Upper Airway Cough Syndrome

인천성모병원 호흡기내과 김윤석

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- Recent researches
- Post-pandemic (after COVID19)

Background

Postnasal drip syndrome

Postnasal Drip Causes Cough and Is Associated with Reversible Upper Airway Obstruction*

Richard S. Irwin, M.D., F.C.C.P.; Melvin R. Pratter, M.D., F.C.C.P.;†
Patricia S. Holland, B.S.; R. William Corwin, M.D.; and
James P. Hughes, M.D.

We prospectively evaluated nine patients with cough from postnasal drip for evidence of extrathoracic upper airway obstruction. Patients compared before treatment to normal control subjects had physiologic evidence of extrathoracic upper airway obstruction; their mean $FIF_{50\%}/FEF_{50\%}$ and $FIF_{25-75\%}/FEF_{25-75\%}$ ratios of 0.88 and 0.98 were significantly less than the values in control subjects of 1.28 and 1.37 ($p < 0.001$). With specific therapy, postnasal drip decreased, cough disappeared and upper airway obstruction physiologically and physically resolved in all patients. We conclude that: 1) when postnasal drip is causally associated with cough, flow-volume loops can provide objective documentation of this clinical association; 2) flow-volume loops can be used as an objective method in comparing the efficacy of different therapeutic agents for cough due to postnasal drip; and 3) normal predicted values of extrathoracic airway function should not include measurements from patients who have recently recovered from cough associated with postnasal drip.

Chest 1984; 85: 346-352

An Algorithmic Approach to Chronic Cough

Melvin R. Pratter, MD; Thaddeus Bartter, MD; Stephen Akers, MD; and James DuBois, MHA

■ *Objectives:* To evaluate a stepwise approach to chronic cough that emphasized initial treatment of all patients with an antihistamine-decongestant for postnasal drip and to determine the value of routine bronchoprovocation challenge in the evaluation of chronic cough.
■ *Design:* Prospective trial using an algorithm for chronic cough in immunocompetent nonsmoking outpatients.
■ *Setting:* University-based pulmonary practice.
■ *Patients:* Forty-five patients met the inclusion criteria. The mean duration of cough was 140 weeks (range, 3 to 2080 weeks), and the mean severity of cough as assessed by patients on a four-point scale was "severe."
■ *Results:* Marked improvement and resolution (mean, 3.1 and 7.1 weeks, respectively), with resolution in 96% of patients. Antihistamine-decongestant therapy was beneficial in 39 of 45 patients and was the only therapy needed for 16 patients. Bronchoprovocation challenge had a negative predictive value of 100% and a positive predictive value of 74% for cough caused by asthma. No significant relationship was found between the time to cough resolution and duration or severity of cough. Eighteen percent of patients experienced a recurrence of cough at a follow-up interval of 3 months.
■ *Conclusions:* A sequential approach to chronic cough that emphasizes initial treatment with an antihistamine-decongestant is effective. Bronchoprovocation challenge is useful in evaluating patients with chronic cough but can be delayed until the initial response to antihistamine-decongestant therapy has been assessed. The 18% incidence of recurrence highlights the fact that cough often is the manifestation of a chronic or recurring process that requires chronic or episodic therapy.

Chronic cough is an important medical and economic problem. The prevalence of chronic cough in the United States among nonsmoking adults is reported to range from 14% to 23% (1, 2). Not only is the symptom itself problematic, but it raises concerns about possible serious underlying disease (3). Chronic cough is the fifth most common symptom seen by outpatient physicians (4) and is estimated to be the primary reason for 30 million physician visits annually (4). In the United States alone, approximately $600 million per year are spent on prescription and over-the-counter antitussives (5).

Major advances in the clinical approach to chronic cough have been made during the last 15 years. In a 1977 review (6), Irwin and colleagues proposed an approach to chronic cough based on the anatomic locations of the receptors and afferent pathways involved in the cough reflex. Using such an approach, Irwin and colleagues reported in 1981 (7) and again in 1990 (8) that the cause of chronic cough could be determined 100% of the time and that subsequent cause-specific treatment was almost always successful. The postnasal drip syndrome, mainly from chronic rhinitis, was the most common cause, followed by asthma (7, 8). These two diagnoses, alone or in combination, accounted for cough in 75% of the patients (7, 8). Gastroesophageal reflux was the next most common cause (7, 8). Poe and colleagues (9) also reported that the postnasal drip syndrome or asthma caused chronic cough in most of their patients.

We evaluated a sequential, stepped approach to chronic cough, emphasizing initial treatment of all patients with an antihistamine-decongestant for possible postnasal drip syndrome caused by rhinitis. We also determined the value of routine bronchoprovocation challenge for predicting whether asthma was a causative factor in cough.

Ann Intern Med. 1993;119:977-983

Postnasal drip syndrome

the cough reflex. Using such an approach, Irwin and colleagues reported in 1981 (7) and again in 1990 (8) that the cause of chronic cough could be determined 100% of the time and that subsequent cause-specific treatment was almost always successful. The postnasal drip syn-

100%, almost always successful ??

Step 1. azatadine/pseudoephedrine bid
→ No improving, step 2
→ Improving at 1 week but persistent, add nasal corticosteroid

Step 2. evaluation for asthma
→ No improving, step 3

Step 3. chest/sinus radiographs
→ No improving, step 4

Step 4. evaluation for GERD
→ No improving, step 5

Step 5. bronchoscopy

Ann Intern Med. 1993;119:977-983

Postnasal drip syndrome

Postnasal drip

: drainage of secretions from the nose or paranasal sinuses into the pharynx

Diagnosis

1. Largely rests on the *reporting from the patient*

Ex) sensation of having something drip down into the throat, nasal discharge, or frequent throat clearing.

2. Nasopharynges or oropharynges of mucoid or mucopurulent secretions,

3. Cobblestoning of the mucosa

***No** objective test for it*

***No** way to quantify the amount of PND or to directly prove that it is causing cough.*

CHEST 2006; 129:63S–71S

THE CATHOLIC UNIVERSITY OF KOREA
CATHOLIC MEDICAL CENTER

Upper Airway Cough Syndrome

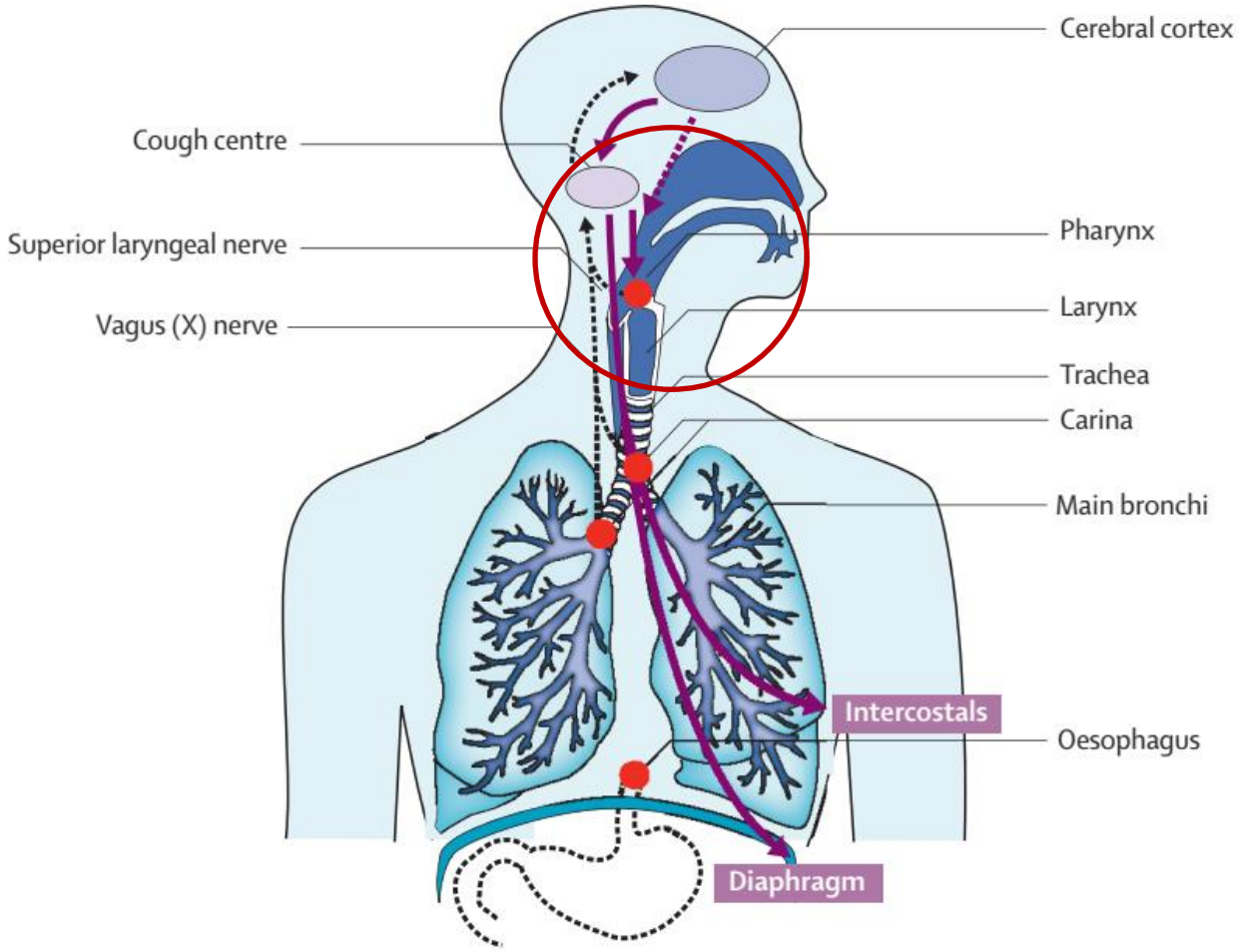


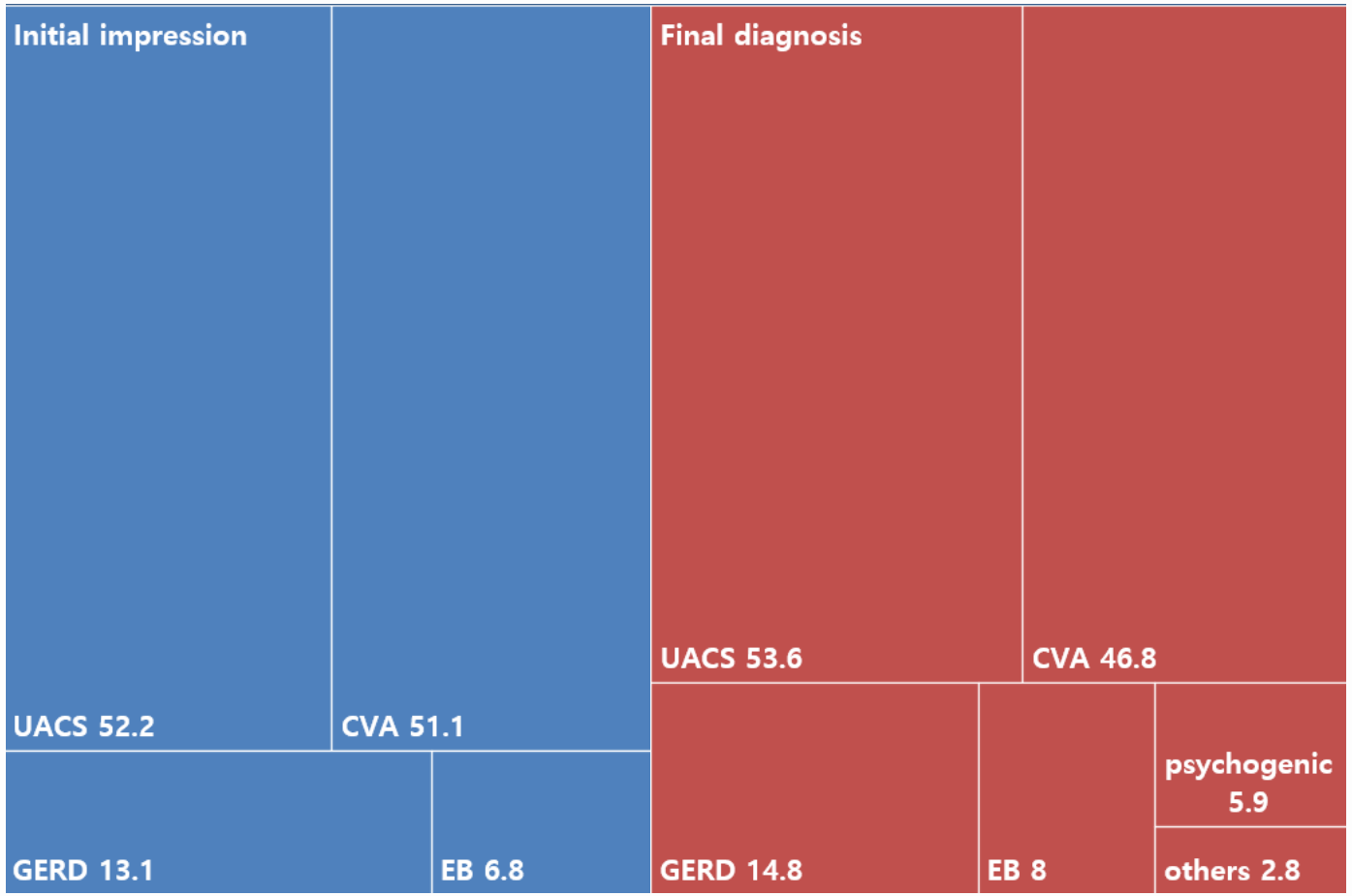
Table 1
Location of cough receptors and associated sensory nerve

