Unexplained Chronic Cough: Approaches and Management

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Contents

- Definition of Chronic cough
- Approaches of Chronic cough
- Management of Chronic cough

Definition of Cough

- All coughs are acute at the outset;

- the duration of the cough is important because it suggests the likely cause.
    - Acute cough lasts for less than 3 weeks,
    - a subacute cough 3 to 8 weeks, and
    - a chronic cough more than 8 weeks.
- The 8-week duration is based on data suggesting that postinfectious coughs due to viral, mycoplasma, or chlamydophila infections should not last longer.

Definition of Cough

- Phenotypes of chronic cough ; Explained
  - Asthmatic cough/eosinophilic bronchitis
  - Reflux cough
  - Upper airways cough syndrome/postnasal drip syndrome
  - Iatrogenic cough

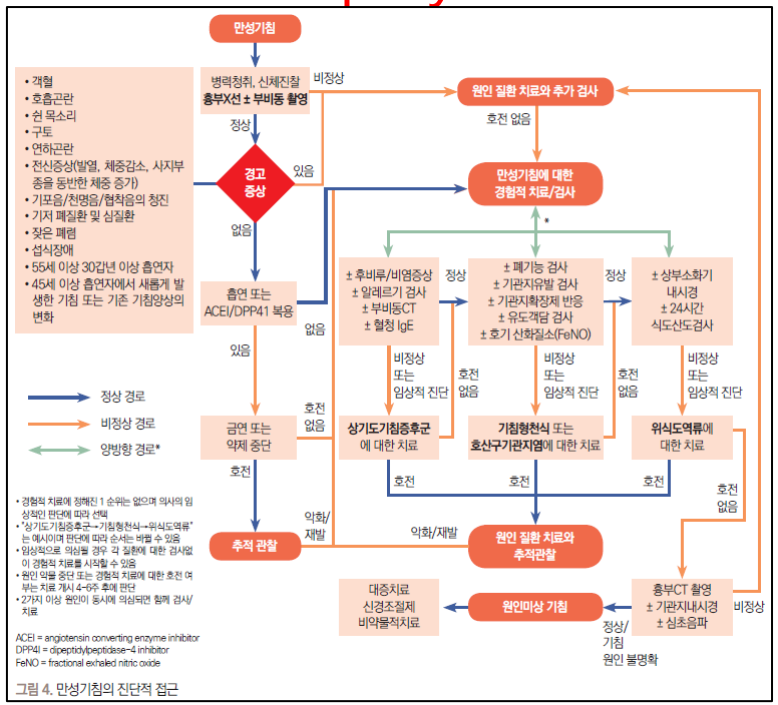


그림 4. 만성기침의 진단적 접근

ERJ 2020 55(1): 1901136
2020 개정 기침진료지침

Definition of Chronic cough

- **Unexplained Chronic Cough (UCC)**
  - 환자가 가이드라인에 따른 완전한 검사를 모두 받았음에도 불구하고, 기침의 원인이 확인되지 않은 경우

  ⇒ 원인 불명으로 남아 있는 상태
- **Explained but Refractory Chronic Cough (RCC)**
  - 천식, GERD, UACS 같은 기침 관련 질환이 진단되었으나 표준 치료를 했음에도 불구하고 기침이 지속되는 경우

  ⇒ 원인은 있지만 치료에 잘 반응하지 않는 상태
- **Unexplained Refractory Chronic Cough**
  - 진단적 검사에서도 원인이 밝혀지지 않고, 경험적 치료에도 반응하지 않는 경우.

  ⇒ 원인 규명도 안 되고, 치료도 듣지 않는 상태

N Engl J Med 2025;392:1203-14.

Prevalence of chronic cough

- Chronic cough affects ~10% of adults in various general populations.
- The prevalence of chronic cough is higher in Europe, America and Australia (10–20%) than in Asia (<5%).

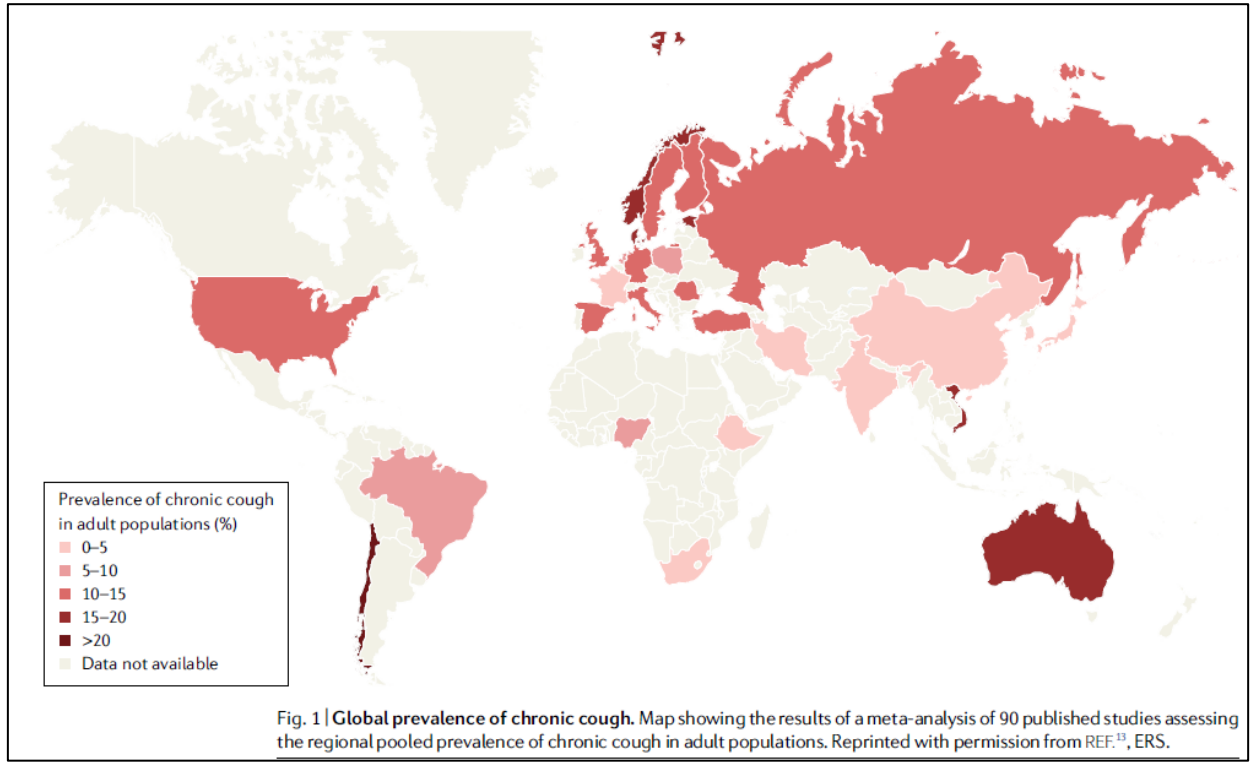


Fig. 1 | **Global prevalence of chronic cough.** Map showing the results of a meta-analysis of 90 published studies assessing the regional pooled prevalence of chronic cough in adult populations. Reprinted with permission from REF.[13], ERS.

Nat Rev Dis Primers. 2022 Jun 30;8(1):45.

Prevalence of chronic cough

- Westernized countries is close to 5% of the general population
  - 5.0% in the USA,
  - 5.5% in Spain and
  - 4.8% in France.
- Refractory chronic cough is estimated to account for approximately 15% of cases among chronic cough patients.

Drugs (2024) 84:763–777
J Allergy Clin Immunol Pract. 2021;9(11):4037–44 (e4032).
Chron Respir Dis. 2022;19:14799731221098722.
ERJ Open Res. 2024;10(2):00806.

Prevalence of chronic cough, Korea

- The point prevalences of acute, subacute, and chronic cough were 2.5 ± 0.2%, 0.8 ± 0.1% and 2.6 ± 0.2%, respectively.

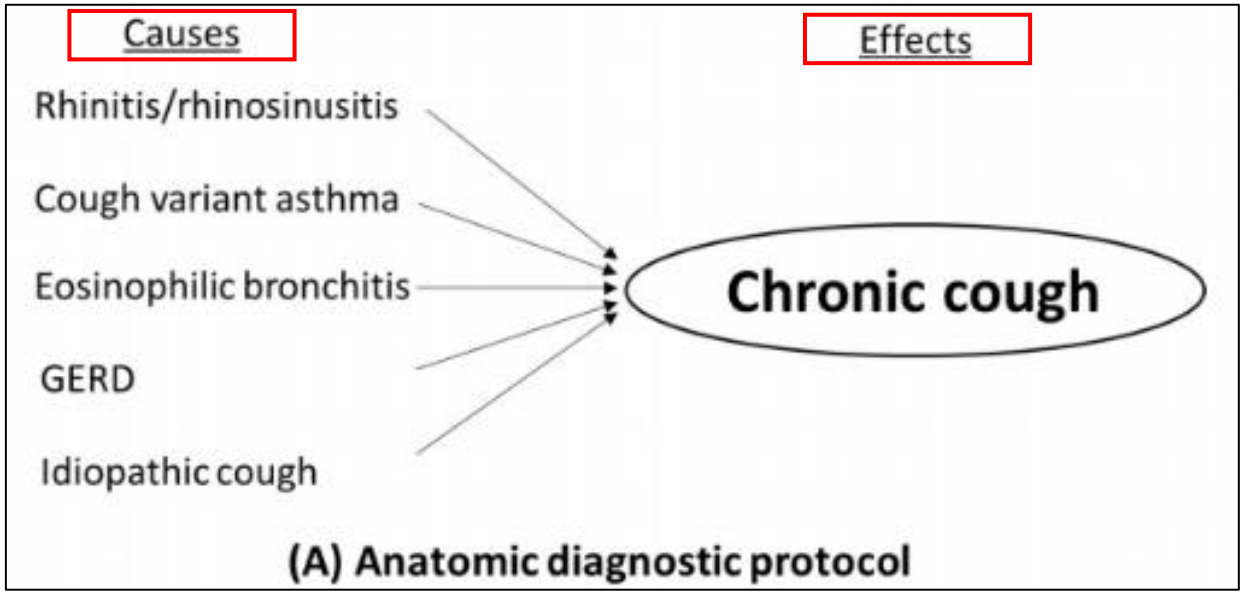
- A total of 610 patients (66.9% women; median age 59.0 years) were recruited from 18 centers, with 176 being RUCC patients (28.9%).

Lung. 2023 Oct;201(5):477-488.

Symptom vs. Disease

- Unlike cough, which is a symptom, many experts consider that chronic cough should be seen as a disease.
- The current International Classification of Diseases (ICD) does not yet include a diagnosis of “chronic cough”; only the symptom code for “cough” exists.
- This reflects the traditional perspective that cough is merely a symptom of other diseases.
- Inevitably leads to the problem that no drug has, to date, been approved or institutionalized as a treatment specifically for “chronic cough.

