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COUGH

Characterization of Codeine Treatment Responders Among Patients with Refractory or Unexplained Chronic Cough: A Prospective Real-World Cohort Study

Ji-Yoon Oh[1] · Sung-Yoon Kang[2] · Noeul Kang[3] · Ha-Kyeong Won[4] · Eun-Jung Jo[5] · Seung-Eun Lee[6] · Ji-Hyang Lee[1] · Ji-Su Shim[7] · Young-Chan Kim[8] · Youngsang Yoo[9] · Jin An[10] · Hwa Young Lee[11] · So-Young Park[12] · Mi-Yeong Kim[13] · Ji-Ho Lee[14] · Byung-Keun Kim[15] · Han-Ki Park[16] · Min-Hye Kim[7] · Sae-Hoon Kim[17] · Sang-Heon Kim[18] · Yoon-Seok Chang[17] · Sang-Hoon Kim[19] · Byung-Jae Lee[3] · Kian Fan Chung[20,21] · Sang-Heon Cho[8] · Woo-Jung Song[1] on behalf of The Korean Chronic Cough Registry Study Group

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Abstract

Purpose Codeine is a narcotic antitussive often considered for managing patients with refractory or unexplained chronic cough. This study aimed to evaluate the proportion and characteristics of patients who responded to codeine treatment in real-world practice.

Methods Data from the Korean Chronic Cough Registry, a multicenter prospective cohort study, were analyzed. Physicians assessed the response to codeine based on the timing and degree of improvement after treatment initiation. Follow-up assessments included the Leicester Cough Questionnaire and cough severity visual analog scale at six months. In a subset of subjects, objective cough frequency was evaluated following the initiation of codeine treatment.

Results Of 305 patients, 124 (40.7%) responded to treatments based on anatomic diagnostic protocols, while 181 (59.3%) remained unexplained or refractory to etiological treatments. Fifty-one subjects (16.7%) were classified as codeine treatment responders (those showing a rapid and clear response), 57 (18.7%) as partial responders, and 62 (20.3%) as non-responders. Codeine responders showed rapid improvement in objective cough frequency and severity scores within a week of the treatment. At 6 months, responders showed significantly improved scores in cough scores, compared to non-responders. Several baseline parameters were associated with a more favorable treatment response, including older age, non-productive cough, and the absence of heartburn.

Conclusions Approximately 60% of chronic cough patients in specialist clinics may require antitussive drugs. While codeine benefits some, only a limited proportion (about 20%) of patients may experience rapid and significant improvement. This underscores the urgent need for new antitussive drugs to address these unmet clinical needs.

Keywords Cough · Codeine · Treatment responders · Real-world study

Abbreviations

RUCC	Refractory or unexplained chronic cough
LCQ	Leicester Cough Questionnaire
VAS	Visual analog scale
CHQ	Cough Hypersensitivity Questionnaire
PROs	Patient-reported outcomes
GERD	Gastroesophageal reflux disease
UACS	Upper airway cough syndrome
FeNO	Fractional exhaled nitric oxide

Introduction

Codeine is a narcotic antitussive agent often considered for managing patients with refractory or unexplained chronic cough (RUCC) in several countries. Historical records indicate that opiates, including codeine, have been used as an antitussive agent for approximately 200 years [1]. Recent studies have shown that codeine- or hydrocodone-containing drugs were reported by 11.9% of patients with chronic cough in

Collaborators of the of the Korean Chronic Cough Registry Study Group are listed in Acknowledgment Section.

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community-based populations in South Korea and by 28.2% in Taiwan [2]. Moreover, reports from several specialist clinics in the United States and South Korea have shown notably high rates of codeine prescriptions for patients with refractory chronic cough, ranging from 54.0% to 79.5% [3–5].

Despite its long historical prescriptions, clinical evidence supporting treatment decisions with codeine remains sparse. Randomized controlled trials evaluating the effects of codeine exhibited methodological limitations, such as small sample sizes, an absent placebo control, unclear baseline comparability, or lack of validated outcome measures [6–9]. One randomized controlled trial found no benefits of codeine over placebo in patients with cough associated with chronic obstructive pulmonary disease [10]; however, this study did not specifically target RUCC patients. The efficacy of low-dose, slow-release morphine was demonstrated in a placebo-controlled trial for patients with RUCC [11]. A recent phase 2 clinical trial found that extended-release oral nalbuphine was more effective than placebo in reducing cough among patients with idiopathic pulmonary fibrosis [12]. Both trials suggest a role for narcotic antitussives in managing patients with refractory cough, but neither specifically focused on codeine.