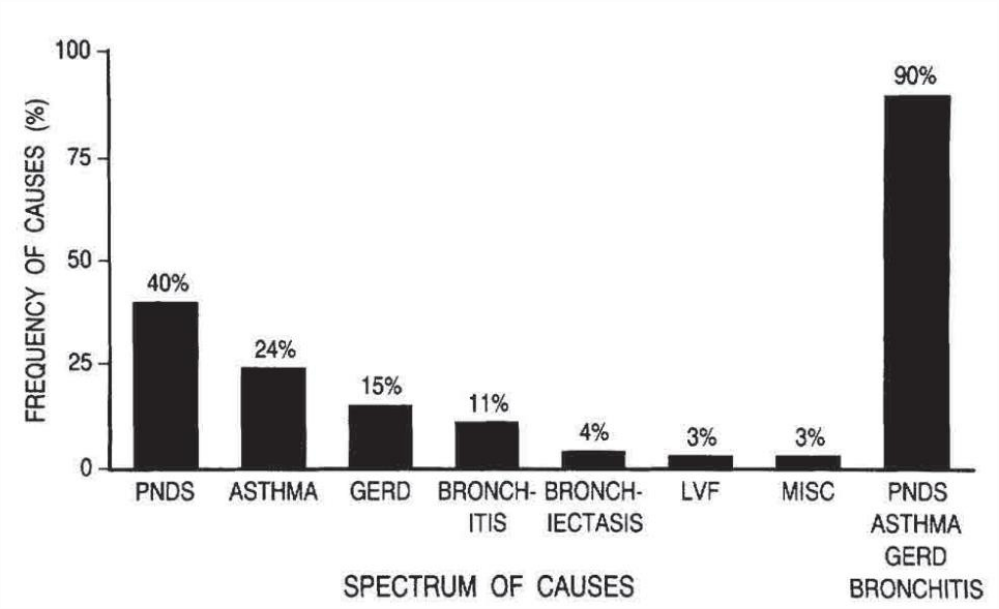
Region	Afferent nerve
Paranasal	Trigeminal (V)
Pharynx	Glossopharyngeal (IX)
Larynx/tracheobronchial tree*	Vagus (X)
External auditory canal/ tympanic membrane	Vagus (X)
Esophagus, stomach, pleura	Vagus (X)
Diaphragm, pericardium	Phrenic

*Greatest concentration of cough receptors.

Lancet 2008; 371: 1364–74
Otolaryngology–Head and Neck Surgery, Vol 134, No 4, April 2006

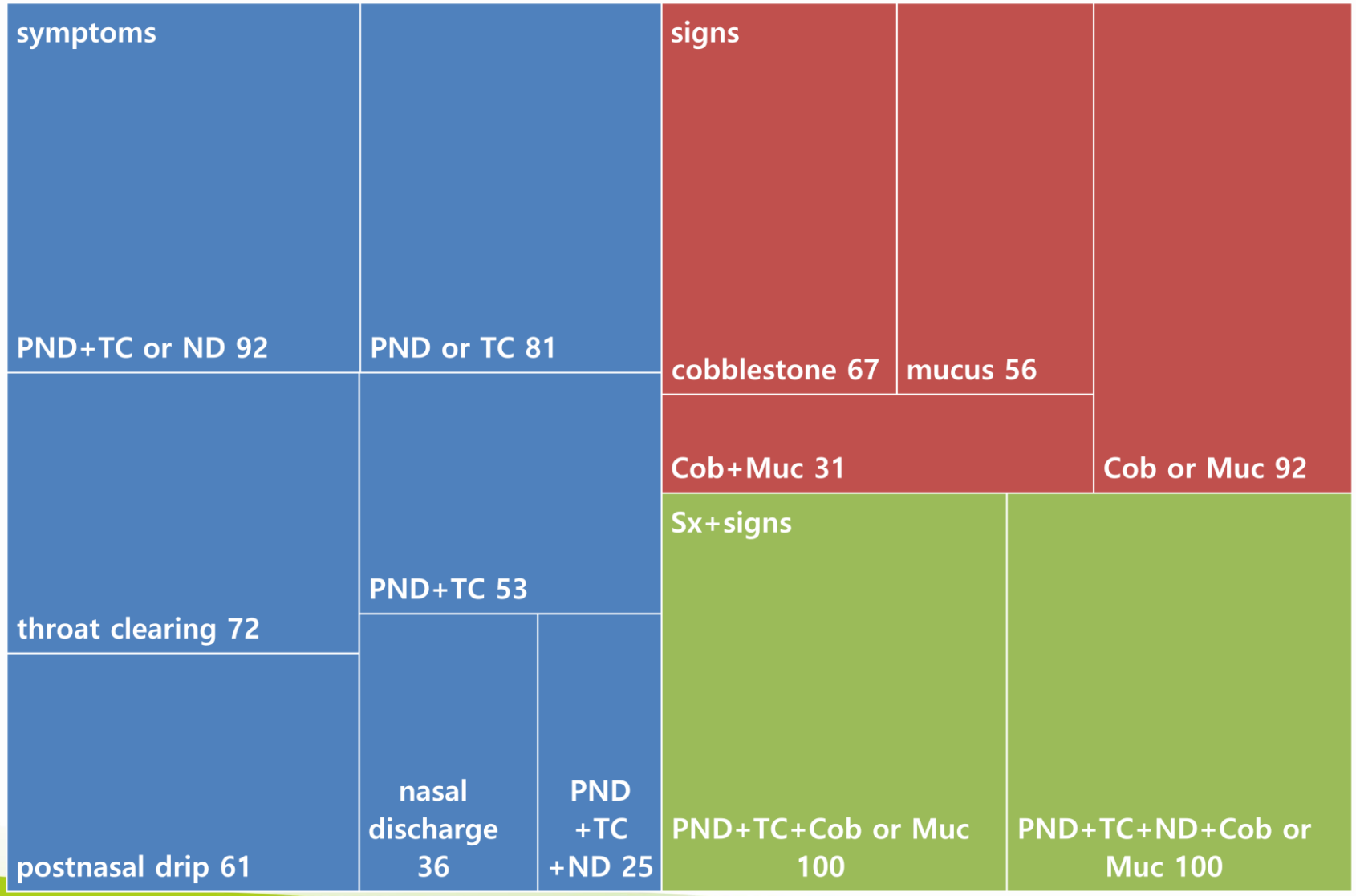
Upper Airway Cough Syndrome





Tuberc Respir Dis (Seoul). 2020 Jan;83(1):31-41
CHEST 1995; 108:991-97

Upper Airway Cough Syndrome



Irwin RS et al. Am Rev Respir Dis. 1990;141(3):640-7
Tuberc Respir Dis (Seoul). 2020 Jan;83(1):31-41

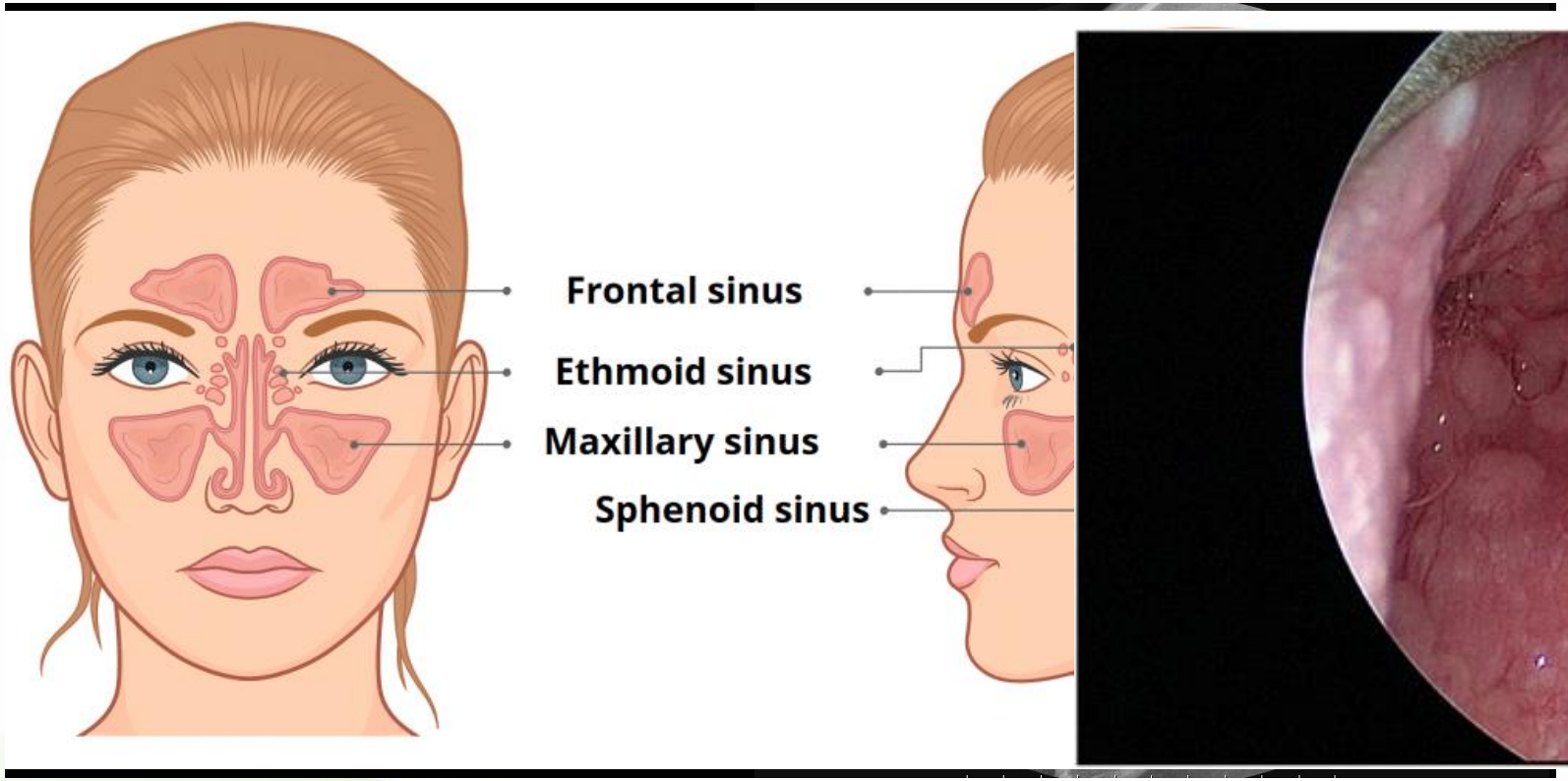
Upper Airway Cough Syndrome

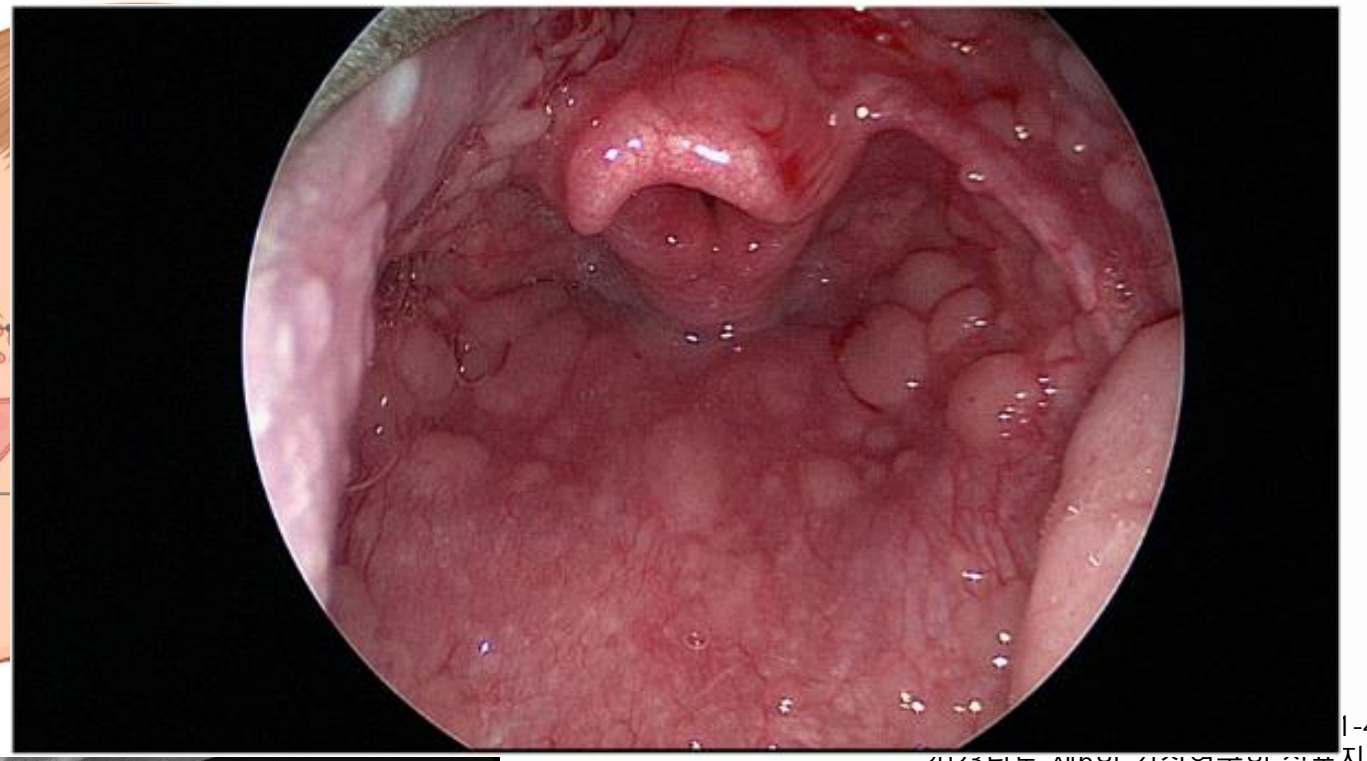
Characteristic	UACS (n=229)	Non-UACS (n=198)	p-value
Age, yr	49.1±15.5	50.2±15.2	0.462
Male sex	61 (26.8)	44 (22.3)	0.292
Cough duration, wk	52.6±127.6	75.3±218.8	0.201
Cough NRS			
Baseline	5.4±1.7	5.2±1.6	0.173
After initial treatment	2.4±1.7	2.8±2.0	0.031
After 4 weeks treatment	1.3±1.5	1.1±1.3	0.173
Treatment response			
After initial treatment	141 (70.5)	94 (55.0)	0.002
After 4 weeks treatment	172 (89.1)	149 (93.7)	0.130