Paradigm shift of chronic cough



(A) Anatomic diagnostic protocol

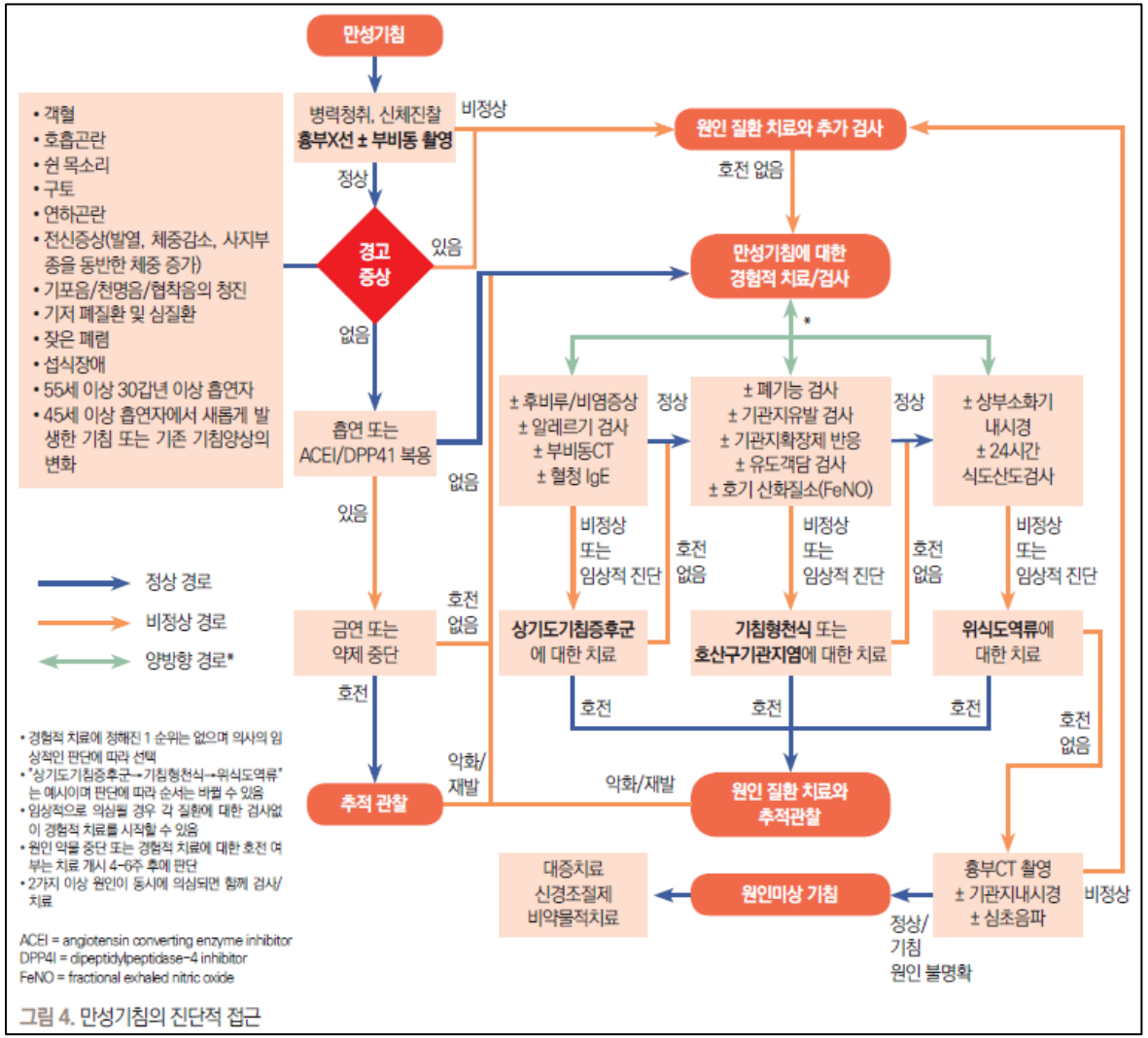
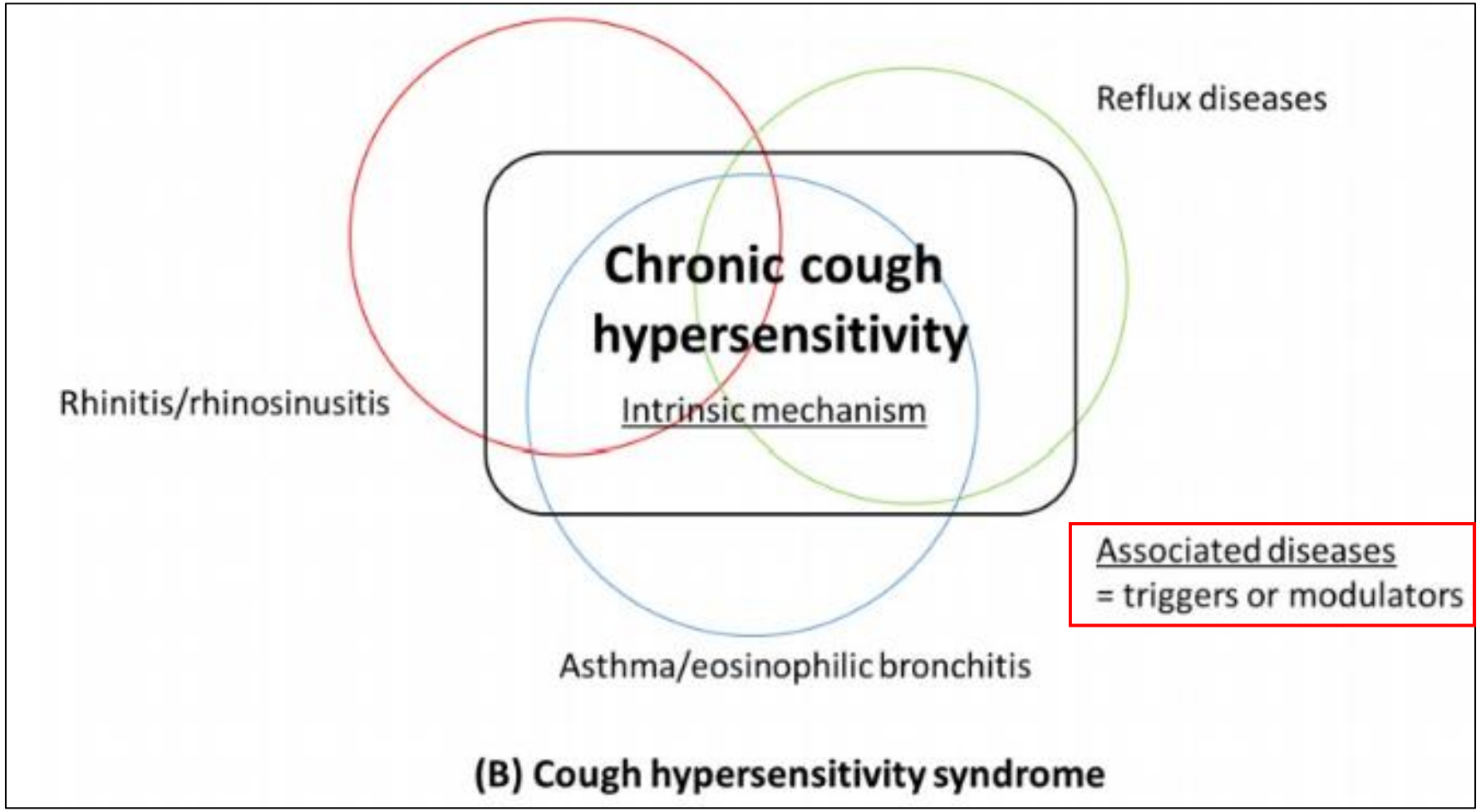
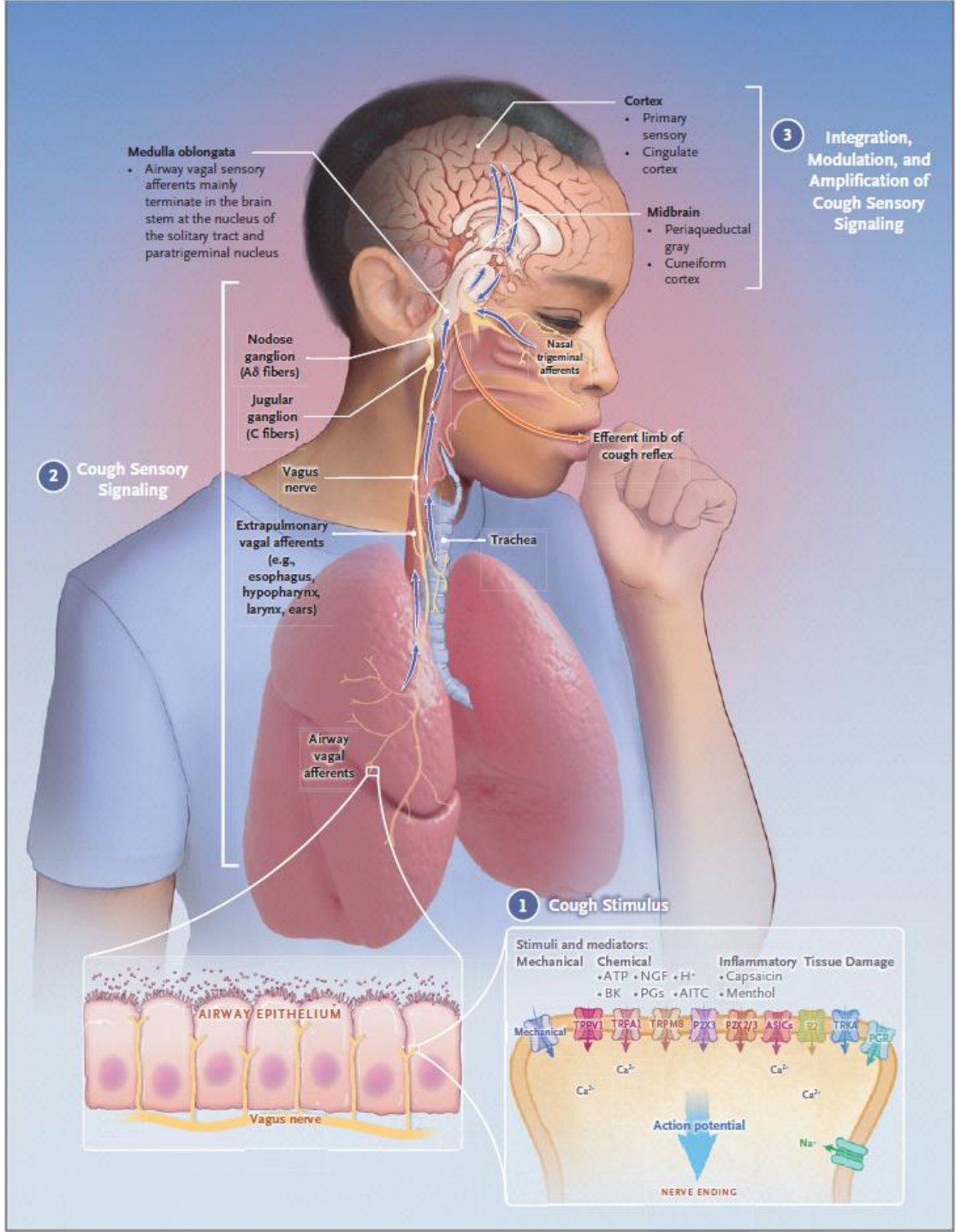