Codeine is a relatively weak opiate, and its short-term use as an antitussive is generally well-tolerated in adults; and the side effects include drowsiness, constipation, dyspepsia, headache, or nausea [9]. Codeine is metabolized to morphine through the cytochrome P450 2D6 (CYP2D6) pathway, and genetic variations in CYP2D6 can influence this conversion, making the efficacy profiles of codeine more variable than morphine [13]. Nevertheless, due to regulatory restrictions on using morphine as an antitussive in many regions, and the absence of approved alternatives, codeine remains a therapeutic option for patients with RUCC in countries where morphine is not permitted for cough treatment [3, 4, 14].

Expert opinions suggest that opiates, including codeine, might be effective for less than 50% of patients with chronic cough, and those who respond to codeine treatment might experience a rapid response that, typically occurs within one or two weeks [11, 15, 16]. However, the proportion and characteristics of codeine treatment responders have not been reported in the literature. In light of this context, our objective was to investigate both the proportion and the characteristics of patients with RUCC who responded to codeine treatment in a real-world patient registry.

Methods

Study Participants

The Korean Chronic Cough Registry study is a multicenter, prospective observational cohort study that enrolls patients with chronic cough recruited from referral allergy, pulmonology, or cough clinics throughout South Korea. The baseline cohort profile and study protocols have been previously described [4].

In brief, eligible subjects were Korean adults aged 19 years or older with an active chronic cough persisting for more than 8 weeks. This included patients who were either newly referred due to chronic cough or were undergoing treatment for RUCC. The exclusion criteria were as follows: (1) the presence of a red-flag sign, such as hemoptysis, severe dyspnea, fever, or history of recurrent pneumonia; (2) abnormal findings on a physical examination or chest X-rays indicating a potentially serious medical condition; or (3) current active conditions such as malignancy, heart failure, stroke, or other severe respiratory diseases. RUCC was defined as a chronic cough of unknown origin or one that remained refractory, even after etiological investigations and treatments are conducted in accordance with current international and national cough guidelines [14, 17, 18]. All participants provided written informed consent. The study protocols received approval from the institutional review boards of each participating institution.

Baseline Assessment

The baseline assessment encompassed (1) demographic characteristics, including age, sex, body mass index (BMI), and smoking history; (2) diagnostic test results and drug prescriptions, and (3) cough characteristics, including cough duration, family history, and cough-specific patient-reported outcomes (PROs), such as the cough severity Visual Analog Scale (VAS), Leicester Cough Questionnaire (LCQ) [19], and Cough Hypersensitivity Questionnaire (CHQ) scores [20].

Diagnostic test results reviewed at baseline included chest X-rays, spirometry, bronchodilator response, methacholine challenge test, fractional exhaled nitric oxide, induced sputum, and blood eosinophil count. Chest X-rays were deemed abnormal if any grossly abnormal parenchymal lesion was identified on a formal interpretation by a radiologist.

Follow-Up Assessment

During the follow-up, study participants received care at the physician's discretion, in accordance with current international and national cough guidelines [14, 18]. Follow-ups were conducted at 6 months, during which the LCQ, CHQ, and cough severity VAS were reassessed. The proportion of subjects with minimal-to-no cough was calculated based on the patient global impression of severity (PGI-S) scale category of the LCQ score (> 16) at the routine 6-month follow-up visit [21].

Cough treatment responses were determined by physicians based on the pre-specified protocols [4]. Physicians categorized study subjects based on diagnostic evaluations and treatment outcomes collected during the six months: (1) cough responsive to a disease-specific treatment according to guideline-based anatomic diagnostic protocols (termed as 'anatomic diagnostic protocol responders') [14, 17, 18], such as cough variant asthma, eosinophilic bronchitis, gastroesophageal reflux disease (GERD), upper airway cough syndrome (UACS), or others, (2) cough not responding to anatomic diagnostic protocols but showing improvement with the administration of central neuro-modulatory drugs, such as codeine or gabapentin, and (3) cough remaining refractory to all forms of trialed treatment, including codeine (termed 'non-responders').

Definition of Codeine Treatment Responder

The primary outcome of this study was the proportion of patients who responded to codeine treatment during the 6-month follow-up. Physicians were instructed to categorize individuals receiving codeine as 'responders' (those showing a rapid and clear response), 'partial responders', or 'non-responders', based on the timing and degree of cough improvement after starting codeine. They were instructed to document treatment responses in medical records at an appropriate time following the administration of codeine. Previous clinical data and experience indicate that a cough response to opiates typically occurs within one or two weeks for responders [11, 15, 16]. Based on this criterion, we defined responders as those who exhibited a rapid and clear improvement in their cough, to the extent that it nearly disappeared within two weeks of receiving a codeine prescription. Partial responders were identified as individuals whose cough did not rapidly disappear but showed some improvement, while those who did not fit into these categories were classified as non-responders. Additionally, the daily dose of codeine administered at the time of evaluating the treatment response was recorded.