Irwin RS et al. Am Rev Respir Dis. 1990;141(3):640-7
Tuberc Respir Dis (Seoul). 2020 Jan;83(1):31-41

Upper Airway Cough Syndrome

	Diagnostic test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
UACS	Abnormal PNS X-ray	29.9	91.9	81.0	53.0	58.5
	UACS symptoms	93.4	76.7	82.4	90.8	85.7

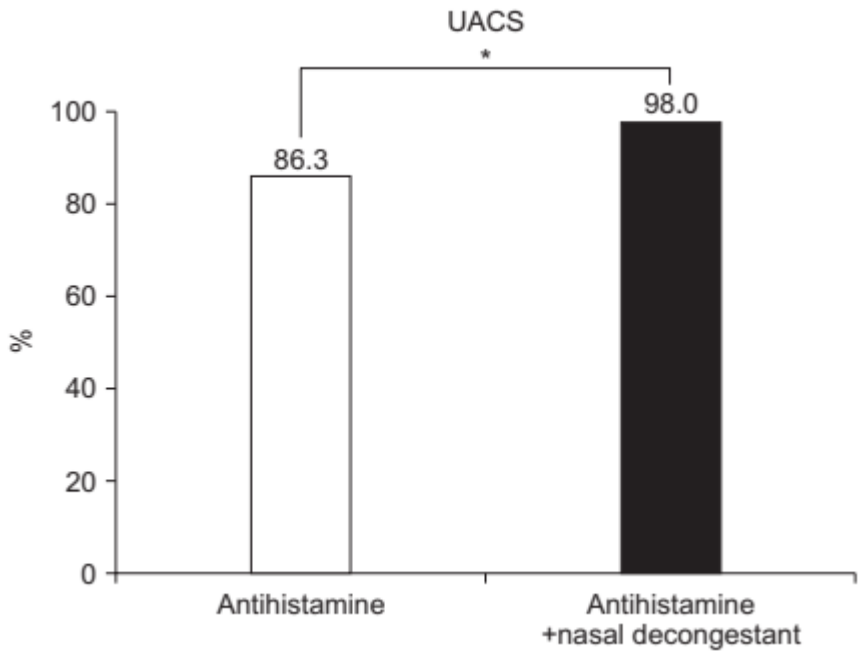




https://teachmeanatomy.info/wp-content/uploads/Anatomy-of-the-Paranasal-Sinuses-1024x489.png

Front. Pediatr. 2020 July 8:379

Upper Airway Cough Syndrome



약물	투여경로	콧물	가려움증	재채기	비충혈
Corticosteroids	비강	+++	+++	+++	+++
항히스타민제	비강	++	+++	+++	++
	경구	++	+++	+++	0/+
비충혈제거제	비강	0	0	0	+++
	경구	0	0	0	+++
항콜린제	비강	+++	0	0	0
비만세포안정화제	비강	+	+	+	0/+
류코트리엔 차단제	경구	+	0/+	+	++

Tuberc Respir Dis (Seoul). 2020 Jan;83(1):31-41
Applied therapeutics: the clinical use of drugs. 10th ed

Recent researches (after guideline)

BTS guideline 'chronic cough in adult'

BTS GUIDELINES

Recommendations for the management of cough in adults

A H Morice, L McGarvey, I Pavord, on behalf of the British Thoracic Society Cough Guideline Group

BTS Clinical Statement

British Thoracic Society Clinical Statement on chronic cough in adults

Sean M Parker,[1] Jaclyn Ann Smith ,[2] Surinder S Birring,[3,4] Sarah Chamberlain-Mitchell,[5] Kevin Gruffydd-Jones,[6] Jemma Haines ,[2,7] Sarah Hennessey,[8] Lorcan P McGarvey,[9] Paul Marsden,[2,7] Matthew James Martin,[10] Alyn Morice,[11,12] James O'Hara,[13,14] Mike Thomas[15]

2006 → 2023

Thorax 2006;61(Suppl I):i1–i24
Thorax 2023;6(suppl 6):3–19

BTS guideline 'chronic cough in adult'

2006 BTS Guidelines

•**Terminology** PNDS → UACS

•**Symptoms and Diagnosis:**

- Postnasal drip Sx..
- *Poor correlation* between the presence of these symptoms and the actual occurrence of cough.

•**Treatment:**

- 2-8weeks trial of topical corticosteroids
- 1st-generation antihistamines, though the efficacy of 2nd-generation antihistamines is debated.

Thorax 2006;61(Suppl I):i1–i24

BTS guideline 'chronic cough in adult'

2023 BTS Guidelines:

- **Terminology**

Upper airway symptoms, chronic rhinosinusitis and laryngeal hypersensitivity(multifactorial)

- **Symptoms and Diagnosis**
  - Nasal, as well as throat
  - Multifactorial ; obesity, reflux, psychogenic problem, etc.
- **Treatment**
  - Minimum 6 weeks of intranasal steroid spray with saline irrigation/rinses
  - ~~Antibiotics should be avoided~~
  - Secondary care referral should be considered if the nasal symptoms are not improved after 12 weeks of therapy.
  - ~~PPI~~s should not be used to treat upper airway symptoms.
  - Consider treatment of laryngeal hypersensitivity

Thorax 2023;6(suppl 6):3–19

BTS guideline 'chronic cough in adult'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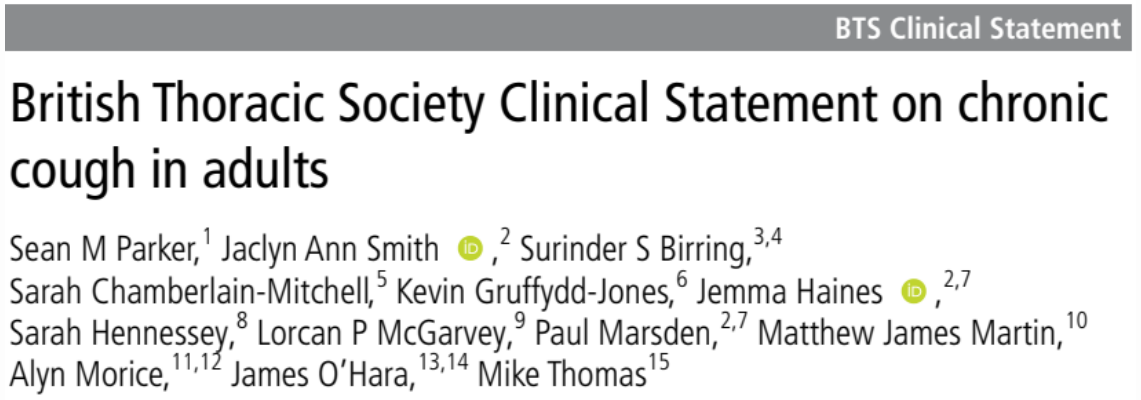
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- Multifactorial
- Antihistamine? ~~PPI, antibiotics~~
- Cough hypersensitivity

Thorax 2006;61(Suppl I):i1–i24
Thorax 2023;6(suppl 6):3–19

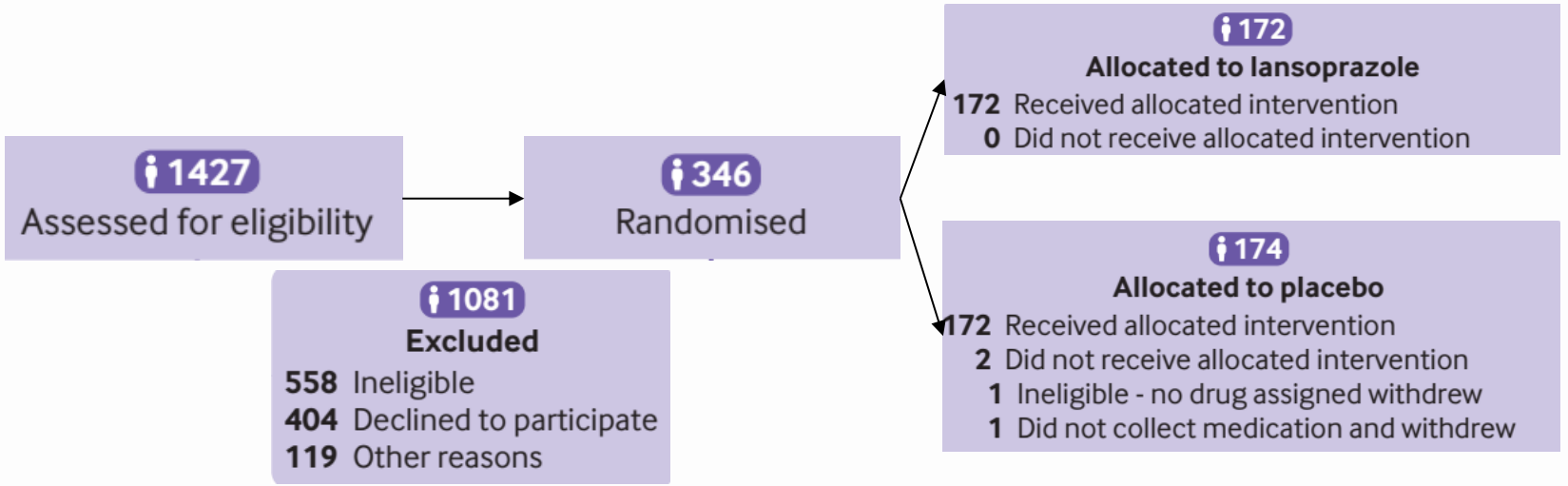
PPIs should not be used to treat upper airway symptoms

RESEARCH

Use of proton pump inhibitors to treat persistent throat symptoms: multicentre, double blind, randomised, placebo controlled trial

James O'Hara,[1,2] Deborah D Stocken,[3] Gillian C Watson,[4] Tony Fouweather,[5] Julian McGlashan,[6] Kenneth MacKenzie,[7] Paul Carding,[8] Yakubu Karagama,[9] Ruth Wood,[4] Janet A Wilson[10]

