, it would be necessary to conduct randomized controlled trials to determine whether these medications are effective in the treatment of coughing.

In some countries, non-sedating first-generation H1-histamine receptor antihistamine (H1RA) is widely prescribed for patients with cough in clinical practice (21-23). A study examining healthcare utilization in a Korean single medical center revealed that H1RA was prescribed in more than 30% of patients with subacute and chronic cough (2). However, the findings of the current study revealed a significantly low prescription rate for H1RA. This is because it extracted antitussives and expectorants with the main component code, and only ketotifen was included in antihistamines. Unfortunately, our

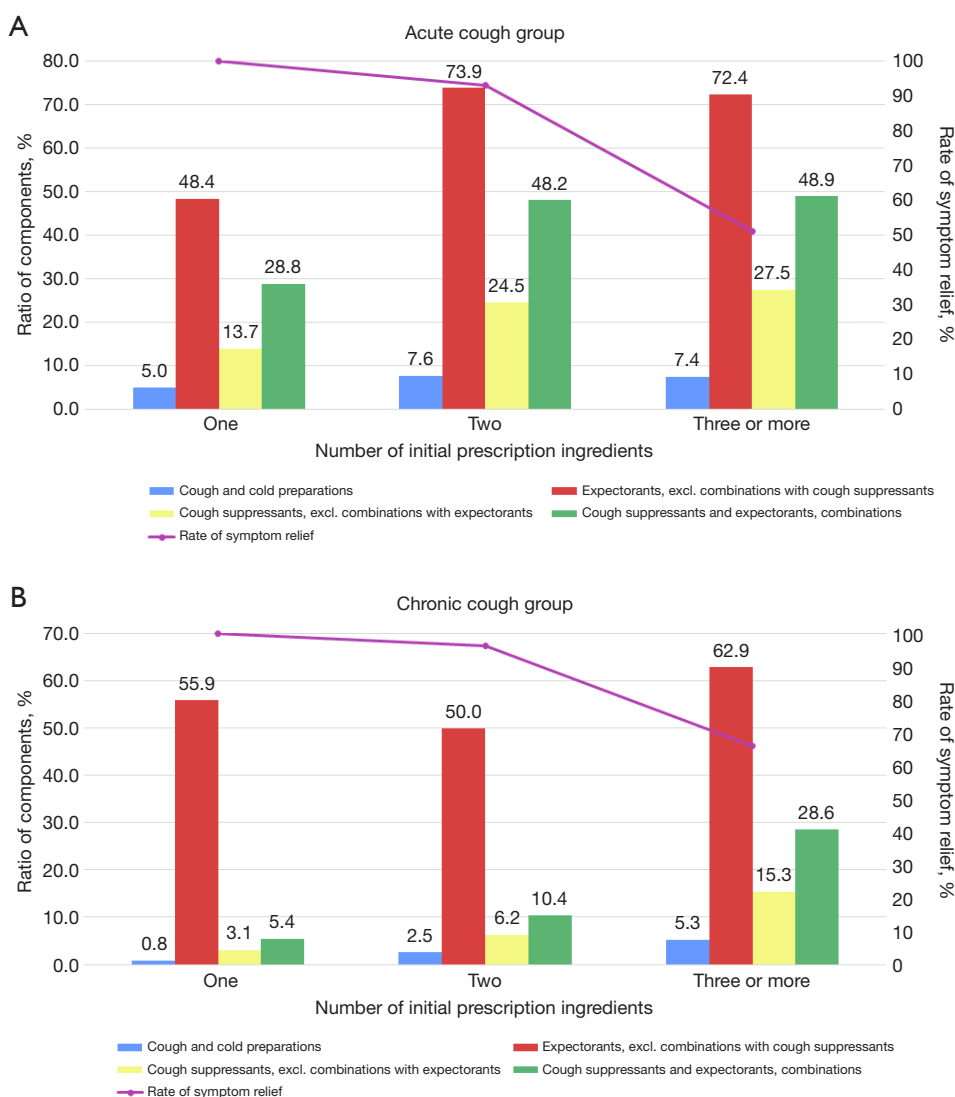


Figure 3 Ratio of drug components and symptom relief rate according to the number of initial prescription drug components in the acute (A) and chronic (B) cough groups. Excl., excluding.

findings do not represent the usage of all types of H1RA.