Objective Cough Frequency Evaluation

Objective cough frequency was continuously monitored for about one week following the initiation of codeine treatment in a subset of the study participants. These individuals were also involved in a study evaluating the feasibility of longitudinal cough frequency monitoring. The data presented in this paper are part of the feasibility study previously published [22]. The Hyfe Cough Tracker, a smartphone application equipped with cough-counting algorithms, was utilized for this monitoring. Daily cough severity scores, ranging from 0 to 10 (with a higher score indicating more severe cough), were also collected.

Statistical Analysis

Descriptive data are presented in formats according to the distribution type of each parameter: means ± standard deviations, medians with interquartile ranges, or percentages. Between-group differences were assessed using the Chi-squared test for categorical variables and t-tests, Mann–Whitney test, or one-way ANOVA for continuous variables. Where necessary, post hoc Tukey's multiple comparison test was employed for intergroup comparisons. A multinomial logistic regression analysis was conducted to examine baseline characteristics associated with the response to codeine treatment, adjusted for age, sex, and baseline parameters that had p values < 0.1 in the univariate analyses. Multiple correspondence analysis was conducted to visually represent interrelationships between baseline categorical parameters that displayed potential significance (p values < 0.1) in the univariate analysis. All statistical analyses were performed using the Stata/SE 17.0 software package (Stata Corporation, College Station, TX, USA) or GraphPad Prism 9.0 (GraphPad Software, La Jolla, CA, USA). All tests were two-sided, and p values were considered significant at < 0.05.

Results

Study Subjects

A total of 305 patients with chronic cough were prospectively evaluated for their response to treatment and completed the 6-month follow-up visits. One hundred and twenty-four subjects (40.7%) were responders to the anatomic diagnostic protocols, while 181 (59.3%) remained unexplained or were refractory to etiological treatments. Fifty-one subjects (16.7%) were classified as codeine treatment responders, (those showing a rapid and clear response), 57 (18.7%) as partial responders, and 62 (20.3%) as non-responders, with the response classification undetermined for 4 subjects (1.3%). Seven patients (2.3%) responded well to gabapentin or amitriptyline. Further analyses focused on the comparison of the 51 codeine treatment responders, 57 partial responders, and 62 non-responders.

Comparison of Clinical Characteristics Based on Codeine Treatment Response

The baseline characteristics were compared based on the codeine treatment response (Table 1). Codeine treatment responders were older than partial responders and non-responders (62.1 ± 11.3 years, 54.6 ± 16.1 years, and 55.1 ± 15.0 years, respectively; p = 0.012). While the proportion of females was higher in the responder and partial

responder groups than in the non-responder groups, the inter-group difference was not significant (76.5%, 75.4%, and 61.3%, respectively; p = 0.130). Among cough-associated symptoms, sputum and heartburn were less frequently reported in codeine responders. Baseline diagnostic test results showed no significant differences among the three groups, including lung function and fractional exhaled nitric oxide levels.