그림 4. 만성기침의 진단적 접근

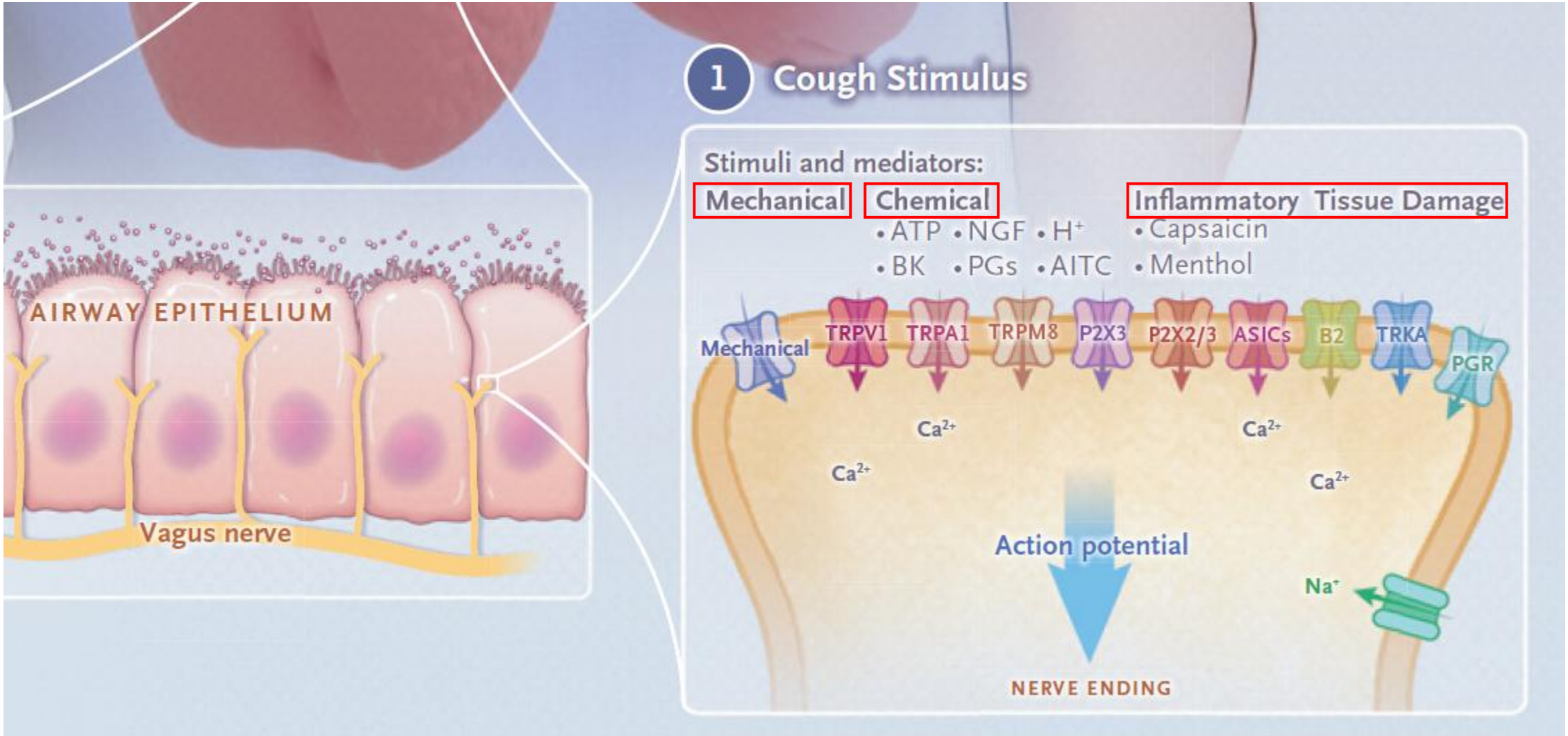
Paradigm shift of chronic cough



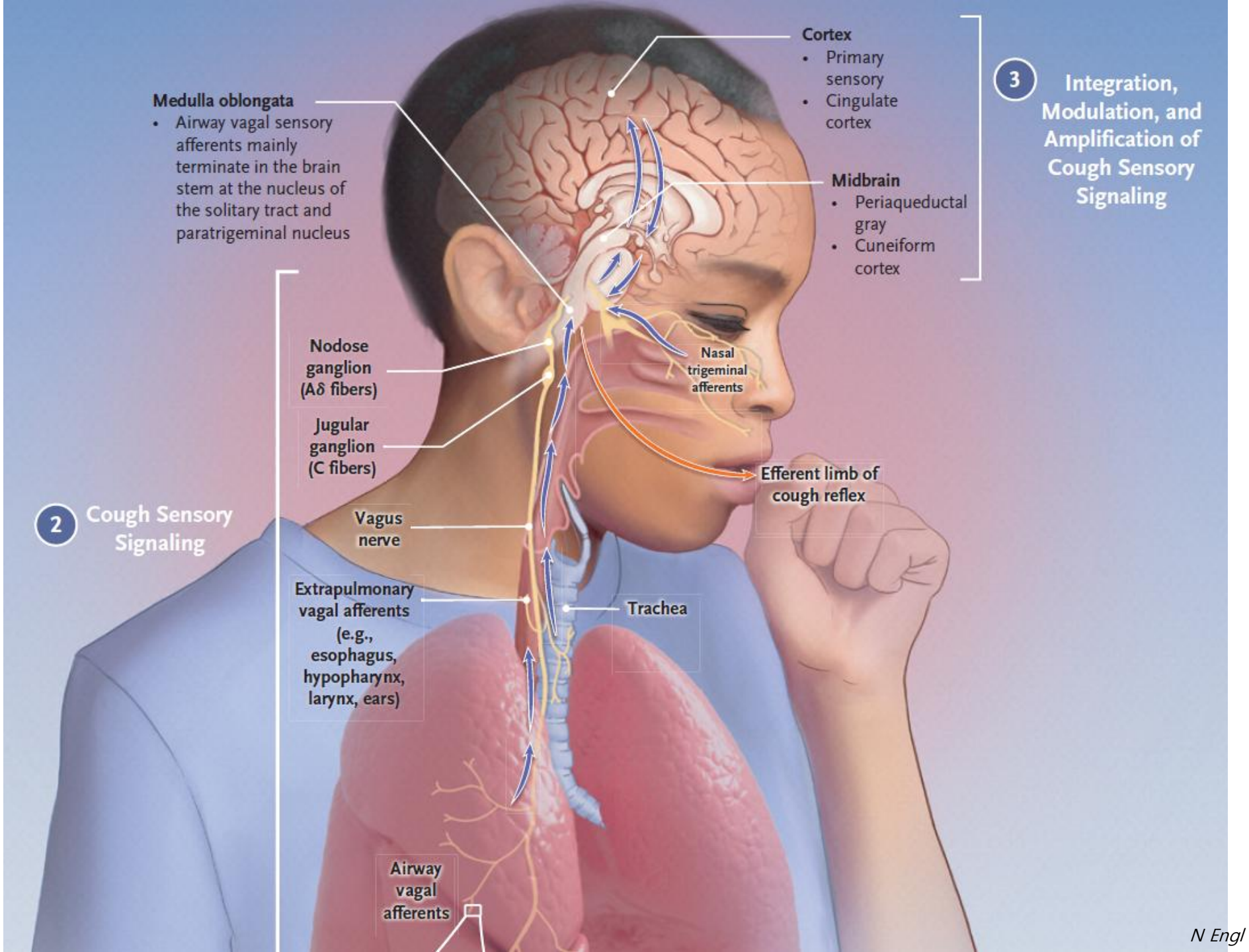
Mechanism of cough



N Engl J Med 2025;392:1203-14.



N Engl J Med 2025;392:1203-14.



N Engl J Med 2025;392:1203-14.

Cough hypersensitivity syndrome

- Most patients with chronic cough exhibit cough hypersensitivity syndrome
- Increased neural responsivity to a wide range of mechanical, chemical, or thermal stimuli.
- Leads to excessive coughing in response to innocuous triggers.
- Proposed by the ERS to emphasize the clinical relevance of the intrinsic neurological processes in chronic cough.

Cough hypersensitivity syndrome

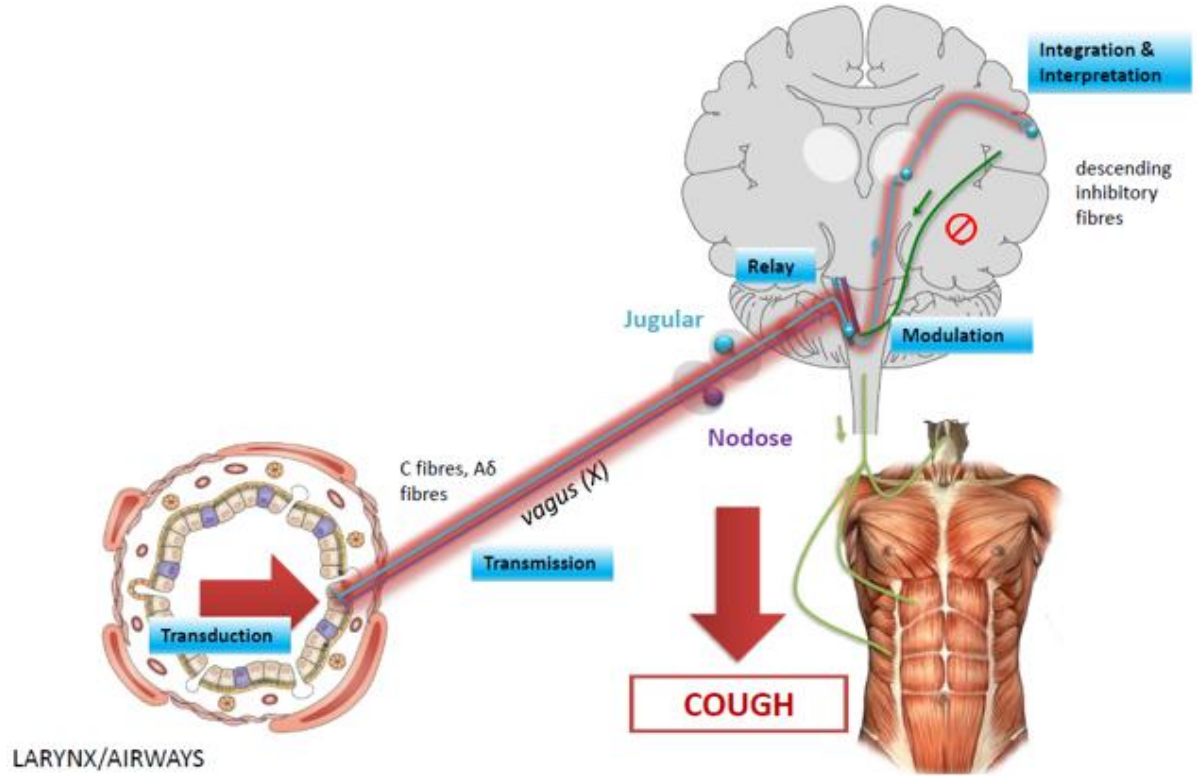
- Peripheral Mechanisms
  - Airway sensory afferents via the vagus nerve:
  - Aδ fibers – respond to mechanical/acidic stimuli.
  - C fibers – respond to chemical, inflammatory, and irritant stimuli.
- Increased expression of multiple receptors and ion channels:
  - TRP channels (TRPV1, TRPA1, TRPM8)
  - P2X3 purinergic receptors (ATP-mediated)
  - ASICs, bradykinin, prostaglandin receptors
- Chronic inflammation and epithelial injury → enhanced receptor expression and peripheral sensitization → excessive cough to innocuous stimuli

Cough hypersensitivity syndrome

- Central Mechanisms
  - Cough is not just a brainstem reflex
  - Signals reach midbrain and cortex, where they are amplified
- Similar to neuropathic pain :
  - Central sensitization → hypersensitive cough pathways
  - Weak inhibition → cannot suppress cough effectively
- Explains why cough persists even when underlying diseases are treated.

Hypertussia and allotussia

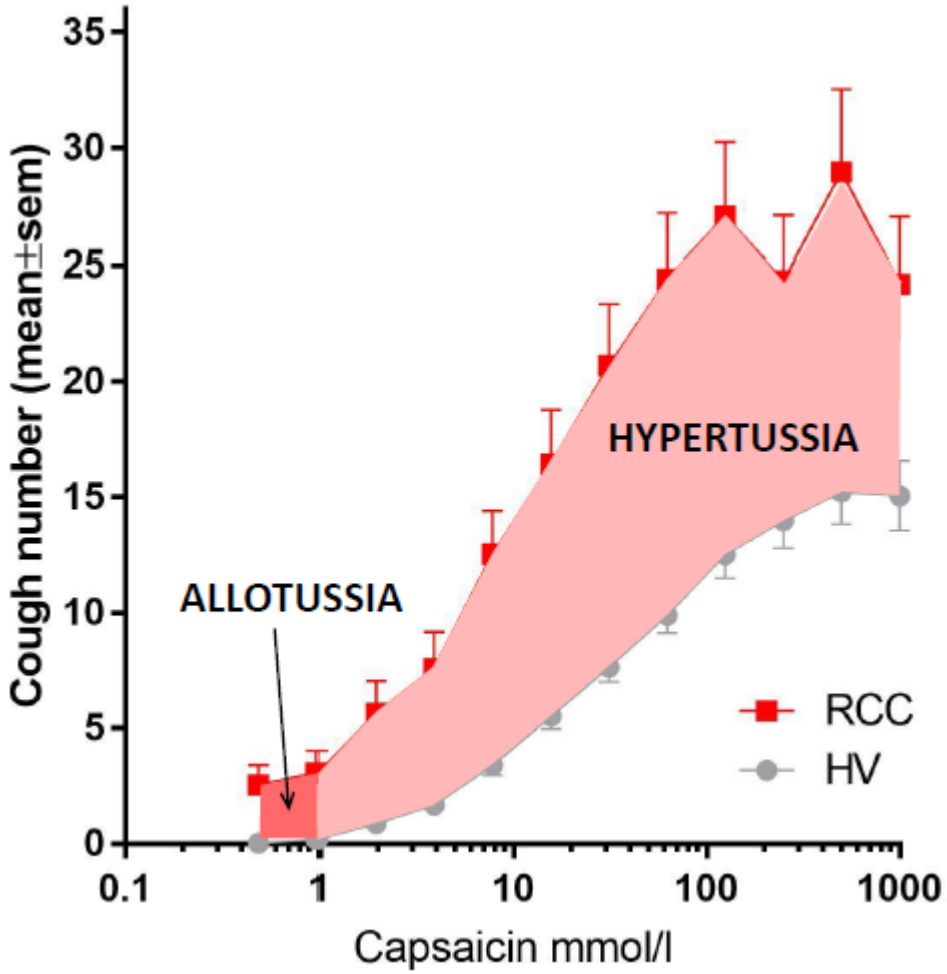
- Increased response to a cough stimulus(hypertussia)
- A cough response to a normally non-cough stimulus (allotussia)



Pain management in Older Adults, 2018

Adapted from Jaclyn Smith ERS 2022

Hypertussia in Refractory Chronic Cough



Holt et at Thorax;69:Suppl2 A77

B40 ASSESSMENT AND TREATMENT OF COUGH AND DYSPNEA / Thematic Poster Session / Monday, May 16/09:30 AM-03:45 PM / Area F, Hall F (North Building, Exhibition Level), Moscone Center

Refractory Chronic Cough Patients Are Indiscriminately Hyper-Responsive to Inhaled Tussive Irritants/Agents

J. King[1], B. Al-Sheklly[2], J. Wingfield Digby[1], S. Sen[1], J. Mitchell[1], P. A. Marsden[3], J. Smith[1]; [1]Division of Infection, Immunity and Respiratory Medicine, University of Manchester, Manchester, United Kingdom, [2]Department of Respiratory Medicine, Manchester University NHS Foundation Trust, Manchester, United Kingdom, [3]North West Lung Centre, Wythenshawe Hospital, Manchester, United Kingdom.

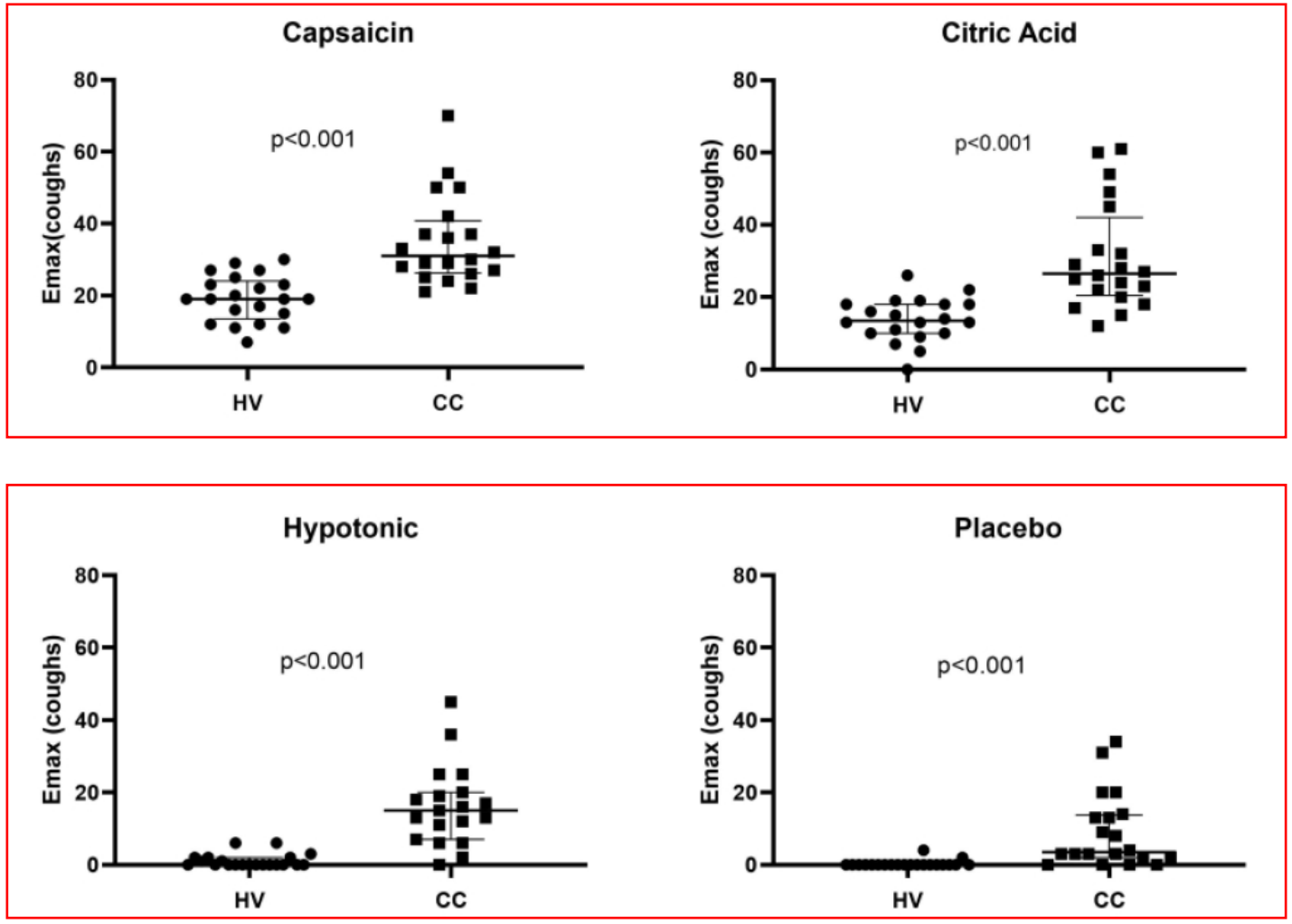
Corresponding author's email: jenny.king@manchester.ac.uk