Acute cough is most commonly caused by an acute respiratory tract infection, and the common etiologies of chronic cough are asthma, post-nasal drip syndrome, COPD, and gastroesophageal reflux disease (24-27). Actually, this study observed differences in the major diagnoses between the acute and chronic cough groups. We found that patients with acute cough have a higher proportion of major diagnoses associated with acute respiratory infectious diseases, while patients with chronic cough represented a higher prevalence of asthma and chronic sinusitis compared to acute cough patients. As such,

this study is valuable in confirming the prescription and major diagnostic patterns of antitussives and expectorants based on population-based data from the NHIS-NHID in Korea.

Another valuable aspect of this study is that we analyzed the cough symptom relief rates according to drug components. The symptom relief rates of antitussives and expectorants were higher in patients with acute cough (84.3%) than those with chronic cough (70.4%). However, approximately 40% of patients with chronic cough do not experience any improvement in coughing. These patients would have a chronic refractory cough that is not controlled

with usual cough suppressants, requiring further evaluation and treatment of chronic cough. These findings suggest that antitussives and expectorants are not always necessary for managing cough. Furthermore, as the number of medications for antitussives and expectorants increases, symptom relief rates decreased in both the acute and chronic cough groups. This reflects a prescribing pattern in clinical practice where these medications are primarily increased due to the inadequate efficacy of coughing. Prolonged use of antitussives and expectorants lead to some problems, such as drowsiness, dizziness, nausea, and constipation (28,29). Therefore, for persistent coughing, additional diagnostic evaluation is necessary rather than increasing medication dosage and prescription duration.

This study had several limitations. First, we classified the acute and chronic cough groups based on the history of medications because this database does not include any individual information on the cough duration of each patient. When patients belong to both acute and chronic cough groups, they were classified as chronic cough, and acute cough patients may be included in the chronic cough group. Second, considering the characteristics of the NHIS-NHID database, it is not clear whether symptomatic relief of coughing indicates the actual treatment effect of the medications, spontaneous improvement, or discontinuation due to a lack of efficacy. Nevertheless, we attempted to indirectly confirm symptom relief by potentially manipulating definitions. Third, we did not confirm the use of all HIRA since this study was conducted using drugs extracted based on the component codes of antitussives and expectorants. Fourth, the use of OTC antitussives and expectorants was not evaluated. Most of these limitations are intrinsic, owing to the nature of a population-based database. Nevertheless, this study is significant as it is the first study to analyze the prescription patterns and symptom relief rates of antitussives and expectorants in patients with acute and chronic cough using a large sample size.

Conclusions

The most commonly prescribed and effective medications for relieving symptoms in patients with cough in Korea, particularly in the acute cough group, are 'expectorants, excl. combinations with cough suppressants'. Further studies are needed to better understand the optimal duration of use for antitussives and expectorants in the management of cough.

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Footnote

Provenance and Peer Review: This article was a standard submission to the series "Cough Section" published in *Journal of Thoracic Disease*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-1744/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-1744/coif>). The series "Cough Section" was commissioned by the editorial office without any funding or sponsorship. W.J.S. served as the unpaid Guest Editor of the series and serves as an unpaid editorial board member of *Journal of Thoracic Disease*. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the National Health Insurance Service (NHIS) Institutional Review Board (IRB) (approval No. NHIS-2020-1-031) and Asan Medical Center (IRB No. 2019-1233). The IRB of the Asan Medical Center waived the requirement for informed consent because this study was conducted using the database

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