Age >18, Cough duration > 6wks, 2nd clinic



BMJ 2021;372:m4903

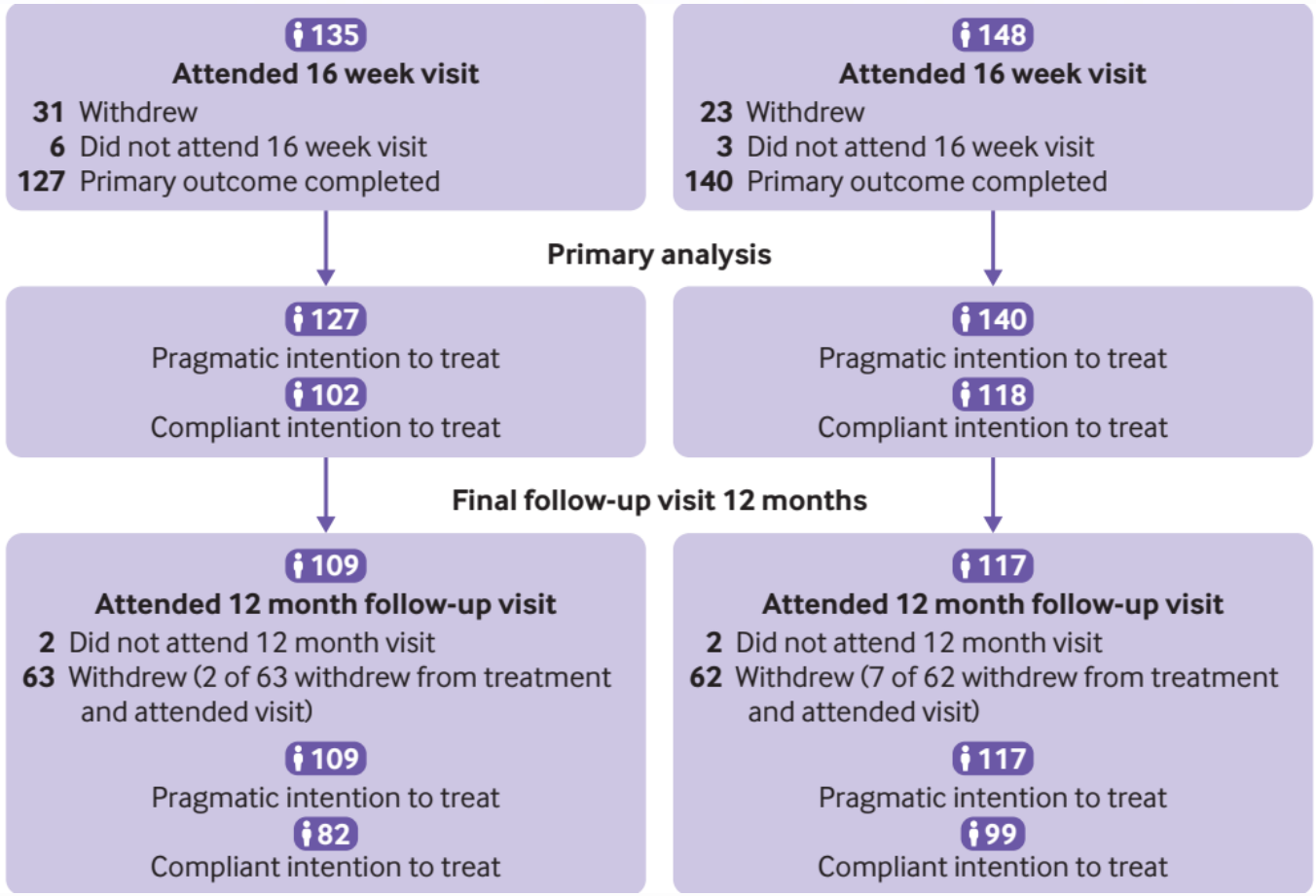
PPIs should not be used to treat upper airway symptoms

RESEARCH

Use of proton pump inhibitors to treat persistent throat symptoms: multicentre, double blind, randomised, placebo controlled trial

James O'Hara,[1,2] Deborah D Stocken,[3] Gillian C Watson,[4] Tony Fouweather,[5] Julian McGlashan,[6] Kenneth MacKenzie,[7] Paul Carding,[8] Yakubu Karagama,[9] Ruth Wood,[4] Janet A Wilson[10]

High dose PPI ; lansoprazole 30mg bid for 16weeks
→primary analysis at 1st 16wk
→secondary analysis at 1yr



BMJ 2021;372:m4903

PPIs should not be used to treat upper airway symptoms

Table 2 | Questionnaire outcome scores for compliant intention-to-treat group

Questionnaires and intervention	No in group	Mean score at follow-up (95% CI)		
		Baseline	16 weeks*	12 months
RSI*:				
Lansoprazole	102	22.0 (20.4 to 23.6)	17.4 (15.5 to 19.4)	16.0 (13.6 to 18.4)
Placebo	118	21.7 (20.5 to 23.0)	15.6 (13.8 to 17.3)	13.6 (11.7 to 15.5)
Difference†		0.3 (−1.7 to 2.3)	1.8 (−0.8 to 4.4)	2.4 (−0.6 to 5.4)
RSI-HB:				
Lansoprazole	102	20.3 (18.8 to 21.7)	16.3 (14.5 to 18.1)	14.7 (12.4 to 16.9)
Placebo	118	19.8 (18.6 to 21.0)	13.9 (12.2 to 15.5)	11.9 (10.1 to 13.7)
Difference†		0.5 (−1.4 to 2.4)	2.4 (−0.0 to 4.8)	2.8 (0.5 to 5.1)
CReSS:				
Lansoprazole	102	50.3 (44.9 to 55.7)	38.9 (33.4 to 44.3)	36.6 (29.8 to 43.5)
Placebo	118	51.1 (46.4 to 55.8)	34.7 (29.6 to 39.9)	31.8 (26.6 to 36.9)
Difference†		−0.8 (−7.9 to 6.3)	4.2 (−3.2 to 11.6)	4.8 (−3.5 to 13.1)
LPR-HRQL:				
Lansoprazole	102	28.9 (24.5 to 33.3)	20.5 (16.1 to 25.0)	18.8 (13.7 to 23.8
Placebo	118	26.5 (22.5 to 30.5)	17.1 (13.3 to 21.0)	13.9 (10.0 to 17.8)
Difference†		2.4 (−3.5 to 8.3)	3.4 (−2.4 to 9.2)	4.9 (−1.3 to 11.1)

RSI=reflux symptom index; RSI-HB=laryngopharyngeal RSI items without the heartburn score; CReSS=comprehensive reflux symptom score; LPR-HRQL=laryngopharyngeal health related quality of life.
*Primary outcome measure.
†Lansoprazole minus placebo is the difference in means (95% confidence intervals).

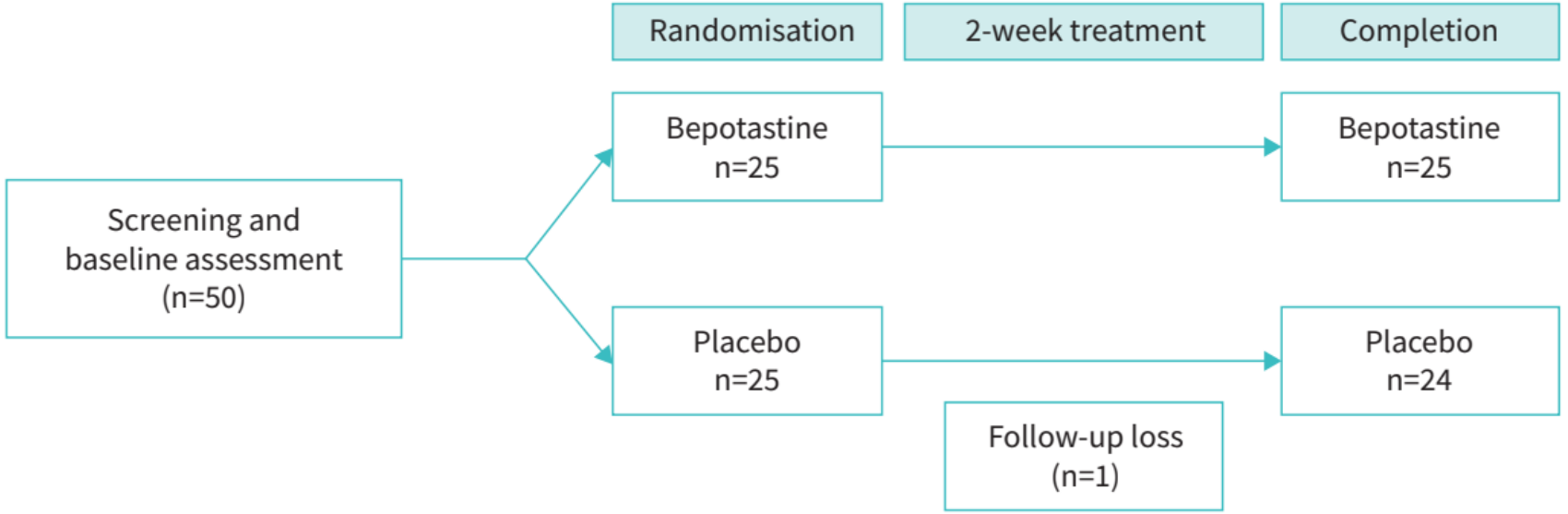
BMJ 2021;372:m4903

Non-sedating H1 receptor antagonist

ERJ OPEN RESEARCH
ORIGINAL RESEARCH ARTICLE
J-H. LEE ET AL.

Effects of bepotastine, a nonsedating H1-antihistamine, for the treatment of persistent cough and allergic rhinitis: a randomised, double-blind, placebo-controlled trial

Ji-Hyang Lee, Ji-Yoon Oh, Hyouk-Soo Kwon, Tae-Bum Kim, You Sook Cho and Woo-Jung Song

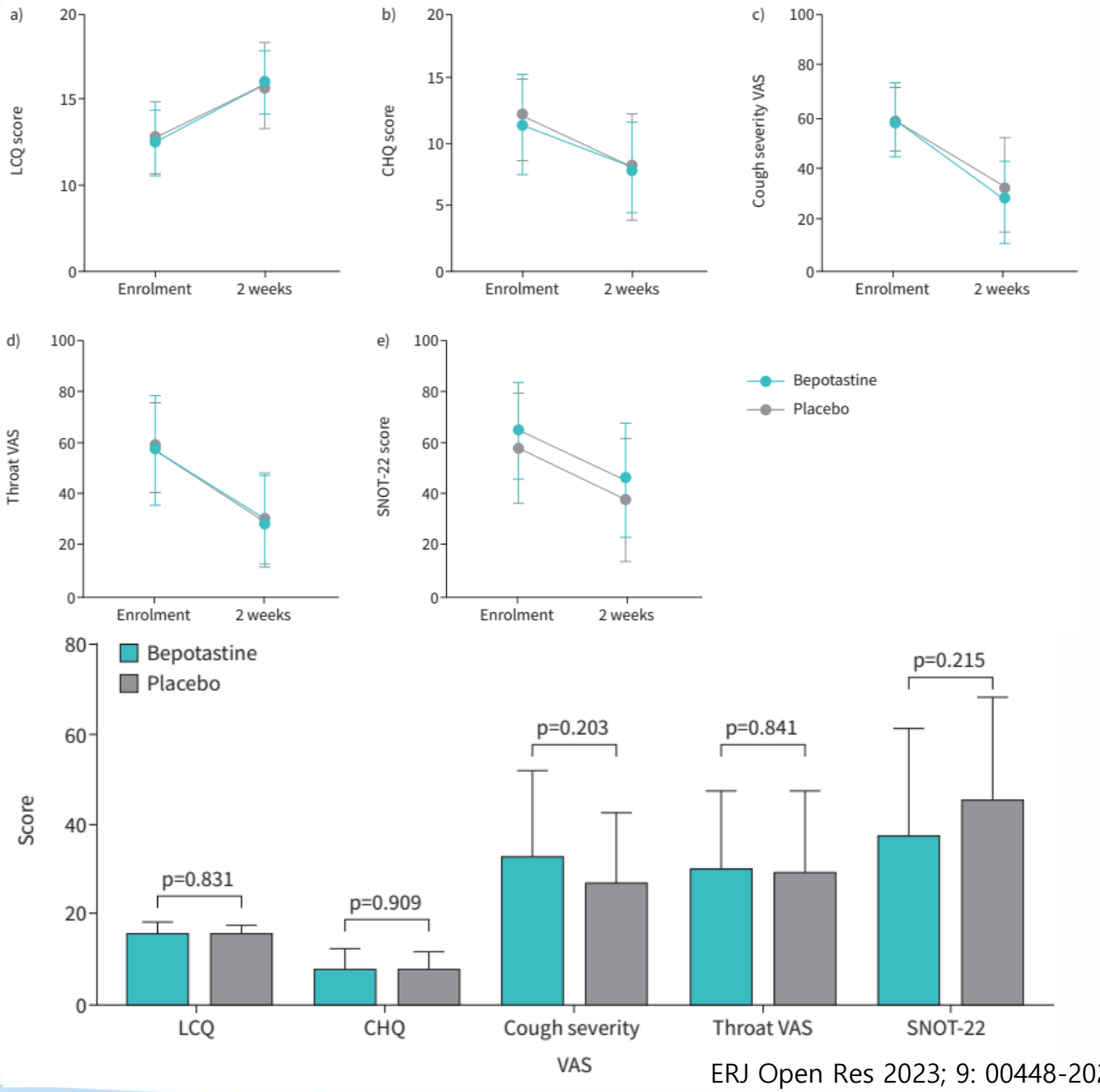


ERJ Open Res 2023; 9: 00448-2023

Non-sedating H1 receptor antagonist

	p-value (bepotastine *versus* placebo)	
	Post-treatment scores	Score difference (post- minus pre-treatment)
Participants		
Outcomes		
LCQ	0.831	0.576
Cough severity VAS	0.203	0.292
Throat VAS	0.841	0.894
CHQ	0.909	0.757
SNOT-22	0.215	0.739

Data are presented as n Questionnaire; SNOT-22: Sinonasal Outcome Test-22.