Table 1 Baseline characteristics

	Non-responder (n = 62)	Partial responder (n = 57)	Responder (n = 51)	*p* value
Demographic factors:				
Age (years)	55.1 ± 15.0	54.6 ± 16.1	62.1 ± 11.3	0.012
Age ≥ 60 years, %	53.2%	45.8%	69.2%	0.041
Cough duration (months)	18 (IQR 9–60)	12 (IQR 5–30)	12 (IQR 5–36)	0.169
Female sex, %	61.3	75.4	76.5	0.130
Smoking, %				0.147
Never	72.6	75.4	86.3	
Former	25.8	17.5	9.8	
Current	1.6	7.0	3.9	
BMI (kg/m^2)	24.9 ± 4.6	25.5 ± 4.4	24.5 ± 3.7	0.470
Family history of chronic cough, %	26.7	26.8	17.7	0.449
Associated symptoms				
Sputum, %	53.3	70.2	44.9	0.026
Dyspnea, %	16.4	22.8	16.0	0.580
Wheeze, %	18.3	15.8	14.0	0.824
Acid regurgitation, %	18.0	21.1	12.0	0.457
Rhinorrhea, %	33.9	31.6	41.2	0.558
Nasal obstruction, %	8.6	21.1	7.8	0.062
Anosmia, %	6.7	7.0	2.0	0.433
Heartburn, %	18.3	15.8	2.0	0.024
Snoring, %	22.7	4.8	11.1	0.209
Comorbidities				
Hypertension, %	25.4	24.6	40.0	0.150
Diabetes mellitus, %	6.8	10.5	16.0	0.303
Arrythmia, %	3.4	1.8	2.0	0.827
Gastroesophageal reflux disease, %	13.3	19.3	18.0	0.663
Asthma, %	8.3	15.8	10.0	0.418
Diagnostic test results				
CXR abnormality, %	15.0	7.8	8.3	0.391
FEV1, %	91.6 ± 13.2	89.4 ± 16.3	94.2 ± 12.5	0.232
FVC, %	88.2 ± 13.2	86.3 ± 14.9	90.6 ± 10.6	0.269
FEV1/FVC ratio	81.1 ± 6.9	82.4 ± 7.2	80.3 ± 5.8	0.362
FeNO, ppb	20.5 ± 13.1	20.3 ± 13.7	20.9 ± 13.3	0.975
Blood eosinophils, % (n/n)	2.5 ± 1.7 (39/62)	2.4 ± 1.7 (31/57)	2.3 ± 1.5 (30/51)	0.955
Sputum eosinophils, % (n/n)	2.2 ± 5.0 (13/62)	0.1 ± 0.4 (8/57)	0.7 ± 1.2 (3/51)	0.486
Bronchodilator response (+), % (n/n)	18.8 (3/16)	0 (0/20)	4.8 (1/21)	0.080
Methacholine challenge test (+), % (n/n)	0 (0/22)	11.1 (2/18)	0 (0/13)	0.133
Baseline cough-specific PRO score				
LCQ score (3–21)	10.5 ± 3.9	10.7 ± 3.5	10.9 ± 3.3	0.887
CHQ score (0–22)	9.4 ± 4.2	9.5 ± 4.0	7.9 ± 3.5	0.068
Cough VAS score (0–100)	66.4 ± 25.4	61.1 ± 23.8	55.7 ± 24.0	0.074

BMI body mass index, *CXR* chest X-ray, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *FeNO* fractional exhaled nitric oxide, *PRO* patient-reported outcome, *LCQ* Leicester Cough Questionnaire, *CHQ* Cough Hypersensitivity Questionnaire, *VAS* visual analogue scale

P values were determined by Chi-squared test or one-way ANOVA test

Furthermore, there were no significant differences in the daily codeine dosages prescribed at the time of codeine treatment response evaluation among the groups: non-responders (36.6 ± 24.8 mg), partial responders (31.5 ± 14.6 mg), and responders (30.8 ± 20.3 mg), respectively (p = 0.248).

Changes in Cough-Specific PRO Scores Over 6 Months of Follow-Up

Cough-specific PRO scores were similar at the time of baseline recruitment. However, at the routine six-month follow-up visit, responders reported significantly improved cough scores compared with non-responders: LCQ score (14.8 ± 3.7 vs. 11.8 ± 3.7, p = 0.001), CHQ score (5.4 ± 3.5 vs. 9.4 ± 4.2, p < 0.001), and cough severity VAS score (29.8 ± 22.9 vs. 55.7 ± 23.6, p < 0.001). The CHQ score at the routine six-month follow-up was also significantly lower for responders than for partial responders, (5.4 ± 3.5 vs. 8.3 ± 4.5, p = 0.008) (Fig. 1).

In an analysis using the PGI-S category of the LCQ score [21], the proportions of subjects with minimal-to-no cough at the six-month follow-up visit (defined as a score > 16.0) were 38.6% for responders, 27.7% for partial responders, and 12.5% for non-responders (p = 0.010).

Characterization of Cough Responses in Codeine Treatment Responders and Non-responders

To confirm cough reduction following the initiation of codeine treatment, we examined both the objective cough frequency and subjective cough severity scores for approximately one week in responders and non-responders. This data was retrieved from our feasibility study [22]: 20 patients with RUCC participated in both the patient registry and feasibility studies, and thus their data were investigated. Of these patients, 6 were classified as responders, 8 as non-responders, and the categorization of the remaining 6 was unclear. Patients who responded to codeine treatment (n = 6) exhibited a rapid reduction in cough frequency after starting the treatment. In contrast, non-responders (n = 8) showed no such reduction (Fig. 2A and B). Similar patterns were observed in daily cough severity scores for both responders and non-responders (Fig. 2C and D).

Predictors for Codeine Treatment Response

A multinomial logistic regression analysis was conducted to identify baseline factors associated with a favorable response to codeine treatment when compared to non-responders. Responders were significantly older (p = 0.020), more likely to be female (p = 0.048) and had less heartburn (p = 0.036) than non-responders (Table 2). Figure 3 further illustrates that while non-responders were more commonly male, responders tended to be older (over 60 years of age), female, and exhibited fewer associated symptoms.