- 20 RCC/UCC (10:10 M:F) and 21HV (10:11 M:F) were recruited.
- 4 single inhalations of ascending concentrations of capsaicin (0.48 - 1000mM), and citric acid (0.03-4M), descending osmolarities of buffered hypotonic saline (300, 250, 200, 150, and 100 mOsm/kg, pH 7.0), and 0.9% saline control.

Am J Respir Crit Care Med 2022;205:A2809

Hypertussia and Allotusia in Refractory Chronic cough

Figure 1: Emax of Each challenge agent for Healthy Volunteers (HV) and Refractory Chronic Cough (CC) patients



Hypertussia

Allotusia

Am J Respir Crit Care Med 2022;205:A2809

- Evaluation and Management

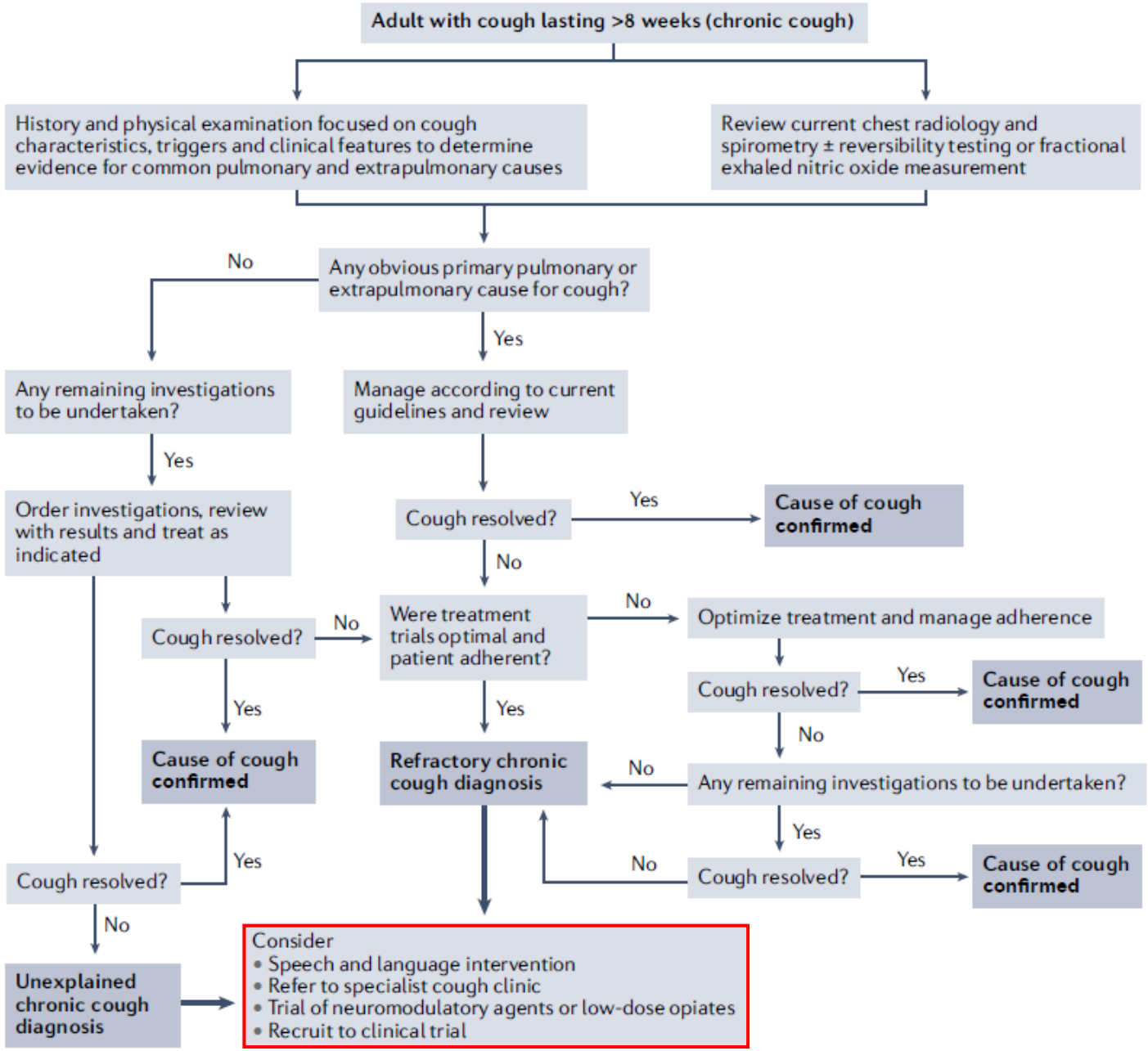


Fig. 4 | **Evaluation and management of chronic cough in adults.** A proposed algorithm for the clinical management of patients with chronic cough, including recommendations for managing difficult-to-treat cough. The algorithm was devised using recommendations contained in existing clinical guidelines and other reference material[3,4,10,46,232].

N Engl J Med 2025;392:1203-14.

Current management steps and treatment options

- Multimodal speech therapy
- Pharmacologic neuromodulation
- Pharmacologic antagonists
- Addressing reactive anxiety and depression

Multimodal speech therapy

- Multimodal speech therapy led to greater decreases in cough-related symptoms and improvements in quality of life.
- As originally reported by Vertigan et al. in 2006, the therapy consisted of education, cough suppression techniques, and breathing exercises.
- The presence of cortical activations that modulate subcortical and brain-stem activities in response to cough stimuli may explain the success of this intervention, although the mechanism is not known

Speech Management

Education
Cough can be triggered by irritation
Cough is not always necessary
Cough has limited physiological benefit in this condition
Cough is under autonomic and voluntary control
Symptom control techniques
Cough suppression swallow
Cough control breathing
Paradoxical vocal fold movement release breathing
Release of laryngeal constriction

Reducing laryngeal irritation
Behavioral management of reflux
Reduce phonotraumatic behaviors
Hydration
Minimize exposure to irritating substances
Psychoeducational counselling
Treatment is hard work
Setting realistic goals

Pharmacologic neuromodulation

- Centrally acting neuromodulators
  - Effective in RCTs: amitriptyline, gabapentin, morphine, baclofen, nalbuphine
  - Combination therapy: speech therapy + pregabalin → better outcomes
  - Adverse effects → must discuss risks/benefits with patients, reassess regularly
- Cautions
  - In COPD, gabapentinoids (gabapentin, pregabalin) ↑ risk of severe exacerbations (39% higher vs controls)
  - Careful consideration required in COPD patients
- Other approaches
  - Superior laryngeal nerve block: small RCT showed QoL improvement, but evidence limited (short duration, small sample, no speech therapy)

Table 1
Summary of guideline recommended options for the pharmacologic treatment of chronic refractory cough [2,3,12].

Drugs	Smith and Woodcock 2016	CHEST Guidelines 2018	ERS guidelines 2020
Morphine	Recommended	Discouraged	Recommended
Gabapentin	Recommended	Recommended	Recommended
Pregabalin	Recommended	Recommended	Recommended
Tramadol	Neither recommended nor discouraged	Neither recommended nor discouraged	Neither recommended nor discouraged
Codeine	Neither recommended nor discouraged	Neither recommended nor discouraged	Not recommended
Dextromethorphan	Neither recommended nor discouraged	Neither recommended nor discouraged	Neither recommended nor discouraged
Amitriptyline	To be considered	Neither recommended nor discouraged	Neither recommended nor discouraged

Drug (publication or clinical trial ID)	**Phase**	**Patients**		**Significant benefit on cough outcome (intervention vs. control)**		
		Disease	**Number**	**Frequency**	**Severity**	**QoL**
Codeine (Smith 2006)	PoC	COPD cough	21	p=0.52*	p=0.96	
Morphine (Morice 2007)	PoC	CRC	27		Not specified	p<0.02*
Morphine (Al-Sheklly 2017†)	PoC	CRC (responder)	22	p<0.05*	p<0.05	p<0.05
Gabapentin (Ryan 2012)	PoC	CRC	62	p=0.028	p=0.029	p=0.004*
Pregabalin (Vertigan 2016)	PoC	CRC	40	p=0.671*	p=0.002*	p=0.024*
Amitriptyline (Jeyakumar 2006††)	PoC	PVVN cough	28			Not specified

Not measured
$p \geq 0.05$
$0.01 \leq p < 0.05$
$0.001 \leq p < 0.01$
$p < 0.001$
TRPV1 antagonist$_a$ = SB-705498

Eur J Intern Med. 2020 Nov;81:15-21.

Expert Opin Pharmacother. 2020 Aug;21(11):1345-1358.

Pharmacologic antagonists

- Effective pharmacologic antagonists of the vagal signaling underlying cough hypersensitivity would be highly desirable for patients with truly unexplained or refractory chronic cough, barring serious adverse effects.
- Since heterogeneous mechanisms may underlie unexplained or refractory cough, multiple types of antagonists may be required to effectively treat different subpopulations of patients.
- Although antagonism of transient receptor potential cation channels (TRPV1 and TRPA1) on vagal C fibers showed initial promise in animal models, such antagonists did not significantly attenuate cough in clinical trials

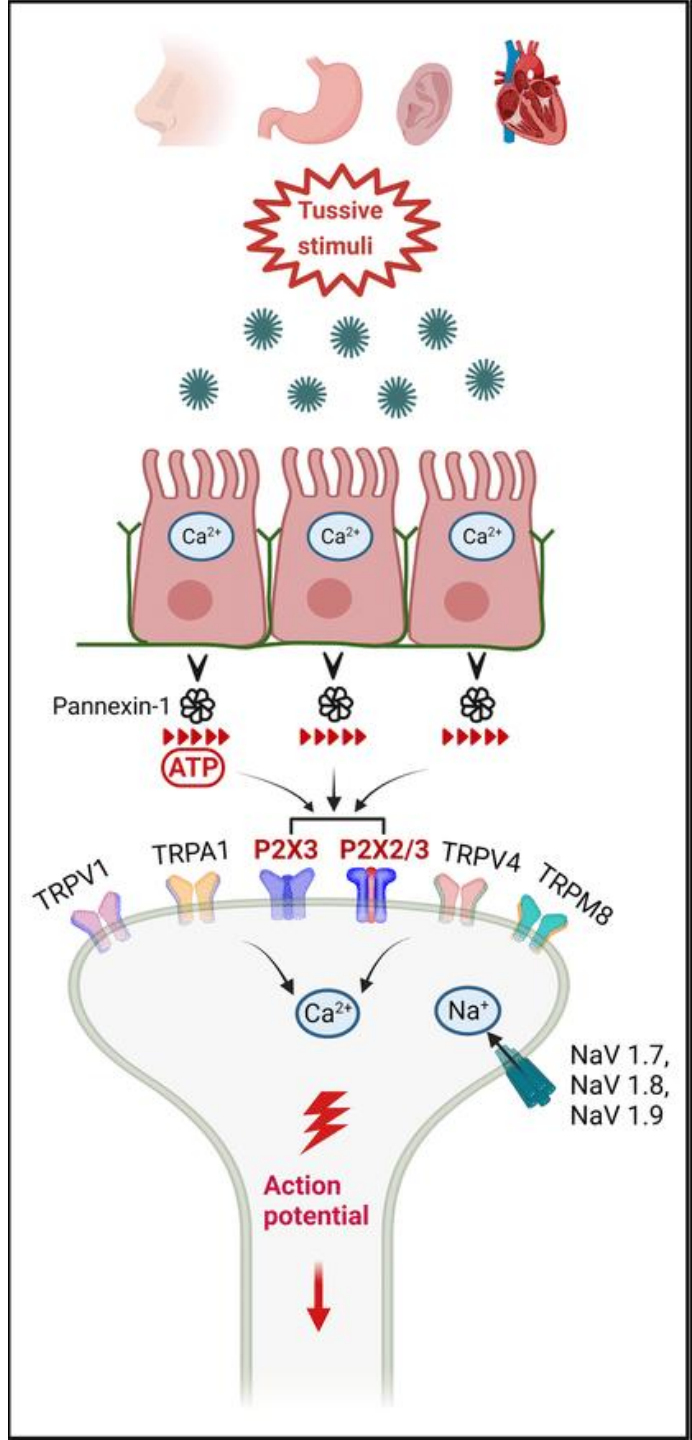


Table 2. Purinergic Receptor Antagonists for Chronic Cough.*

Antagonist	Compound Name	Comments
Gefapixant[45]	AF-219, MK-7264	Low selectivity for P2X3 over P2X2/3; frequent taste disturbances; not FDA-approved as effective for chronic cough but licensed for clinical use in the European Union, Switzerland, and Japan
Eliapixant[83]	BAY-1817080	Decreased 24-hr cough counts in phase 2b trial; selectivity for P2X3 over P2X2/3; low rate of taste disturbances; clinical trials suspended for risk of hepatotoxicity
Camlipixant[84,85]	BLU-5937	High selectivity for P2X3 over P2X2/3; low rate of taste disturbances; clinical trials under way
Sivopixant[86]	S-600918	No significant decrease in 24-hr cough frequency in phase 2b trial; selectivity for P2X3 over P2X2/3; mild-to-moderate taste disturbances; 0in clinical trials, not approved for clinical use
Filapixant[87]	BAY-1902607	Decreased 24-hr cough frequency in phase 1–2a trial; high selectivity for P2X3 over P2X2/3; taste disturbances mild to moderate but frequent at higher doses; in clinical trials, not approved for clinical use
Aspirex[88]	DT-0111	Water-soluble inhalational drug candidate; antagonist of P2X2/3; studies in animals and in vitro
PSFL2915[89]	—	Nanomolar-affinity P2X3 inhibitor based on quercetin; no taste disturbance in animal model; studies in animals and in vitro
Quercetin[89]	—	P2X3 inhibitor; no taste disturbance in animal model; studies in animals and in vitro