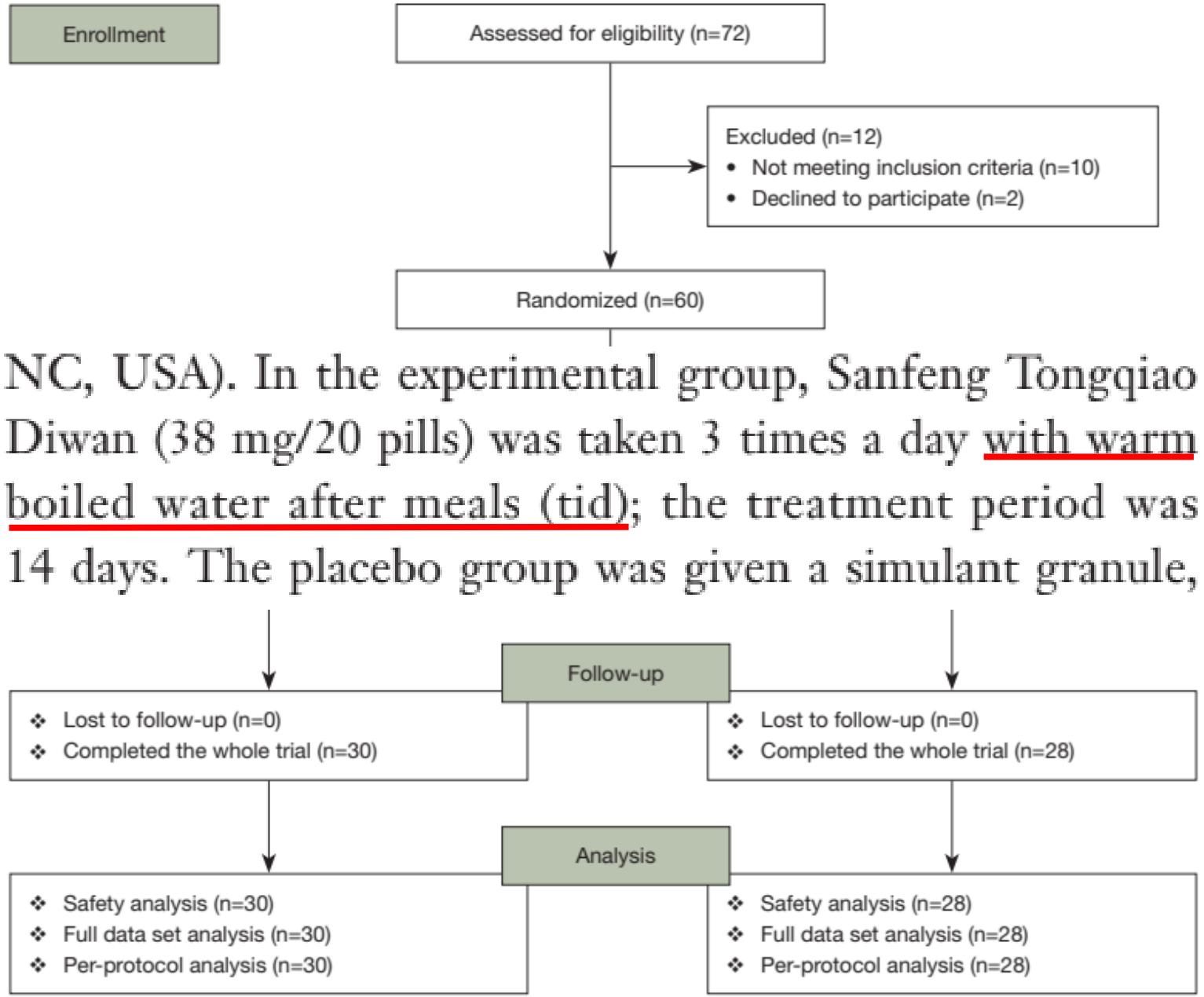


ERJ Open Res 2023; 9: 00448-2023

Original Article

Efficacy and safety c
of upper airway coug
placebo-controlled c

Wanjun Wang[1#], Mo Xian[1#], Xu S
Rundong Qin[1], Jing Li[1,2]



NC, USA). In the experimental group, Sanfeng Tongqiao Diwan (38 mg/20 pills) was taken 3 times a day with warm boiled water after meals (tid); the treatment period was 14 days. The placebo group was given a simulant granule,

ough the follow

of histamines

J Thorac Dis 2023;15(4):1716-1725

Sanfeng Tongqiao Diwan

Table 2 Comparison of the clinical efficacy in the 2 groups of patients with UACS

Clinical efficacy	Experimental group (n=30), n (%)	Placebo group (n=28), n (%)	Difference (95% CI)	P value
Completely recovered	1 (3.3)	0	3.3 (–9.0, 16.7)	0.330
Significantly effective	11 (36.7)	0	36.7 (17.6, 54.5)	<0.001
Effective	14 (46.7)	2 (7.1)	39.6 (16.9, 57.5)	<0.001
Total efficacy	26 (86.7)	2 (7.1)	79.6 (57.0, 89.1)	<0.001

Table 4 Comparison of LCQ-MC scores before and after treatment in the 2 groups of patients with UACS

Group	Time	Physiological score	Social score	Psychological score	Total score
Experimental group	Before treatment	30.7±5.5	19.8±2.5	26.3±5.2	78.8±7.9
	After treatment	41.4±3.9$^{\#*}$	24.0±2.9$^{\#*}$	40.5±4.3$^{\#*}$	109.6±6.5$^{\#*}$
Placebo group	Before treatment	31.4±4.1	21.6±3.4	26.8±5.5	80.9±8.1
	After treatment	30.7±4.3	20.4±3.5	28.1±5.4	81.2±7.3

miscellanous

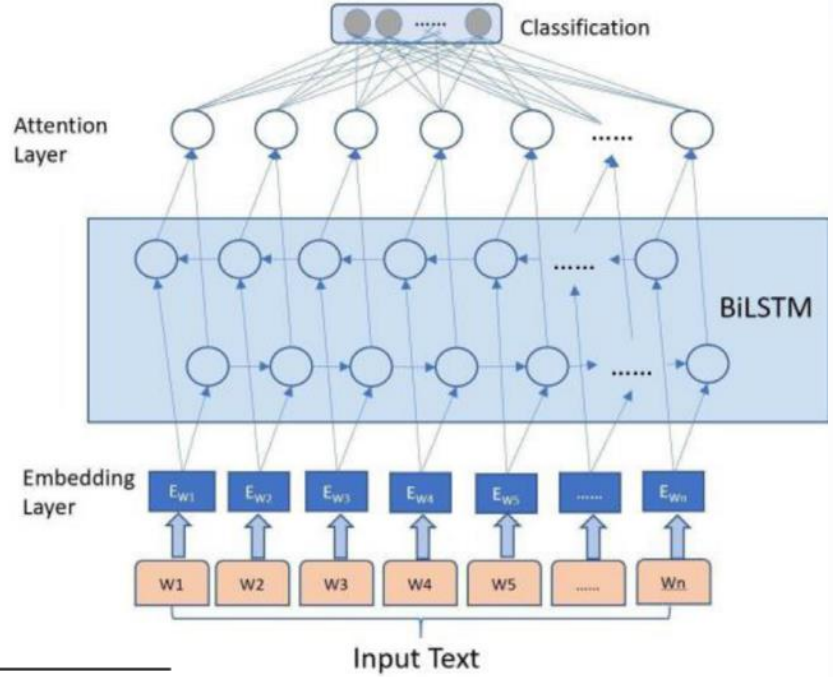
Contents lists available at ScienceDirect

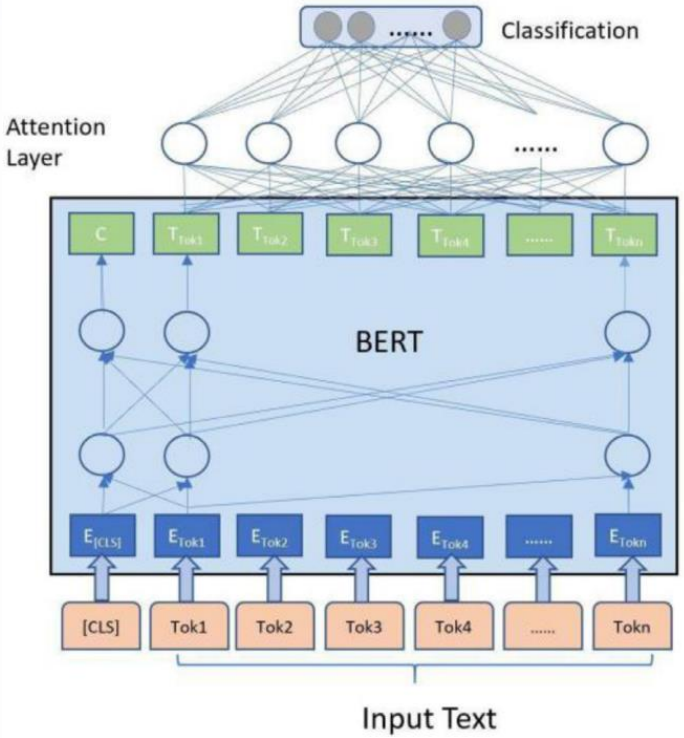
Computer Methods and Programs in Biomedicine

journal homepage: www.elsevier.com/locate/cmpb

Applying interpretable deep learning models to identify chronic cough patients using EHR data

Xiao Luo[a,*], Priyanka Gandhi[a], Zuoyi Zhang[b], Wei Shao[b], Zhi Han[b,d], Vasu Chandrasekaran[c,*], Vladimir Turzhitsky[c], Vishal Bali[c], Anna R. Roberts[d], Megan Metzger[d], Jarod Baker[d], Carmen La Rosa[c], Jessica Weaver[c], Paul Dexter[b,d,e], Kun Huang[b,d,*]





	Category	Non-CC (N = 23,572)	CC (N = 23,572)
Age	Mean (SD)	45(18)	54(17)
Gender	Male	9015(38.25)	8088(34.31)
	Female	14,566(61.75)	15,484(65.69)
	Unknown	1	–
Race	Black	4835(20.51)	4043(17.15)
	Other	4397(18.65)	1062(4.51)
	White	14,340(60.83)	18,467(78.34)
Urbanicity	Rural	2058(9.19)	2695(12.05)
	Urban	20,332(90.81)	19,663(87.95)
	Unknown	1182	1214

miscellanous

Original Article

The Predicative Clinical Features Associ
Chronic Cough That Has a Single Underl

Kefang Lai, MD, PhD*, Wenzhi Zhan, MD*, Hu Li, MD*, Fang Yi, MD, PhD, Wen P
Jiaman Tang, MD, Liting Zhang, MD, Li Long, MD, Ruchong Chen, MD, PhD, Wei
Mei Jiang, MD, PhD, and Nanshan Zhong, MD† *Guangzhou, Guangdong, P.R. China*

TABLE IV. Univariate and multiple logistic regression of predictors of

	Univariate analysis		Multiple analysis		
Characteristic	OR	95% CI	OR	95% CI	*P* value
Age	0.980	0.964-0.997	0.986	0.969-1.004	.1193
Sex: female	0.628	0.403-0.980	0.723	0.450-1.161	.1789
Postnasal dripping	3.240	2.056-5.105	2.317	1.425-3.767	.0007
Frequent throat clearing	2.965	1.879-4.678	2.228	1.378-3.601	.0011
History of sinusitis	5.079	3.113-8.288	4.137	2.483-6.892	<.0001
Nasal itching	1.671	1.049-2.663			
Nasal congestion	2.147	1.375-3.353			
Runny nose	2.226	1.417-3.498			
History of rhinitis	1.689	1.068-2.670			

TABLE V. Predictive clinical features for common causes of chronic cough

Cause	Clinical feature	Sensitivity	Specificity
UACS	History of sinusitis	35.7%	90.2%
	Postnasal dripping	43.5%	80.8%
	Rhinitis/sinusitis-related symptoms§	72.9%	46.1%

J Allergy Clin Immunol Pract 2021;9:426-32

Post-pandemic (after COVID19)

Post COVID19 cohort

Lung (2022) 200:161–168
https://doi.org/10.1007/s00408-022-00525-2

COUGH

Cough in the Elderly During the COVID-19 Pandemic

Johanna Tuulikki Kaulamo[2,3] · Anne Marika Lätti[1] · Heikki Olavi Koskela[1,2]

Characteristic	No current cough (n=4874)	Acu (n=
Age, years	72.5 (5.0)	72.8
Female gender, %	66.0	70.6
Body mass index, kg/m^2	27.3 (4.5)	27.2
Current smoker, %	1.7	2.4
Ever-smoker, %	34.5	34.1
Family history of chronic cough, %	21.9	25.0
Acute respiratory infection at onset of cough, %	NA	41.2
COVID-19 infection, %	0.3	2.4*

Characteristic	Adjusted OR and 95% CI
Bronchiectasis	4.84 (2.30–10.17)***
COVID-19 infection	2.91 (1.07–7.91)*
Current asthma[a]	2.58 (1.99–3.35)***
Chronic rhinosinusitis[a]	2.38 (1.87–3.03)***
Pulmonary fibrosis	2.36 (1.02–5.49)*
Family history of chronic cough	1.79 (1.48–2.16)***
Gastro-oesophageal reflux disease[a]	1.66 (1.35–2.03)***
Allergy	1.44 (1.11–1.88)**
Obstructive sleep apnoea[a]	1.43 (1.19–1.72)***
Dog ownership	1.39 (1.06–1.81)*
Age[b]	1.17 (1.01–1.34)*
Somatic symptom score[c]	1.13 (1.08–1.18)***