Drug Prescription at 6-Month Follow-Up Visit

Codeine treatment responders were prescribed a mean of 1.1 ± 1.3 medications at the 6-month follow-up visit, which was significantly lower than the 2.0 ± 1.5 drugs prescribed to partial responders or the 2.8 ± 1.5 prescribed to non-responders (p < 0.001; Table 3). The most common medication prescribed to codeine treatment responders was codeine (95.2%), followed by histamine H1-receptor antagonist (H1RA) (23.8%) and leukotriene receptor antagonist (LTRA) (23.8%). Codeine was still frequently prescribed to non-responders (78.9%), followed by inhaled corticosteroids (ICS) (50.0%), H1RA (43.1%), LTRA (41.2%), proton pump inhibitors (PPI) (34.6%), and macrolides (25.5%) (Table 3).

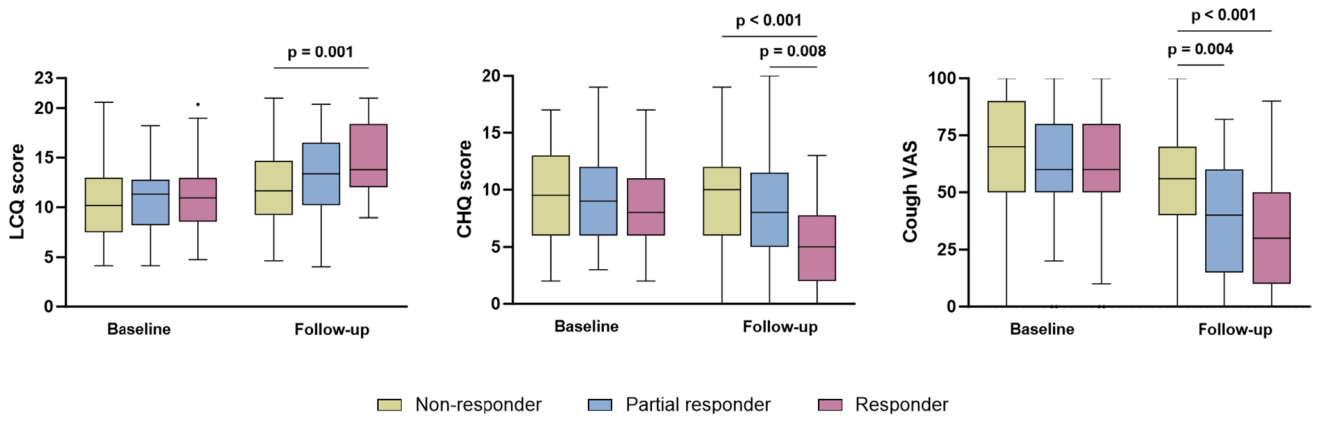

Fig. 1 Comparison of cough-specific patient reported outcomes at baseline and 6-month follow-up visits by codeine treatment response. Only p values with statistical significance (< 0.05) are indicated for inter-group comparisons. *LCQ* Leicester Cough Questionnaire, *CHQ* Cough Hypersensitivity Questionnaire, *VAS* visual analogue scale