Efficacy and safety of gefapixant, a $P2X_3$ receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials

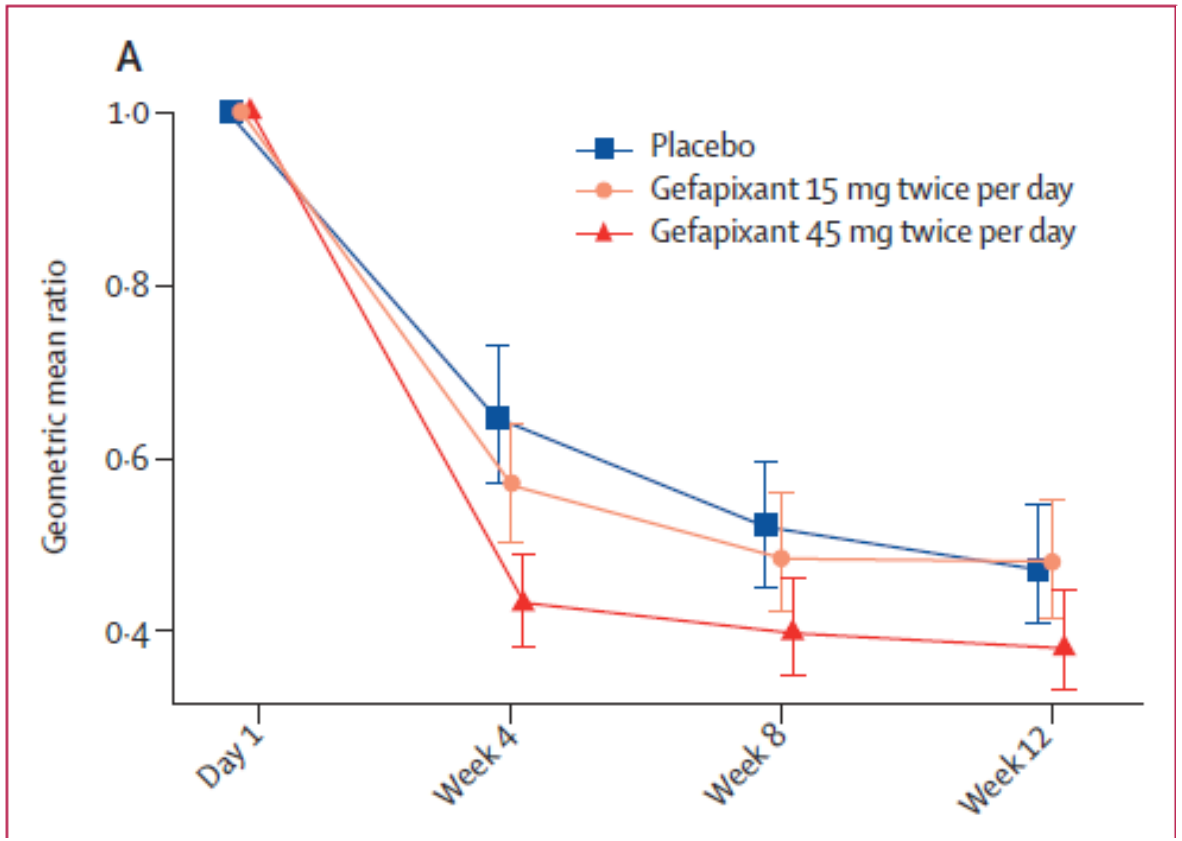
*Lorcan P McGarvey, Surinder S Birring, Alyn H Morice, Peter V Dicpinigaitis, Ian D Pavord, Jonathan Schelfhout, Allison Martin Nguyen, Qing Li, Anjela Tzontcheva, Beata Iskold, Stuart A Green, Carmen La Rosa, David R Muccino, Jaclyn A Smith, COUGH-1 and COUGH-2 Investigators**

- Double-blind, randomized, parallel-group, placebo-controlled, phase 3
- COUGH-1 ; 156 care sites in 17 countries, 12 weeks with a 40-week blinded extension period.
- COUGH-2 ; 175 sites in 20 countries, 24 weeks with a 28-week blinded extension period.
- 1:1:1 – placebo: gefapixant 15mg BID: gefapixant 45mg BID

Lancet 2022; 399: 909–23

	Placebo	Gefapixant 15 mg twice per day	Gefapixant 45 mg twice per day	Total
COUGH-1				
Number of participants	243	244	243	730
Sex				
Female	181 (74·5%)	181 (74·2%)	180 (74·1%)	542 (74·2%)
Male	62 (25·5%)	63 (25·8%)	63 (25·9%)	188 (25·8%)
Age (years)				
Mean	57·9 (13·1)	59·6 (11·7)	59·4 (13·1)	59·0 (12·6)
Range	21–81	22–89	19–85	19–89
Race				
American Indian or Alaska native	7 (2·9%)	6 (2·5%)	8 (3·3%)	21 (2·9%)
Asian	35 (14·4%)	35 (14·3%)	34 (14·0%)	104 (14·2%)
Black or African American	4 (1·6%)	3 (1·2%)	4 (1·6%)	11 (1·5%)
Multiple	8 (3·3%)	5 (2·0%)	11 (4·5%)	24 (3·3%)
White	189 (77·8%)	195 (79·9%)	186 (76·5%)	570 (78·1%)
Duration of chronic cough (years)				
Mean	11·7 (9·9)	11·8 (9·1)	11·2 (9·4)	11·6 (9·5)
Range	2–59	2–45	2–56	2–59

COUGH-2				
Number of participants	435	440	439	1314
Sex				
Female	326 (74·9%)	329 (74·8%)	329 (74·9%)	984 (74·9%)
Male	109 (25·1%)	111 (25·2%)	110 (25·1%)	330 (25·1%)
Age (years)				
Mean	58·0 (12·6)	58·6 (11·4)	57·8 (12·4)	58·1 (12·1)
Range	19–84	22–88	19–87	19–88
Race				
American Indian or Alaska native	20 (4·6%)	28 (6·4%)	24 (5·5%)	73 (5·6%)
Asian	15 (3·4%)	14 (3·2%)	15 (3·4%)	44 (3·3%)
Black or African American	5 (1·1%)	9 (2·0%)	14 (3·2%)	28 (2·1%)
Multiple	36 (8·3%)	31 (7·0%)	37 (8·4%)	104 (7·9%)
White	355 (81·6%)	356 (80·9%)	346 (78·8%)	1057 (80·4%)
Duration of chronic cough (years)				
Mean	10·7 (8·8)	11·9 (10·7)	10·9 (9·9)	11·2 (9·8)
Range	2–51	1–75	2–65	1–75



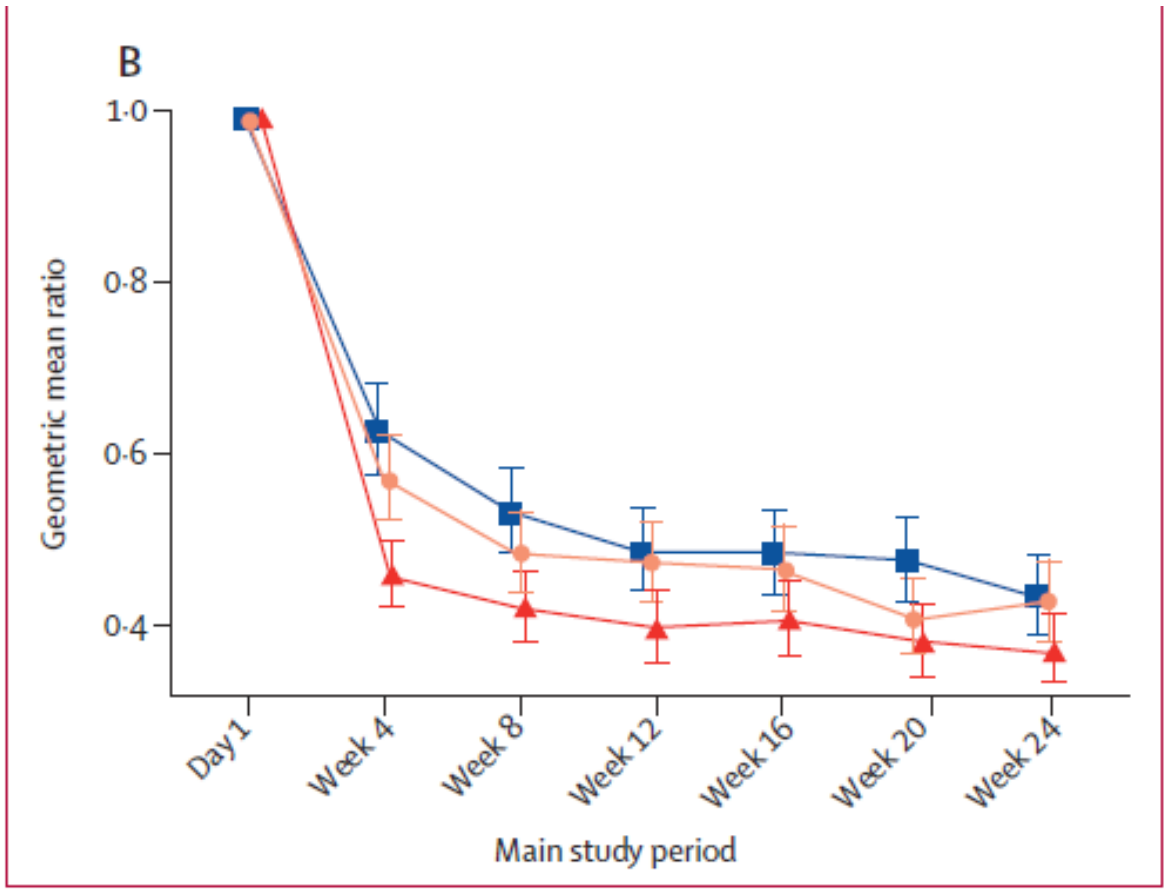
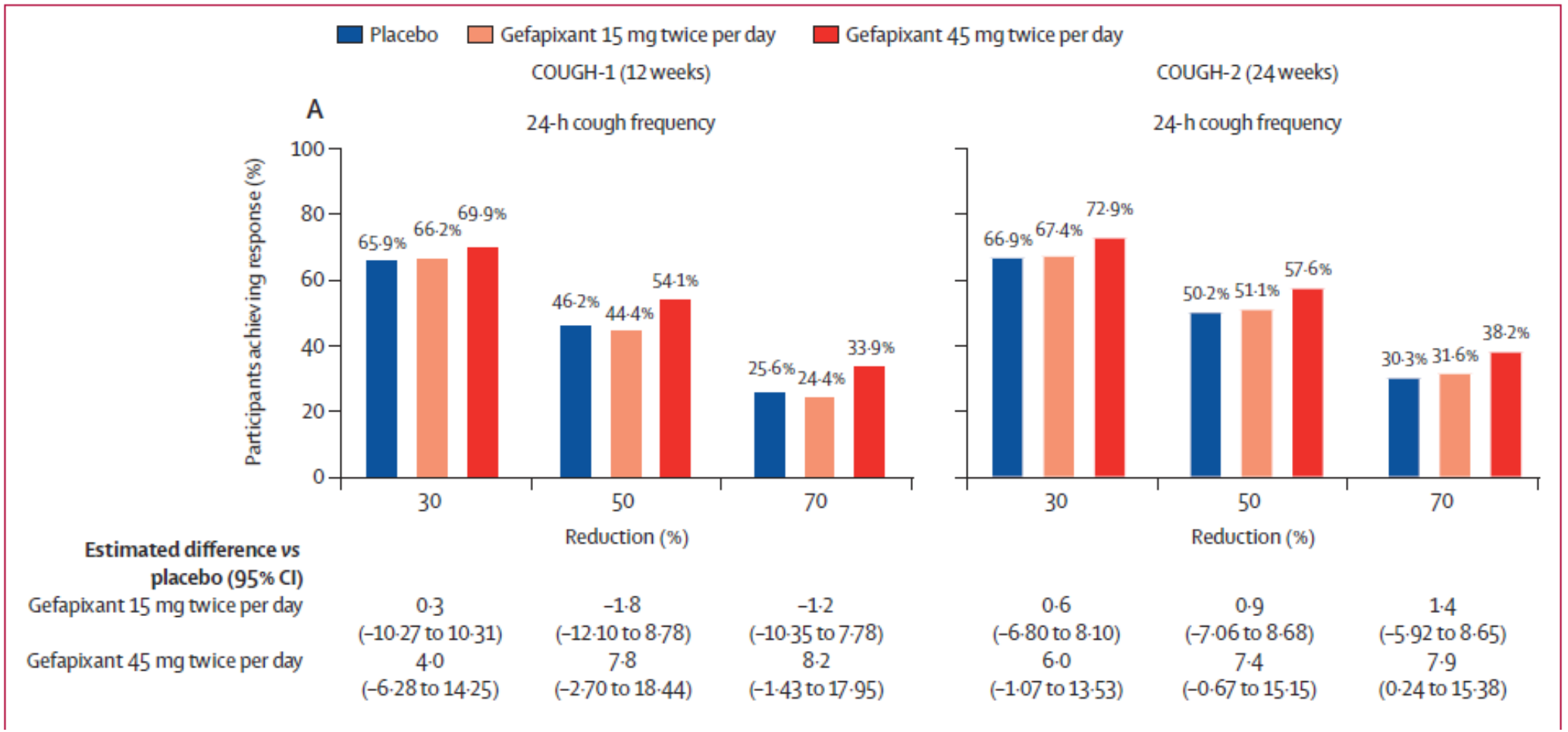
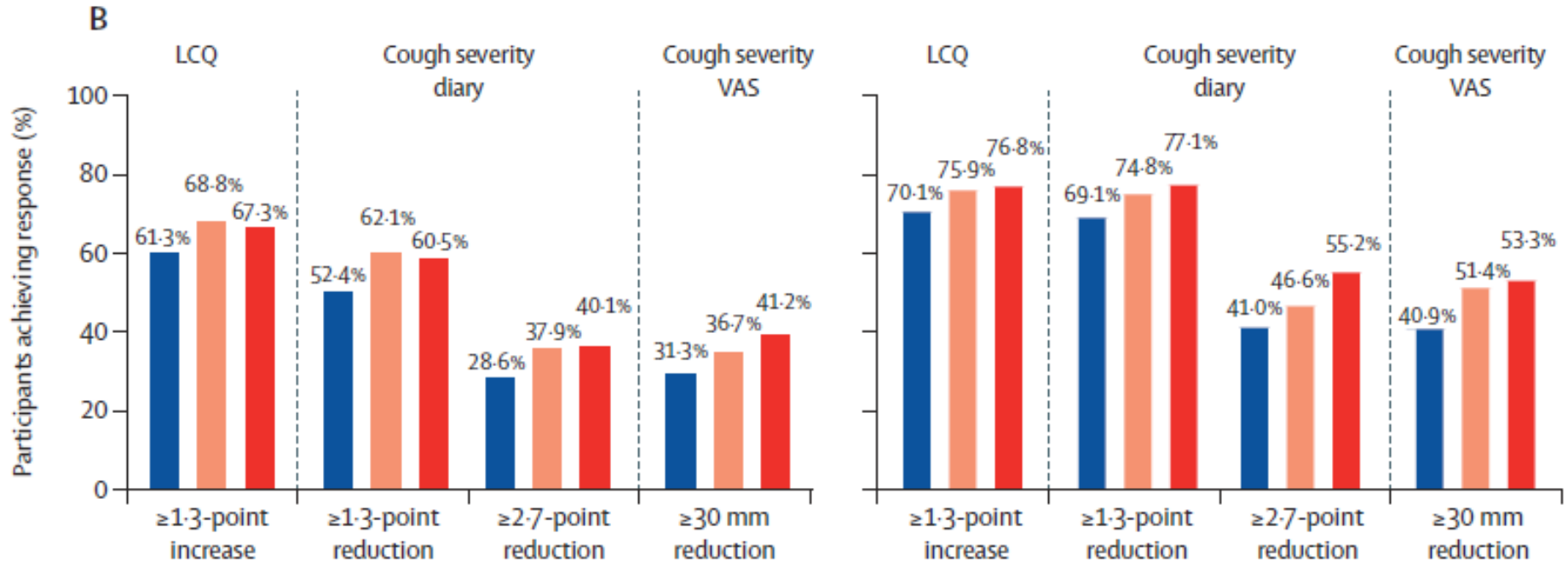