Post COVID19 cohort

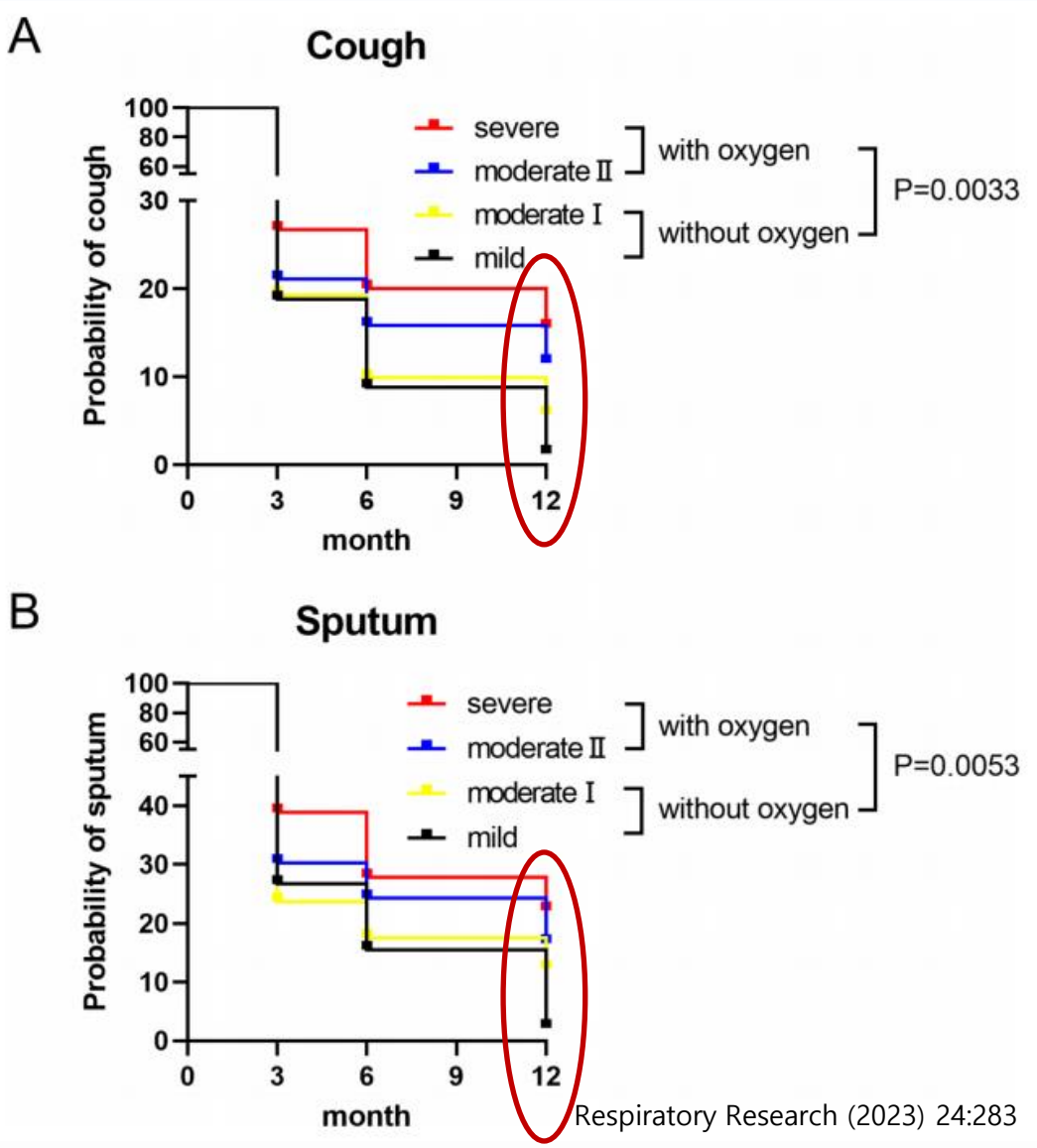
RESEARCH Open Access

Cough and sputum in long COVID are associated with severe acute COVID-19: a Japanese cohort study

Mayuko Watase[1,5], Jun Miyata[1*], Hideki Terai[1,2*], Keeya Sunata[1], Emiko Matsuyama[1], Takanori Asakura[1], Ho Namkoong[3], Katsunori Masaki[1], Kazuma Yagi[1], Keiko Ohgino[1], Shotaro Chubachi[1], Ichiro Kawada[1,4], Takao Mochimaru[5], Ryosuke Satomi[5], Yoshitaka Oyamada[5], Keigo Kobayashi[6], Toshiyuki Hirano[6], Takashi Inoue[6], Ho Lee[7], Kai Sugihara[7], Nao Omori[7], Koichi Sayama[7], Shuko Mashimo[8], Yasushi Makino[8], Tatsuya Kaido[8], Makoto Ishii[9] and Koichi Fukunaga[1]

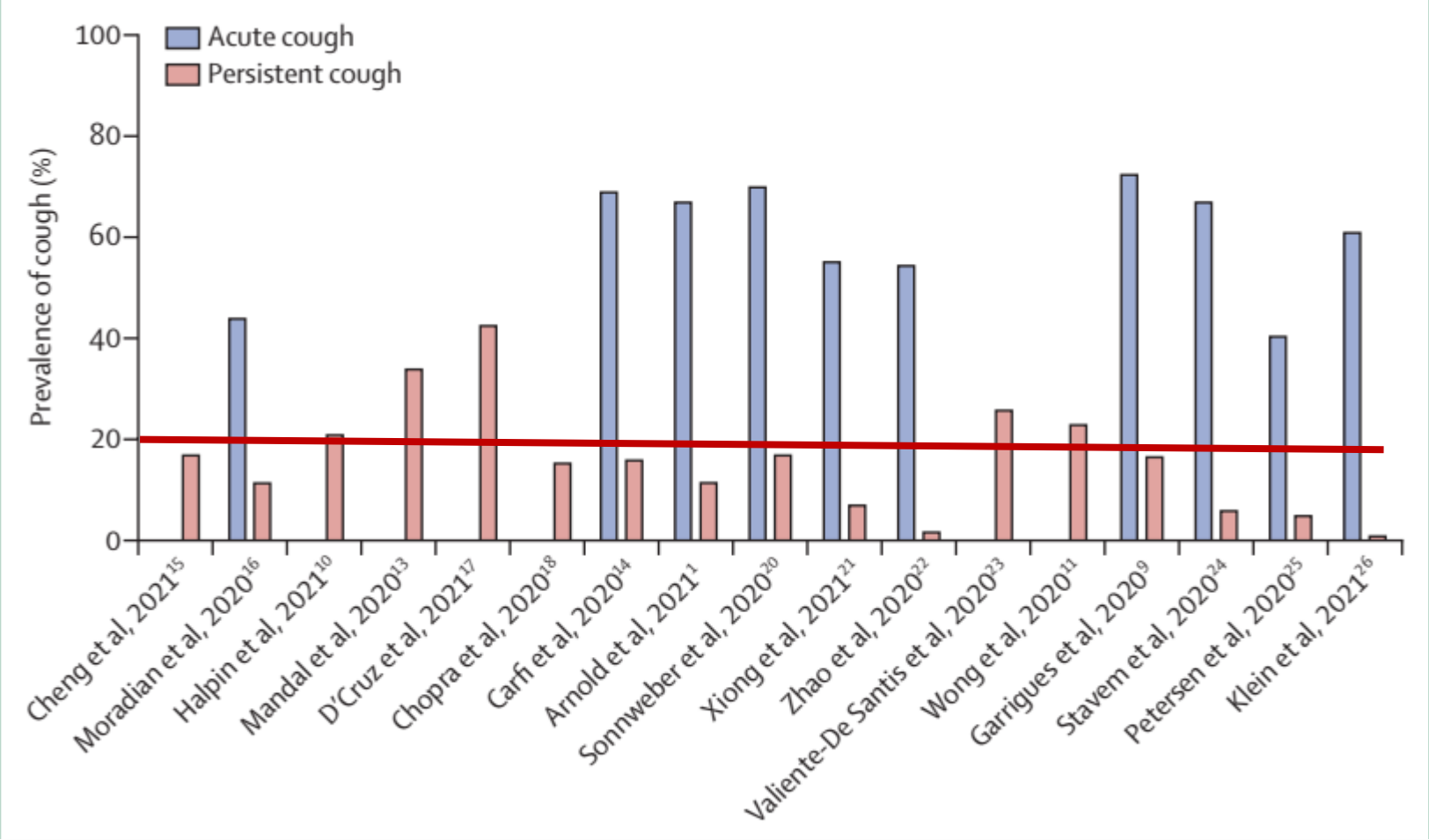
Table 2 Clinical symptoms of patients with and without cough or sputum in PRO after 12 months

	Cough			Sputum		
	Symptom (+) (N = 32)	Symptom (-) (N = 692)	*p* value	Symptom (+) (N = 36)	Symptom (-) (N = 688)	*p* value
Clinical symptoms on admission, n (%)						
Fever	23 (71.9)	587 (84.8)	0.049[a]	29 (80.6)	581 (84.4)	0.532[a]
Cough	26 (81.3)	406 (58.7)	< 0.001[a]	27 (75.0)	405 (58.9)	0.054[a]
Sputum	22 (68.8)	248 (35.8)	< 0.001[a]	28 (77.8)	242 (35.2)	< 0.001[a]
Sore throat	12 (37.5)	194 (28.0)	0.189[a]	16 (44.4)	191 (27.7)	0.006[a]
Taste impairment	9 (28.1)	250 (36.1)	0.356[a]	16 (44.4)	215 (31.3)	0.098[a]
Smell impairment	6 (18.8)	235 (34.0)	0.074[a]	11 (30.6)	200 (29.1)	0.848[a]
Dyspnea	22 (68.8)	319 (46.1)	0.012[a]	22 (61.1)	315 (45.8)	0.072[a]
Abdominal pain	5 (15.6)	65 (9.4)	0.002[a]	5 (13.9)	65 (9.4)	0.379[a]
Diarrhea	4 (12.5)	151 (21.8)	0.209[a]	7 (19.4)	148 (21.5)	0.768[a]