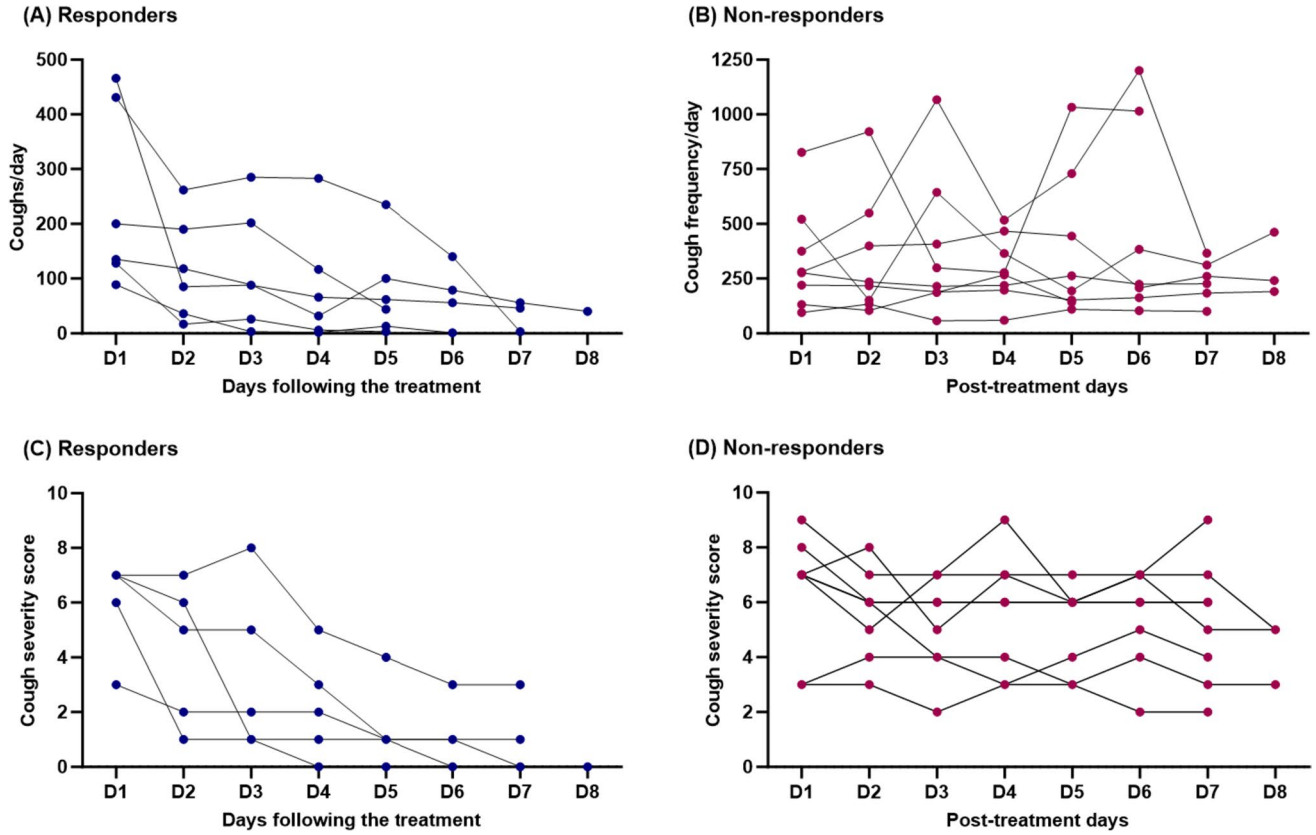

Fig. 2 Changes in daily objective cough frequency (**A**, **B**) and cough severity scores (**C**, **D**) following codeine treatment in responders (n = 6) and non-responders (n = 8). Cough severity score data was unavailable in one responder

Table 2 Multinomial logistic regression for codeine treatment response

vs. Non-responder (as reference)	Partial responder		Responder	
Baseline parameter	Adjusted OR (95% CI)*	*p* value	Adjusted OR (95% CI)*	*p* value
Age (years)	1.00 (0.98–1.03)	0.865	1.04 (1.01–1.07)	0.020
Female (vs. male)	1.91 (0.82–4.45)	0.134	2.64 (1.01–6.91)	0.048
Sputum (yes vs. no)	2.18 (0.96–4.95)	0.063	0.88 (0.38–2.06)	0.773
Nasal obstruction (yes vs. no)	3.01 (0.94–10.01)	0.063	1.05 (0.20–5.43)	0.952
Heartburn (yes vs. no)	0.72 (0.25–2.10)	0.551	0.10 (0.01–0.86)	0.036
CHQ (score)	0.99 (0.90–1.10)	0.910	0.93 (0.83–1.04)	0.220
Cough VAS (score)	0.99 (0.97–1.00)	0.149	0.99 (0.97–1.00)	0.124

OR, odds ratio*; 95% CI,* 95% confidence intervals

*Adjusted for age, sex, sputum, nasal obstruction, heartburn, CHQ score, and cough VAS score

CHQ Cough Hypersensitivity Questionnaire, *VAS* visual analogue scale

Discussion

To our knowledge, this is the first study to characterize patients with RUCC responding to codeine treatment in a real-world patient registry. We conducted a prospective analysis of 305 participants from the Korean Chronic Cough Registry. Our findings indicated that 40.7% of these participants were responders to the anatomic diagnostic protocol, whereas 59.3% did not respond to these protocols and required antitussive drugs. Out of the total participants, 36.7% responded to codeine treatment, with about half of these exhibiting a clear and rapid response. This data aligns with expert opinions suggesting that less than 40% of patients with chronic cough may experience a favorable response to opiates [15]. However,

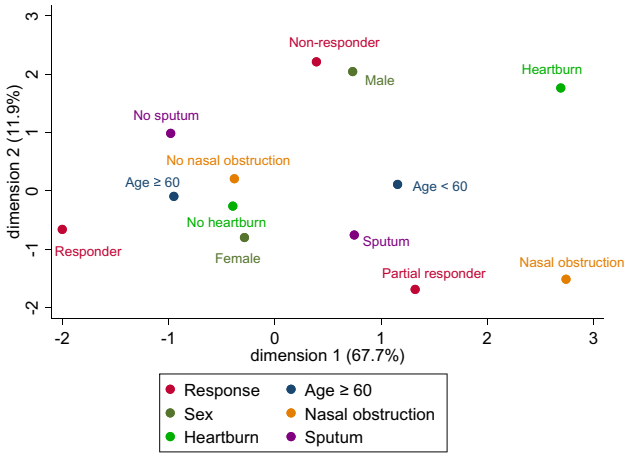

Fig. 3 Multiple correspondence analysis for predictors of codeine treatment response