Figure 2: 24-h cough frequency over 12 weeks in COUGH-1 (A) and 24 weeks in COUGH-2 (B)

Lancet 2022; 399: 909–23



Estimated difference vs placebo (95% CI)	COUGH-1 (12 weeks) 24-h cough frequency 30 Reduction (%)	COUGH-1 (12 weeks) 24-h cough frequency 50 Reduction (%)	COUGH-1 (12 weeks) 24-h cough frequency 70 Reduction (%)	COUGH-2 (24 weeks) 24-h cough frequency 30 Reduction (%)	COUGH-2 (24 weeks) 24-h cough frequency 50 Reduction (%)	COUGH-2 (24 weeks) 24-h cough frequency 70 Reduction (%)
Gefapixant 15 mg twice per day	0·3 (–10·27 to 10·31)	–1·8 (–12·10 to 8·78)	–1·2 (–10·35 to 7·78)	0·6 (–6·80 to 8·10)	0·9 (–7·06 to 8·68)	1·4 (–5·92 to 8·65)
Gefapixant 45 mg twice per day	4·0 (–6·28 to 14·25)	7·8 (–2·70 to 18·44)	8·2 (–1·43 to 17·95)	6·0 (–1·07 to 13·53)	7·4 (–0·67 to 15·15)	7·9 (0·24 to 15·38)



Estimated difference vs placebo (95% CI)								
Gefapixant 15 mg twice per day	8·4 (−1·83 to 18·65)	9·7 (−0·90 to 19·49)	7·7 (−1·77 to 17·27)	5·5 (−4·12 to 14·91)	5·5 (0·73 to 10·29)	6·0 (−1·25 to 12·94)	5·5 (−2·65 to 13·60)	10·4 (2·45 to 18·37)
Gefapixant 45 mg twice per day	6·6 (−3·92 to 16·82)	8·3 (−2·39 to 18·23)	7·9 (−1·75 to 17·46)	9·8 (0·25 to 19·78)	6·6 (2·24 to 10·83)	8·3 (1·21 to 15·18)	14·1 (5·96 to 22·21)	12·3 (4·35 to 20·33)

***Figure 4*: Responder analyses for cough frequency and patient-reported outcome endpoints**

Adverse events

	Placebo	Gefapixant 15 mg twice per day	Gefapixant 45 mg twice per day
COUGH-1			
Number of participants	243	244	243
Any adverse event	184 (75·7%)	186 (76·2%)	208 (85·6%)
Serious adverse events	14 (5·8%)	17 (7·0%)	13 (5·3%)
Adverse events related to treatment*	47 (19·3%)	49 (20·1%)	158 (65·0%)
Adverse events of special interest			
Taste-related adverse events	11 (4·5%)	31 (12·7%)†	144 (59·3%)†
Most common adverse events (>8% in a single treatment group)			
Ageusia	0	3 (1·2%)	33 (13·6%)†
Back pain	19 (7·8%)	14 (5·7%)	20 (8·2%)
Dysgeusia	8 (3·3%)	22 (9·0%)‡	88 (36·2%)†
Headache	31 (12·8%)	34 (13·9%)	29 (11·9%)
Hypogeusia	1 (0·4%)	5 (2·0%)	13 (5·3%)†
Nasopharyngitis	51 (21·0%)	47 (19·3%)	50 (20·6%)
Taste disorder	2 (0·8%)	2 (0·8%)	24 (9·9%)†

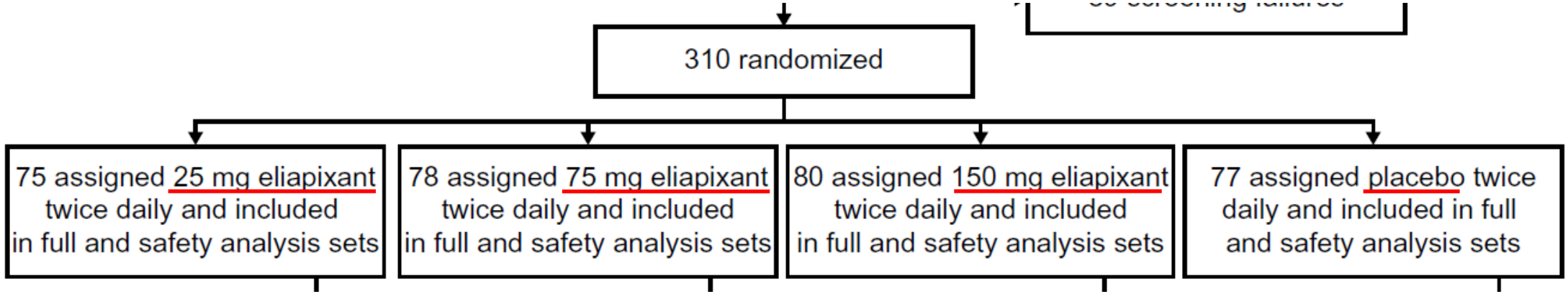
	Placebo	Gefapixant 15 mg twice per day	Gefapixant 45 mg twice per day
COUGH-2			
Number of participants	432	442	440
Any adverse event	349 (80·8%)	373 (84·4%)	399 (90·7%)
Serious adverse events	25 (5·8%)	24 (5·4%)	25 (5·7%)
Adverse events related to treatment*	91 (21·1%)	145 (32·8%)	312 (70·9%)
Adverse events of special interest			
Taste-related adverse events	36 (8·3%)	89 (20·1%)†	303 (68·9%)†
Most common adverse events (>8% in a single treatment group)			
Ageusia	6 (1·4%)	13 (2·9%)	67 (15·2%)†
Dysgeusia	28 (6·5%)	56 (12·7%)‡	193 (43·9%)†
Headache	67 (15·5%)	74 (16·7%)	70 (15·9%)
Hypogeusia	3 (0·7%)	17 (3·8%)‡	60 (13·6%)†
Influenza	35 (8·1%)	30 (6·8%)	24 (5·5%)
Nasopharyngitis	70 (16·2%)	93 (21·0%)	70 (15·9%)
Nausea	32 (7·4%)	26 (5·9%)	47 (10·7%)
Taste disorder	1 (0·2%)	8 (1·8%)‡	37 (8·4%)†
Upper respiratory tract infection	27 (6·3%)	38 (8·6%)	30 (6·8%)

Efficacy and Safety of Eliapixant in Refractory Chronic Cough: The Randomized, Placebo-Controlled Phase 2b PAGANINI Study

Peter V. Dicpinigaitis[1] · Alyn H. Morice[2] · Jaclyn A. Smith[3] · Mandel R. Sher[4] · Michael Vaezi[5] · Laurent Guilleminault[6,7] · Akio Niimi[8] · Kerstin Gude[9] · Ulrike Krahn[10] · Riitta Saarinen[11] · Philippe Vieira Pires[10] · Melanie Wosnitza[10] · Lorcan McGarvey[12] on behalf of the PAGANINI Investigators

- Randomized, double-blind, parallel-group, placebo-controlled, dose-finding efficacy and safety study at 99 centers in 19 countries.
- Adults aged ≥ 18 years with RCC lasting ≥ 12 months, with persistent cough for ≥ 8 weeks before screening, and with cough severity ≥ 40 mm measured on a 100 mm visual analog scale (VAS) at screening
- The primary efficacy endpoint was change from baseline in 24-h cough count after 12 weeks of intervention.

Lung. 2023 Jun;201(3):255-266.