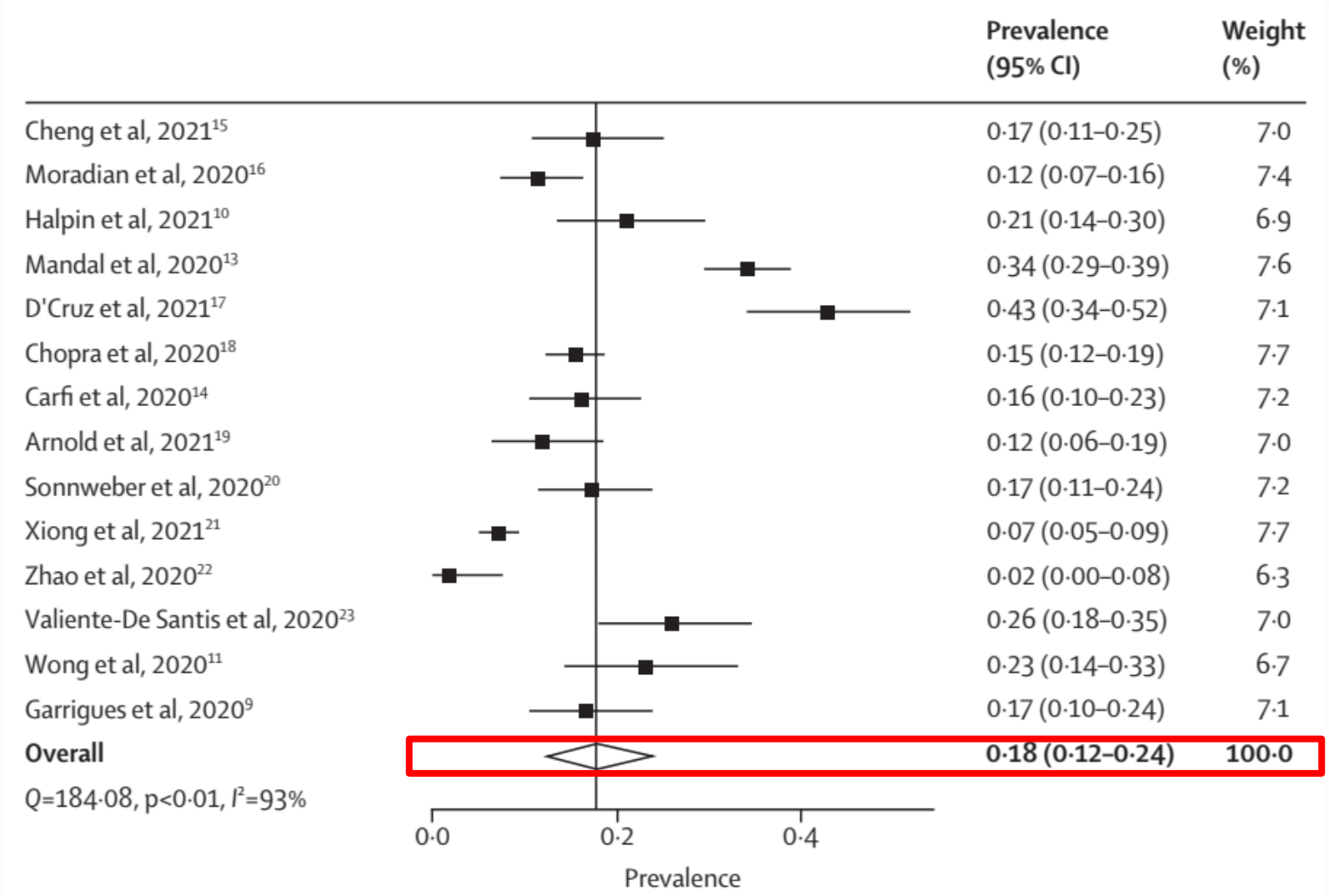
Respiratory Research (2023) 24:283

Post-COVID19 cough



Lancet Respir Med 2021; 9: 533–44

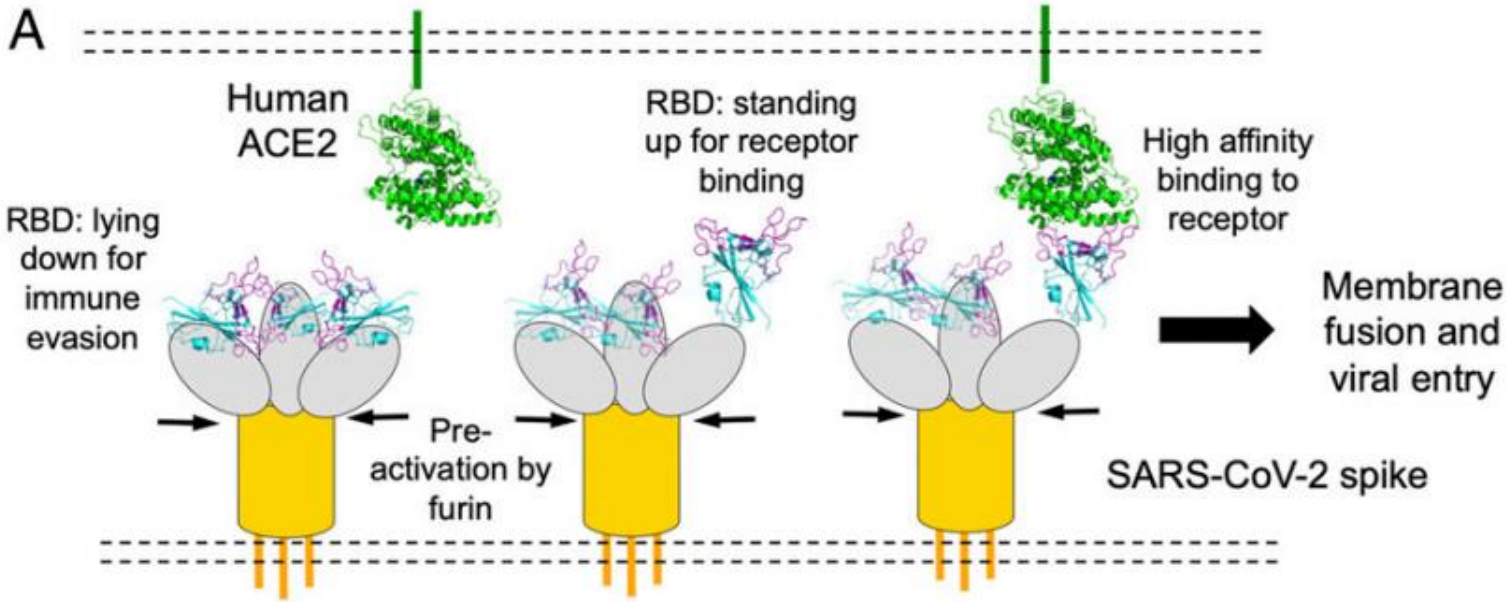
Post-COVID19 cough



Lancet Respir Med 2021; 9: 533–44

Angiotensin converting enzyme 2

A

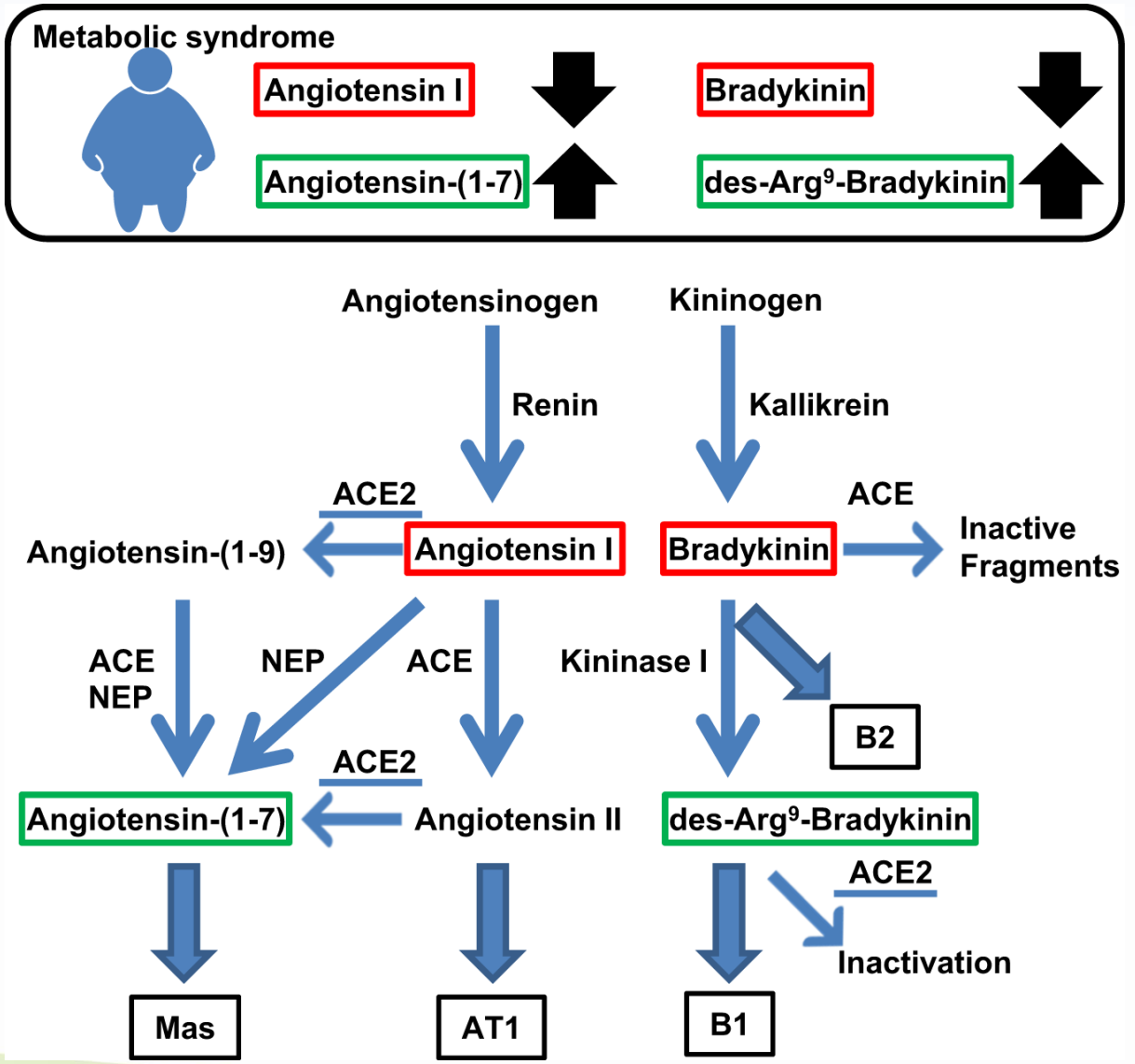


B

Features of viral entry	SARS-CoV	SARS-CoV-2	Implications for SARS-CoV-2
Frequency of RBD standing up	High	Low	Immune evasion (hidden RBD)
Human ACE2-binding affinity by RBD	Low	High	Enhanced entry (compensation for hidden RBD)
Pre-activation by furin	No	Yes	Enhanced entry into some types of cells (compensation for hidden RBD)

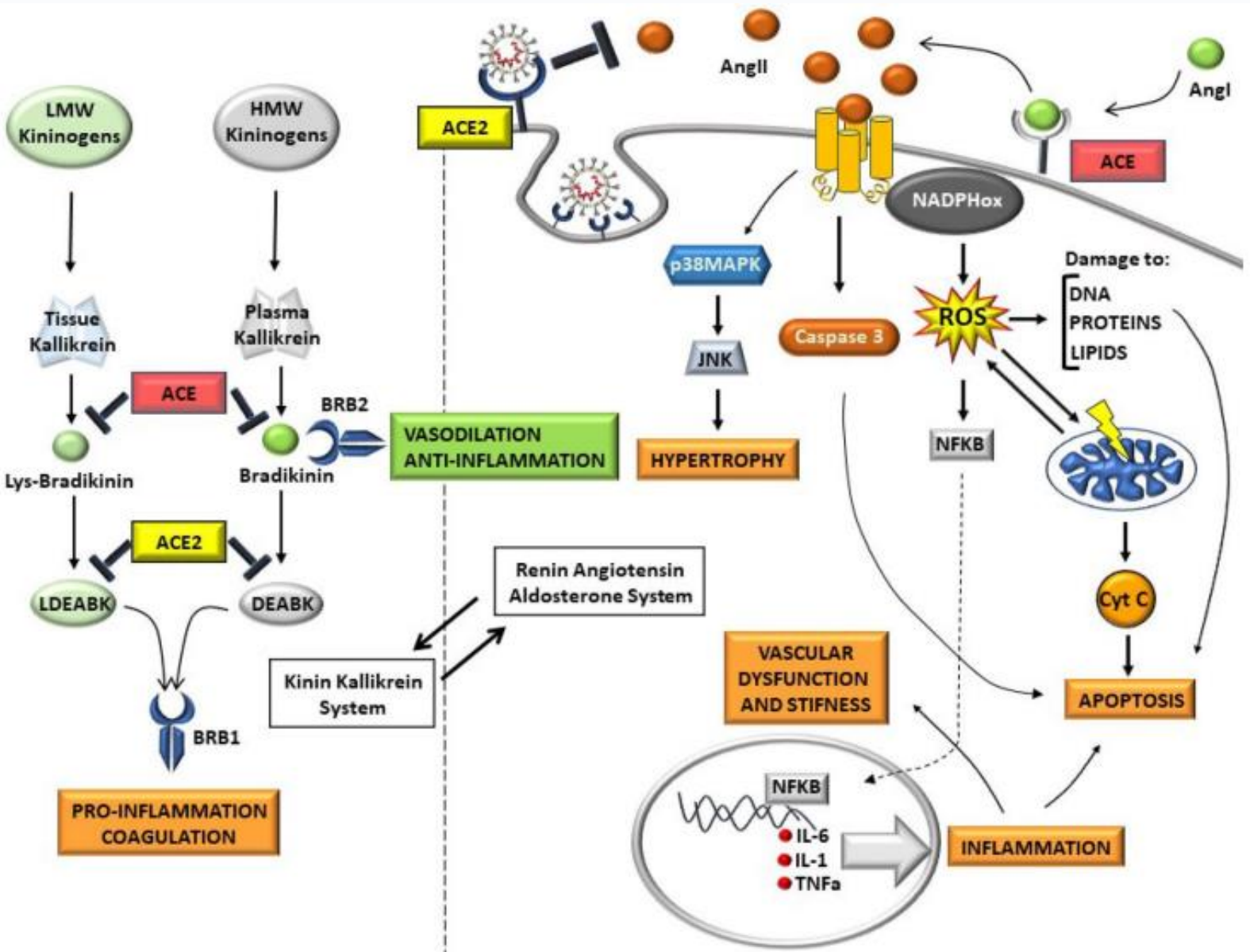
Proc Natl Acad Sci U S A. 2020 May 26;117(21):11727-11734

Angiotensin converting enzyme 2



Hypertens Res 44, 1034–1036 (2021)