Table 3 Medications prescribed at the 6-month follow-up visit

	Non-responder (n = 51)	Partial responder (n = 53)	Responder (n = 42)	*p* value
Codeine, %	78.9	77.4	95.2	0.043
H1RA, %	43.1	43.4	23.8	0.090
H2RA, %	5.8	5.7	4.8	0.974
ICS, %	50.0	37.7	16.7	0.004
OCS, %	19.2	1.9	7.1	0.008
PPI, %	34.6	17.3	7.1	0.004
LTRA, %	41.2	22.6	23.8	0.074
LABA, %	40.4	34.0	14.3	0.019
LAMA, %	2.0	5.7	2.4	0.530
Gabapentin, pregabalin, or amitriptyline, %	15.4	26.9	11.9	0.136
Macrolide, %	25.5	5.8	0.0	< 0.001
Number of medications (except codeine)	2.8 ± 1.5	2.0 ± 1.5	1.1 ± 1.3	< 0.001

H1RA histamine H1-receptor antagonists, *H2RA* histamine H2-receptor antagonists, *ICS* inhaled corticosteroids, *OCS* oral corticosteroids, *PPI* proton pump inhibitors, *LTRA* leukotriene receptor antagonists, *LABA* long-acting beta2-agonists, *LAMA* long-acting muscarinic receptor antagonists

non-responders and partial responders still represent a significant portion. The high rate of poor response underscores the existence of an unmet clinical need.

While it is often conceived that certain patient phenotypes, such as those with dry cough and laryngeal sensations, might respond better to codeine, this was not fully supported by our findings. The baseline CHQ scores, which reflect the degree of cough-related laryngeal sensations and cough triggers, were similar between codeine responders and non-responders. Instead, our multivariate analysis suggested several baseline parameters that were positively associated with a better response to codeine, including older age, female sex, and fewer concomitant symptoms. Given that females tend to have a heightened cough reflex sensitivity compared to males, the action of codeine on the neural network in the brainstem might be more effective in females [23]. We also observed that codeine responders experienced less sputum or heartburn. This implies that managing cough-triggering conditions could enhance the efficacy of antitussive drugs. However, such clinical information still does not provide mechanistic insights into how the antitussive drugs work. Therefore, an endotype approach may be necessary to identify biomarkers indicative of responsiveness to antitussive treatments.

Codeine treatment non-responders were prescribed more medications than responders (2.8 ± 1.5 vs. 1.1 ± 1.3, $p < 0.001$), while the cough control status remained poor among the non-responders. These individuals represent a group of patients with urgent, unmet clinical needs that require better treatment options. Surprisingly, codeine was still frequently prescribed to non-responders (78.9%) at 6-month follow-up visit; we speculate that there are two possible explanations. First, codeine prescription might have been unavoidable in non-responders due to the lack of effective alternative antitussive drugs. The prescription rate of cough neuromodulators, such as gabapentin or amitriptyline, was only 15.4%, and these neuromodulators were not effective in these patients. Second, it is also possible that clinicians were not well-informed about codeine response characteristics. Therefore, implementing stewardship or training programs focused on the use of narcotic antitussives may be necessary. Indeed, there is a recognized need for specialized cough training, which should include guidance on the proper use of antitussive drugs, as highlighted in a recent Delphi study [24].

The data from the six-month follow-up visit, comparing the number of drug prescriptions, suggest that the use of appropriate antitussives may lead to a reduction in overall medication usage in patients with RUCC. However, the PRO scores at 6 months suggest that codeine alone may not completely alleviate the cough, even among those who were considered to have responded to it. According to the PGI-S category-based analysis, only 38.6% of codeine treatment responders had minimal-to-no cough at the follow-up visit (as indicated by a LCQ score > 16.0 [21]), although this proportion was still higher than that of partial responses (27.7%) or non-responders (12.5%).

Several limitations should be noted. First, our definition of treatment responses was primarily based on physician assessments, rather than on changes in PROs before and

after codeine treatment. The cohort study was not specifically designed to focus on codeine treatment; rather, its purpose was to collect data on clinical status during routine 6-month follow-up intervals. Throughout these follow-ups, care was administered at the physician's discretion, and specific treatment decisions, including the use of codeine, were not controlled by the study protocols.