- The primary efficacy endpoint was change from baseline in 24-h cough count after 12 weeks of intervention.
- Secondary efficacy endpoints included:
  - the percentage of participants with ≥ 30% reduction from baseline 24-h cough count after 12 weeks;
  - change from baseline 24-h cough count after 2, 4, and 8 weeks;
  - change from baseline awake cough count per hour after 2, 4, 8, and 12 weeks;
  - change from baseline cough severity after 12 weeks measured by the cough severity VAS;
  - the percentage of participants with ≥ 30-scale unit reduction from baseline after 12 weeks measured by the cough severity VAS;
  - change from baseline cough related QoL after 12 weeks measured by the LCQ;
  - and the percentage of participants with ≥ 1.3-point increase from baseline after 12 weeks measured by LCQ total score

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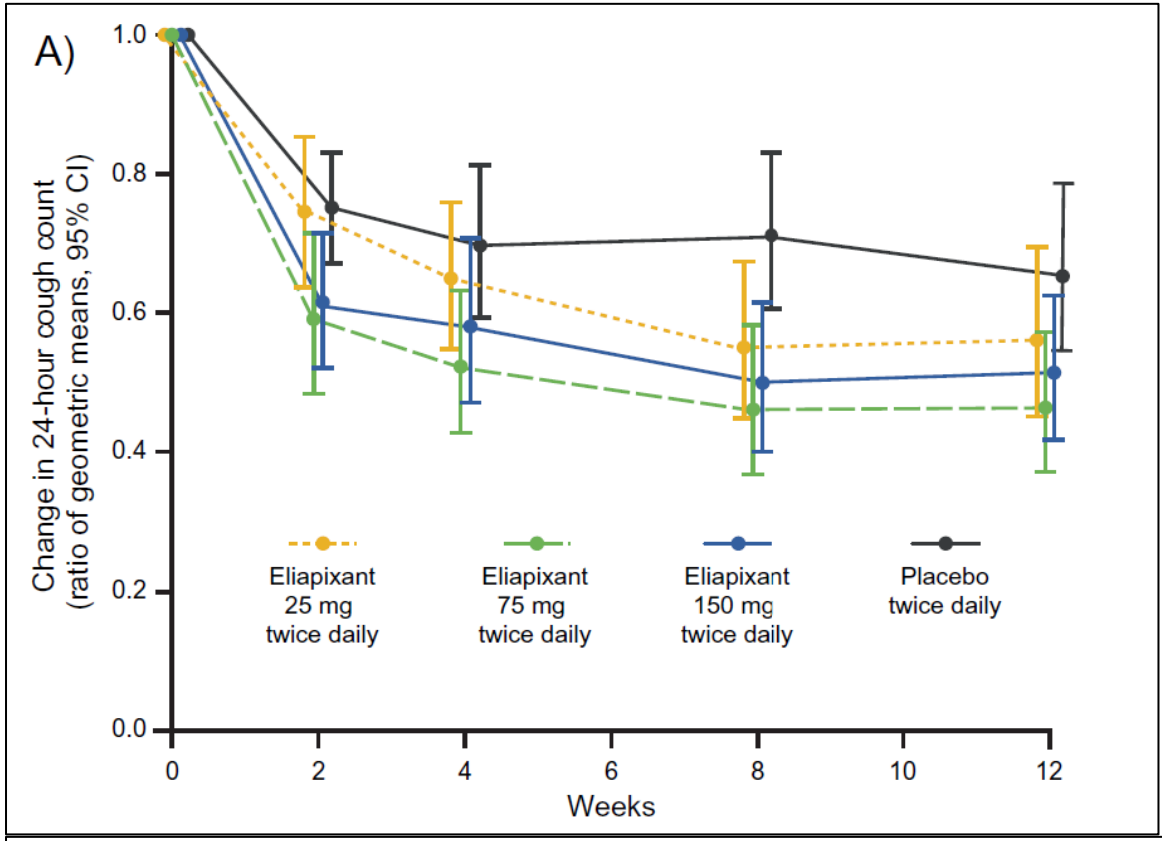
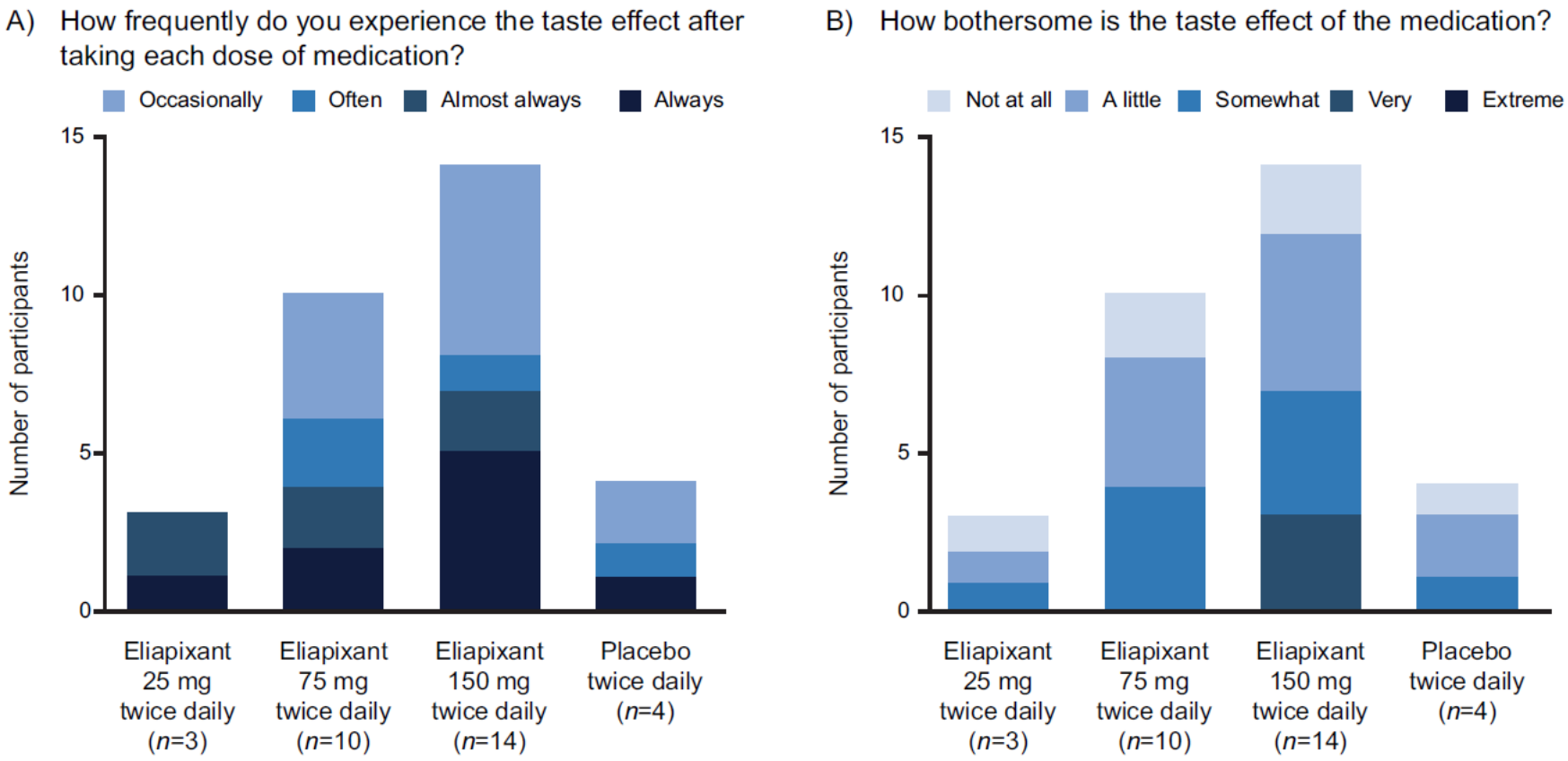


Table 2 Change from baseline in 24-h cough count after 12 weeks of intervention (per protocol set)

	Eliapixant 25 mg twice daily ($n=67$)	Eliapixant 75 mg twice daily ($n=69$)	Eliapixant 150 mg twice daily ($n=73$)	Placebo twice daily ($n=74$)
Baseline geometric mean (SD) 24-h coughs, per hour	17.5 (2.9)	19.2 (2.9)	15.6 (2.3)	17.6 (3.1)
Week 12 geometric mean (SD) 24-h coughs, per hour	9.0 (4.0)	9.1 (3.8)	8.1 (2.7)	11.3 (3.1)
Relative change of geometric means for 24-h cough at Week 12, % (95% CI)	−44 (−55 to −29)	−53 (−62 to −42)	−48 (−57 to −36)	−36 (−47 to −23)
Change in 24-h cough count at Week 12 relative to placebo, % (95% CI)	−12 (−30 to 11)	−27 (−41 to −9)	−18 (−33 to < 1)	

Lung. 2023 Jun;201(3):255-266.

Patients, *n* (%)	Eliapix-ant 25 mg	Eliapixant 75 mg twice daily	Eliapixant 150 mg	Placebo twice daily
Any AE relating to "taste and smell disorders"[b]	3 (4)	12 (15)	19 (24)	5 (6)



[a]n = 31 patients who spontaneously reported a taste-related AE and completed the taste questionnaire

Fig. 3 End-of-study assessment on taste disturbances (safety analysis set[a])

Lung. 2023 Jun;201(3):255-266.

Adverse effects

Patients, *n* (%)	Eliapix-ant 25 mg	Eliapixant 75 mg twice daily	Eliapixant 150 mg	Placebo twice daily
Any AE relating to "drug-related hepatic disorders – comprehensive search"[b]	0	1 (1)	3 (4)	0

- This DILI contributed to the need for intensified liver monitoring in clinical trials with eliapixant and the subsequent discontinuation of the entire development program in all indications by Bayer AG.

Lung. 2023 Jun;201(3):255-266.

Camlipixant in Refractory Chronic Cough: A Phase 2a, Randomized Controlled Trial (RELIEF)

Camlipixant in Refractory Chronic Cough

A Phase 2b, Randomized, Placebo-controlled Trial (SOOTHE)

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- Multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-finding trial
- aged 18–80 years with persistent cough of>1 year
- an awake cough frequency of>25 coughs/h (main population)
- score>40mm on the cough severity visual analog scale
- Primary Efficacy Endpoint
  - Change from baseline to Day 28 in 24-hour cough frequency

Am J Respir Crit Care Med. 2025 Jun;211(6):1038-1048.

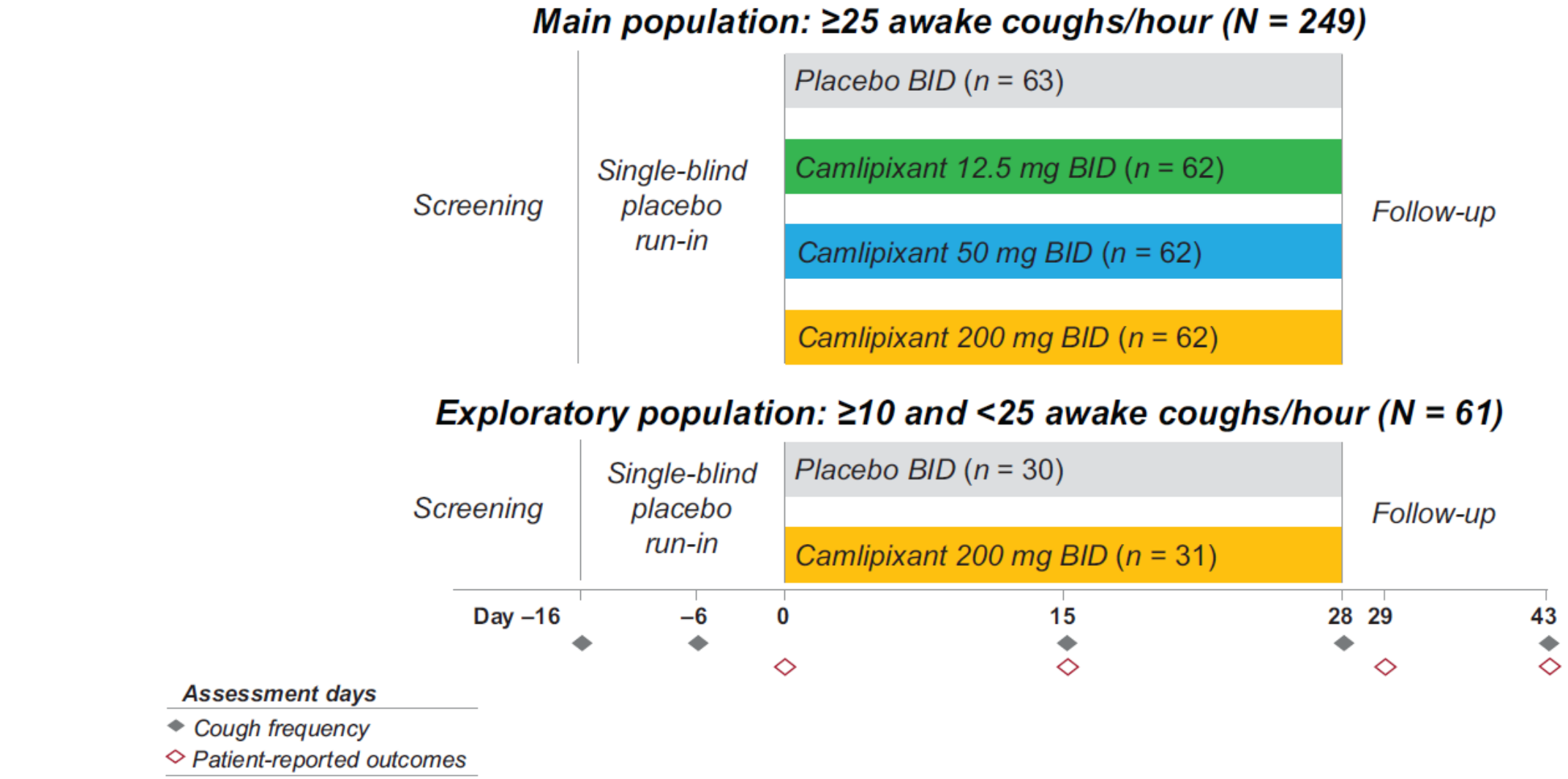

Figure 1. SOOTHE study design. BID = twice daily.

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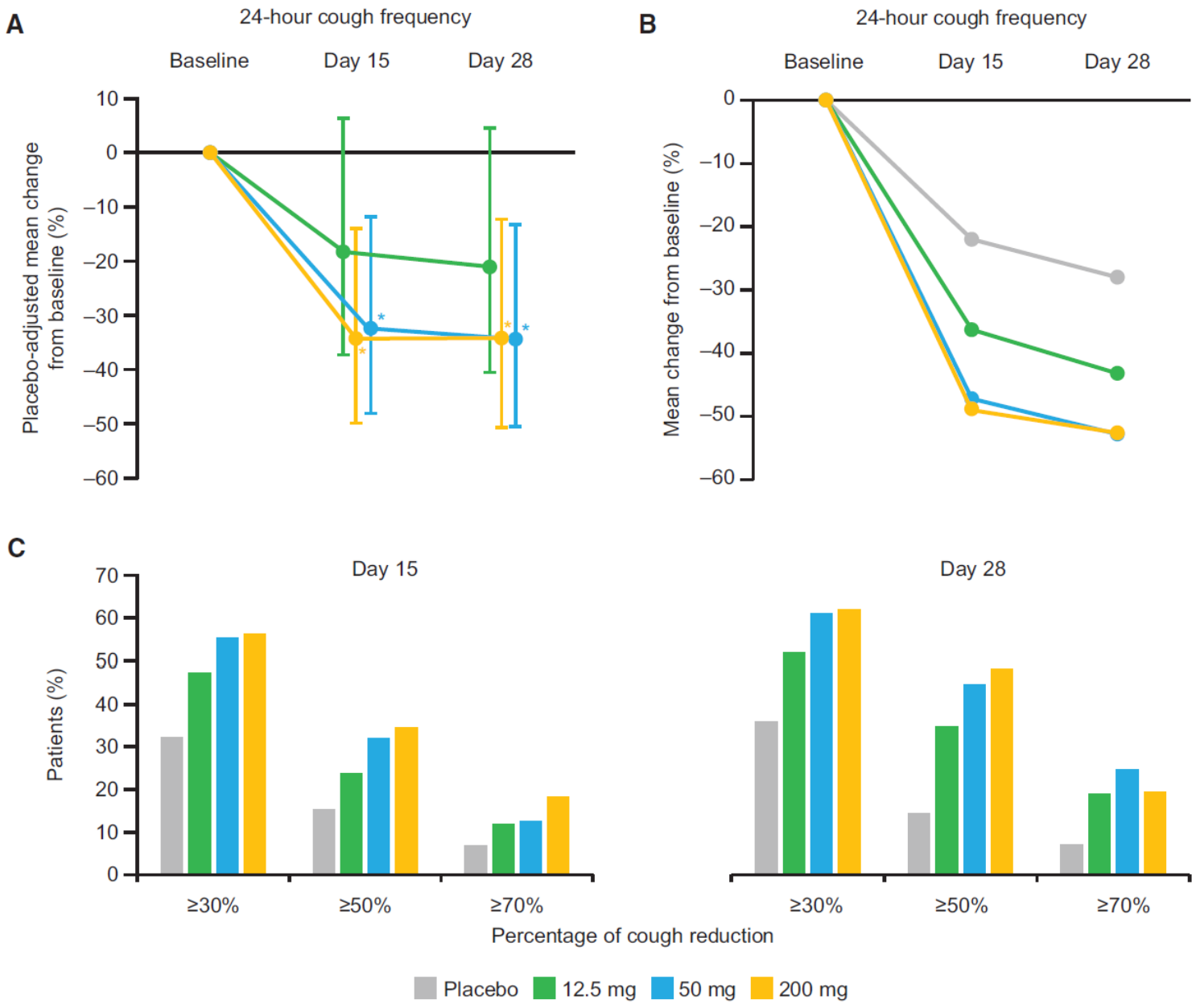
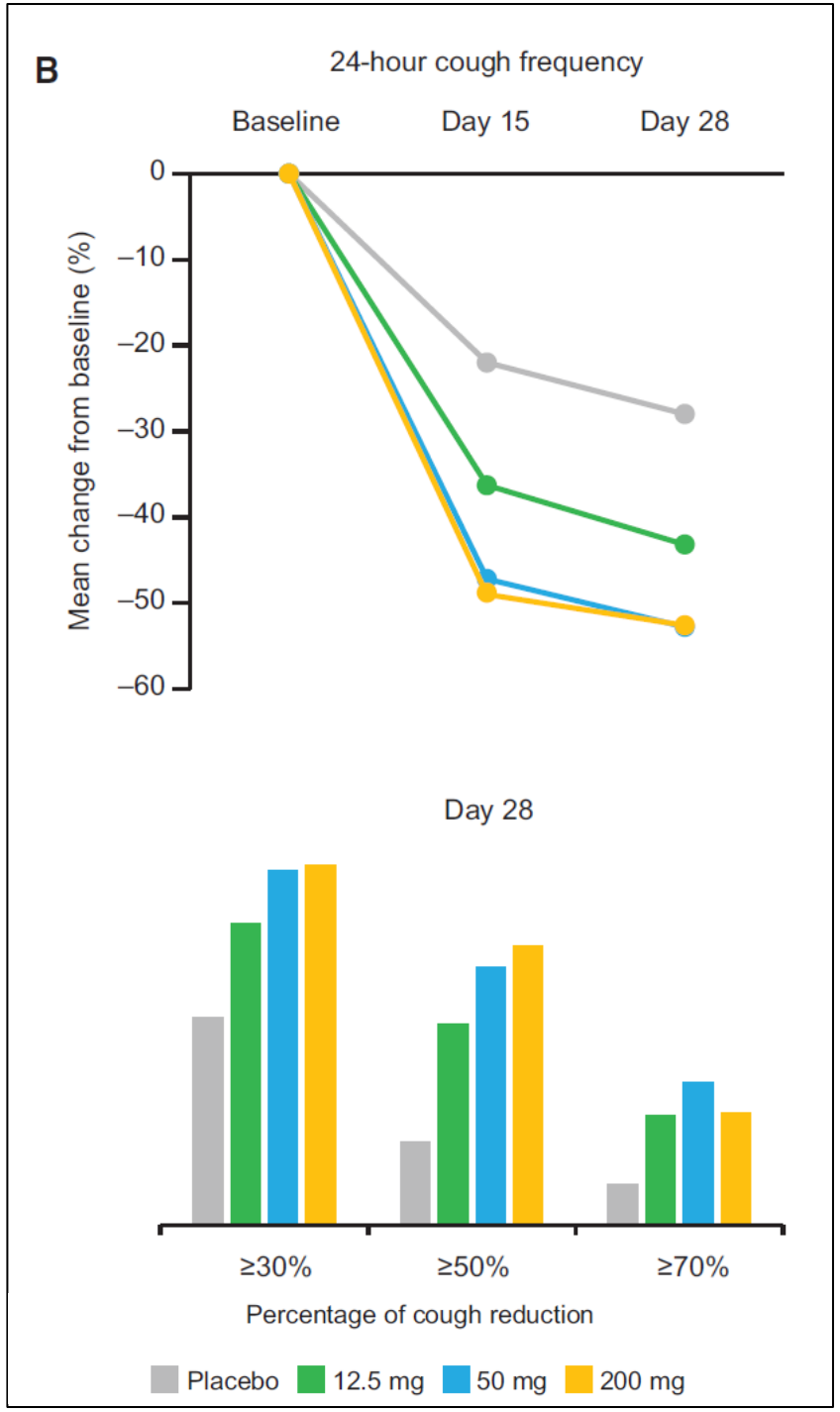
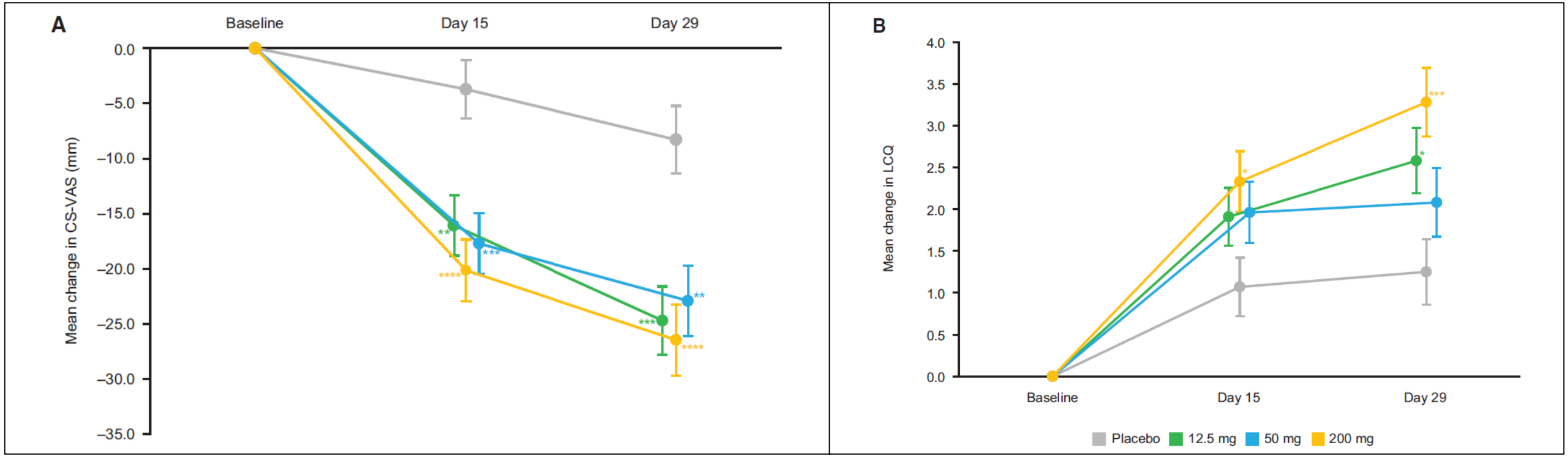


Am J Respir Crit Care Med. 2025 Jun;211(6):1038-1048.

Table 2. Efficacy Results (Main Population: Awake Cough Frequency of ⩾25 Coughs/h)

	Placebo (*n* = 63)	Camlipixant (Twice Daily) 12.5 mg (*n* = 62)	50 mg (*n* = 62)	200 mg (*n* = 62)
Primary efficacy endpoint				
24-h cough frequency (Day 28), *n*	56	58	61	52
Baseline, coughs/h, arithmetic mean (SD)	49.7 (46.07)	49.4 (35.98)	45.2 (28.88)	39.9 (23.21)
Day 28, coughs/h, geometric mean (log scale SD)	28.5 (0.95)	22.7 (0.63)	18.6 (0.86)	16.8 (0.83)
Day 28, coughs/h, arithmetic mean (SD)	41.1 (44.55)	27.7 (19.56)	25.7 (21.19)	23.4 (26.75)
Change in mean cough frequency from baseline, %	−28.0	−43.2	−52.8	−52.6
Change in mean cough frequency from placebo, %	NA	−21.1	−34.4	−34.2
95% CI	NA	−40.5 to 4.5	−50.5 to −13.3	−50.7 to −12.2
P value	NA	0.0976	0.0033	0.0047





Am J Respir Crit Care Med. 2025 Jun;211(6):1038-1048.

Table 3. Treatment-Emergent Adverse Events (Main Population: Awake Cough Frequency ⩾25 Coughs/h)

	Placebo (*n* = 63)	Camlipixant (Twice Daily)		
		12.5 mg (*n* = 62)	50 mg (*n* = 62)	200 mg (*n* = 62)
Patients with ⩾1 TEAE, *n* (%)	22 (34.9)	23 (37.1)	13 (21.0)	19 (30.6)
Patients with ⩾1 TESAE, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with TEAE leading to discontinuation,* *n* (%)	1 (1.6)	0 (0.0)	0 (0.0)	2 (3.2)
Patients with taste disturbance TEAE leading to discontinuation, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Most common TEAEs (⩾5% at any dose),† *n* (%)				
Nausea	0 (0.0)	0 (0.0)	5 (8.1)	2 (3.2)
Dysgeusia (taste alteration)	0 (0.0)	3 (4.8)	4 (6.5)	3 (4.8)
Incidence of taste disturbance TEAE,‡ *n* (%)				
Dysgeusia (taste alteration)	0 (0.0)	3 (4.8)	4 (6.5)	3 (4.8)
Hypogeusia (partial taste loss)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ageusia (complete taste loss)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Description of taste disturbance TEAE, *n* (%)				
Not bothersome	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Slightly bothersome	0 (0.0)	3 (4.8)	1 (1.6)	3 (4.8)
Moderately bothersome	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)
Severely bothersome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Extremely bothersome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Conclusion - Camlipixant

- Reduced cough frequency,
- Improved patient-reported outcomes
- Acceptable safety profile
- The potential to be a new treatment option for patients with RCC who currently have limited treatment options.
- The ongoing global, multicenter phase 3 CALM-1 (A 52-Week Study of the Efficacy and Safety of BLU-5937 in AdultsWith Refractory Chronic Cough; ClinicalTrials.gov identifier NCT05599191) and CALM-2 (A 24-Week Study of the Efficacy and Safety of BLU-5937 in Adults With Refractory Chronic Cough; ClinicalTrials.gov identifier NCT05600777) trials will provide further insights into the efficacy and safety of camlipixant in this underserved patient population.

Addressing reactive anxiety and depression

- Reactive anxiety, depression, or both can develop as complications of unresolved chronic cough and should be addressed if present.
- These cough related complications are ameliorated when the cough improves.

Summary

- Chronic cough is a distinct clinical syndrome, not merely a symptom
- Cough hypersensitivity underlies the pathophysiology
  - Peripheral sensitization (Aδ, C fibers, receptor upregulation)
  - Central sensitization (brainstem + higher cortical amplification)
- Management requires a multimodal approach
  - Speech therapy to enhance voluntary cough control
  - Pharmacologic neuromodulation for refractory cases
  - Novel therapies (e.g., P2X3 antagonists) show promise, but safety challenges remain
- Future direction: Towards personalized treatment and endotyping of cough

- 감사합니다