Second, placebo effects could not be controlled in this study. Distinguishing a genuine treatment response from either a placebo effect or natural cough improvement can be challenging in an observational study of chronic respiratory conditions [25, 26]. Also, these effects might be influenced by prior treatment experiences. Our definition was based on the typical characteristics of opioid treatment responses of cough that are rapid and clearly shown within 1–2 weeks of initiation among its responders [11, 15, 16]. We also presented the changes in objective cough frequency and cough severity scores following codeine treatment, although these observations were limited to a small subset of the study subjects.

Third, our analysis did not focus on calculating the effect size of codeine treatment, as cough PRO scores were collected at routine 6-month intervals during cohort follow-ups, but not at the time of maximum codeine response. The mean dose of 30 mg might be considered low for demonstrating optimal clinical effects. However, the treatment dosage regimen was not dictated by the study protocols but was instead determined by the physician's discretion. Also, the actual doses taken could not be verified. Therefore, the observed responses are reflective of the effectiveness outcomes obtained in real-world practice. The pharmacokinetics of the commonly used dose and impact of CYP2D6 genetic polymorphism on the codeine treatment responses warrant further investigation.

Fourth, there is a potential risk of recall bias in the treatment response definition. However, physicians were instructed to document these responses in medical records at an appropriate time after codeine treatment. Fifth, the present study did not collect information on the tolerability and side effects of codeine treatment. It is important to note that potential benefits and harms should be weighed when considering the use of narcotic antitussives for cough control. Finally, our study did not include objective measures of cough frequency in all subjects. This limitation stems from the study design, which relies on real-world clinical practice. While we reported changes in cough frequency among some participants, the reliability of the cough-counting mobile application requires further investigation in real-world settings. Despite these limitations, our research is the first to report in detail the characteristics of codeine treatment responders in a prospective patient registry.

In conclusion, approximately 60% of patients with chronic cough referred to specialist clinics may not respond to anatomic diagnostic protocols but require antitussive drugs. Phenotypic parameters such as older age, female sex, and the presence of an isolated dry cough were associated with a better response to codeine. However, only about 20–30% of patients may respond well to codeine treatment. This highlights the urgent need for new antitussive drugs to address the unmet clinical needs of patients with RUCC.

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Declarations

Conflict of interest WJS declares grants from Merck Sharp & Dohme Corp. and AstraZeneca, consulting fees from Merck, AstraZeneca, Shionogi, Bellus, and GSK, and lecture fees from Merck, AstraZeneca, GSK, Sanofi, and Novartis. Other authors declare that they have no competing interests.

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Authors and Affiliations

Ji-Yoon Oh[1] · Sung-Yoon Kang[2] · Noeul Kang[3] · Ha-Kyeong Won[4] · Eun-Jung Jo[5] · Seung-Eun Lee[6] · Ji-Hyang Lee[1] · Ji-Su Shim[7] · Young-Chan Kim[8] · Youngsang Yoo[9] · Jin An[10] · Hwa Young Lee[11] · So-Young Park[12] · Mi-Yeong Kim[13] · Ji-Ho Lee[14] · Byung-Keun Kim[15] · Han-Ki Park[16] · Min-Hye Kim[7] · Sae-Hoon Kim[17] · Sang-Heon Kim[18] · Yoon-Seok Chang[17] · Sang-Hoon Kim[19] · Byung-Jae Lee[3] · Kian Fan Chung[20,21] · Sang-Heon Cho[8] · Woo-Jung Song[1] on behalf of The Korean Chronic Cough Registry Study Group

✉ Woo-Jung Song
swj0126@amc.seoul.kr

[1] Department of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-Ro 43-Gil, Songpa-Gu, Seoul 05505, Korea

[2] Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Korea

[3] Division of Allergy, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

[4] Department of Internal Medicine, Veterans Health Service Medical Center, Seoul, Korea

[5] Department of Internal Medicine, School of Medicine, Pusan National University, Busan, Korea

[6] Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan, Korea

[7] Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul, Korea

[8] Division of Allergy and Clinical Immunology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

[9] Department of Allergy and Clinical Immunology, Gangneung Asan Hospital, University of Ulsan College of Medicine, Gangneung, Korea

[10] Department of Pulmonary, Allergy and Critical Care Medicine, Kyung Hee University Hospital at Gangdong, College of Medicine, Kyung Hee University, Seoul, Korea

[11] Division of Allergy, Department of Internal Medicine, Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

[12] Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea

[13] Department of Internal Medicine, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea

[14] Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea

[15] Division of Pulmonology, Allergy and Critical Care Medicine, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea

[16] Department of Allergy and Clinical Immunology, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Daegu, Korea

[17] Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

[18] Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Korea

[19] Department of Internal Medicine, Eulji University College of Medicine, Seoul, Korea

[20] National Heart and Lung Institute, Imperial College London, London, UK

[21] Royal Brompton and Harefield Hospitals, London, UK