Angiotensin converting enzyme 2

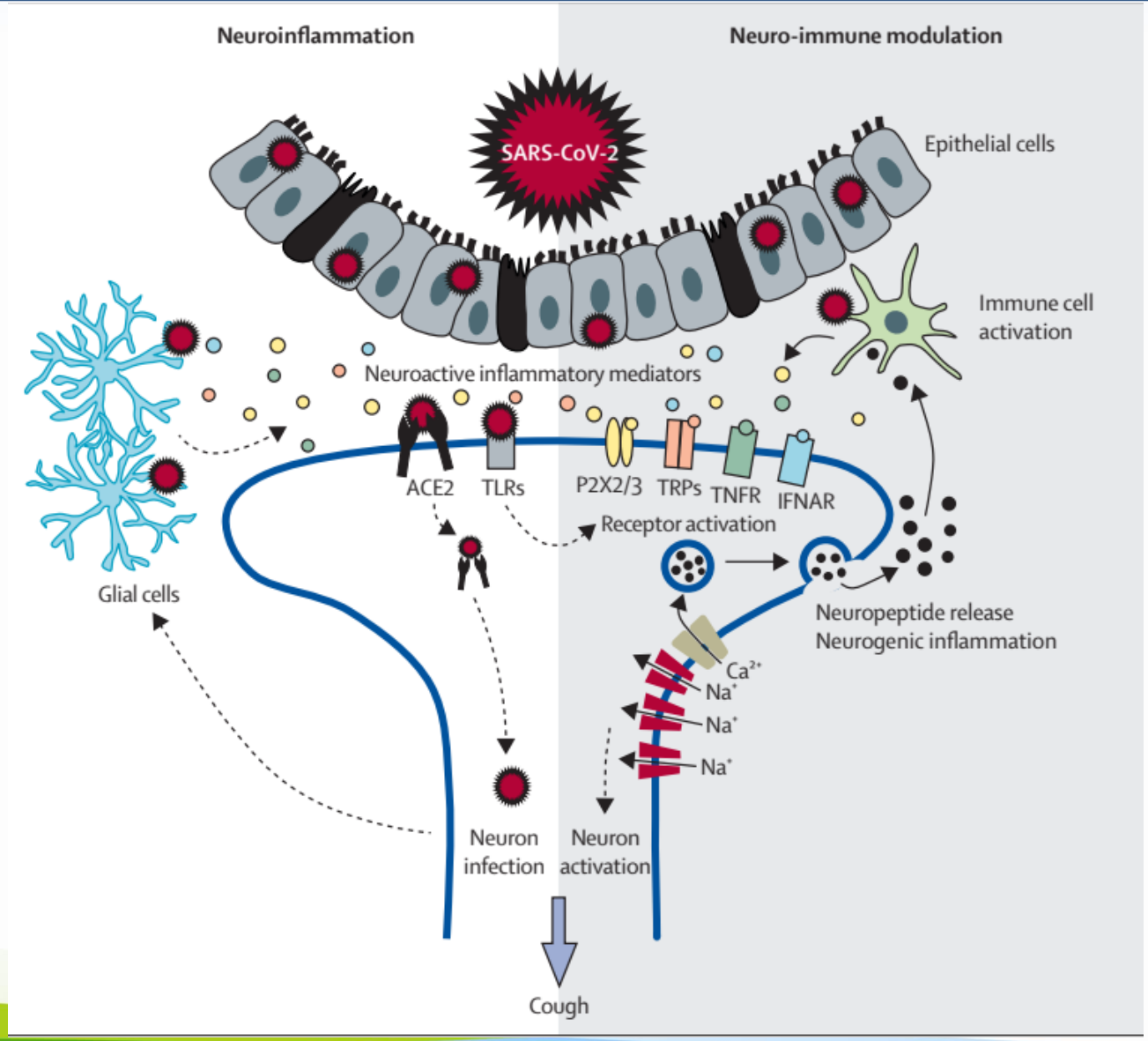


Bradykinin accumulation
→Smooth m. contraction
→Bronchoconstriction

Intracellular signaling pathway
→Inflammatory cytokine aggreagation
→inflammation

Lung (2020) 198:867–877

Neuronal mechanisms of hypersensitivity

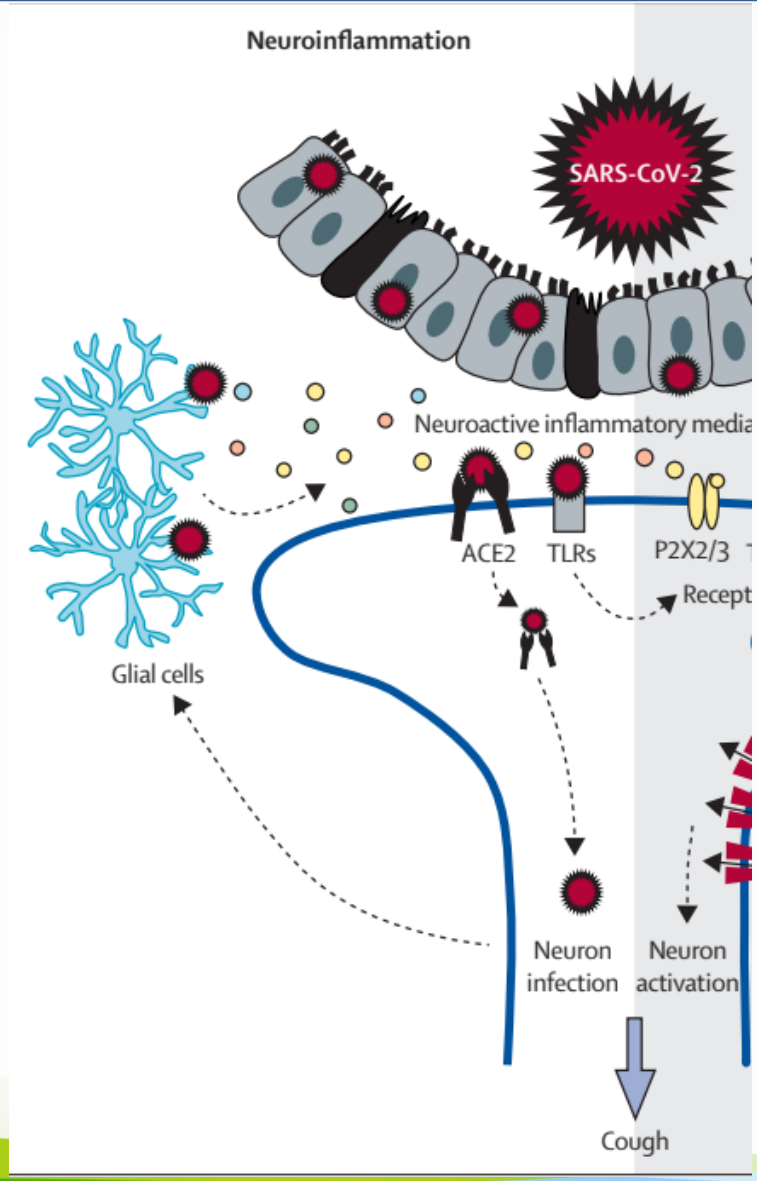


Neuro-inflammation

Neuro-immunemodulation

Lancet Respir Med 2021; 9: 533–44

Neuronal mechanisms of hypersensitivity

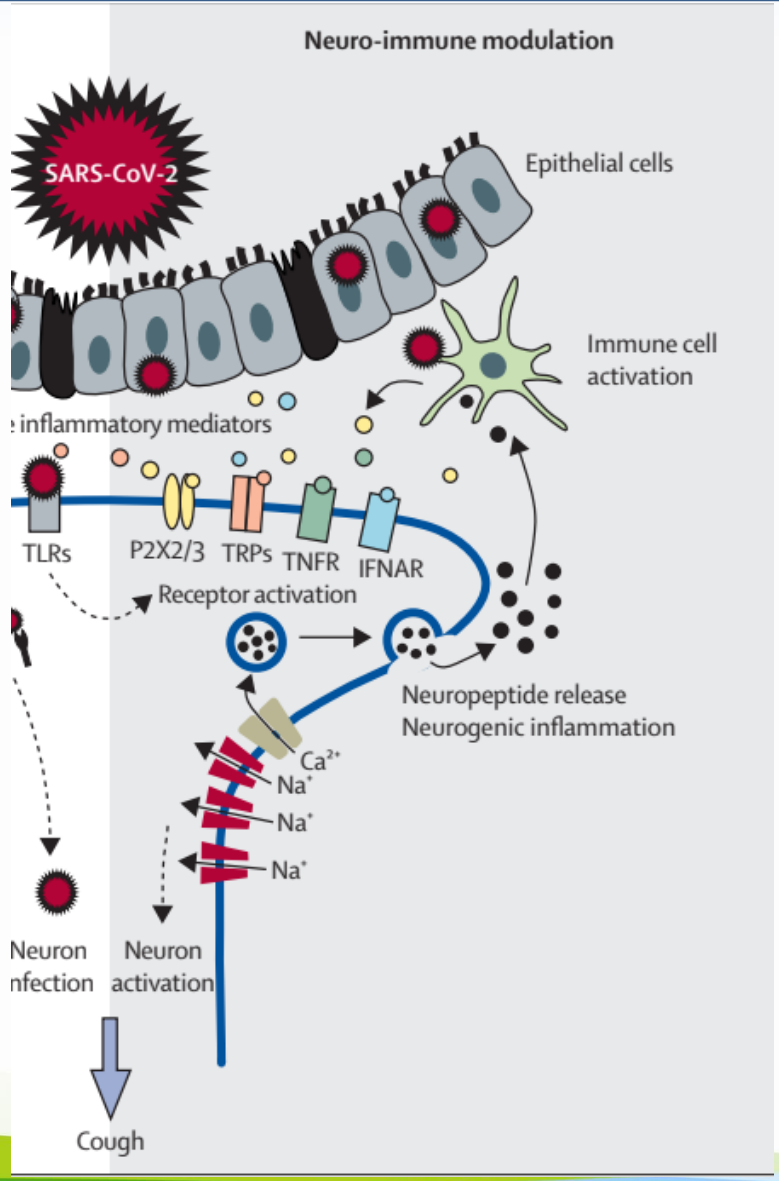


Neuro-inflammation

1. Direct invasion of sensory neuron(vagal n.)
2. Every airway epithelium that vagal n. innervates
3. Interferons, glial-derived ATP ;mediator
4. Can explain “Long COVID19 syndrome” ;direct invasion of dorsal root ganglion on vagal n.

Lancet Respir Med 2021; 9: 533–44

Neuronal mechanisms of hypersensitivity

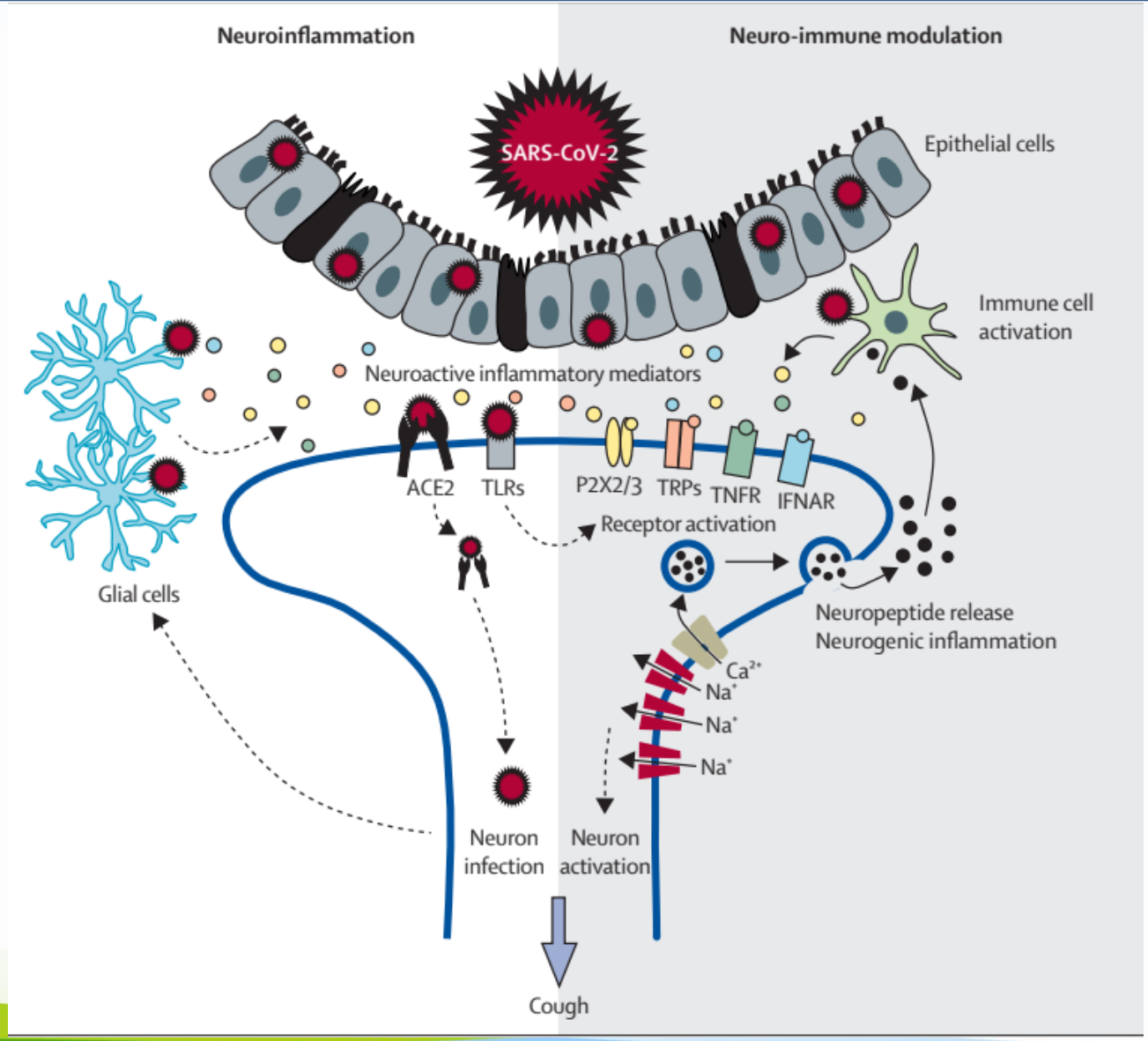


Neuro-immunemodulation

1. Classic inflammatory cells
   ; Antiviral interferon, cytokine, prostanoid, lipid mediator, ATP
2. Vagal neuronal activity elevation
3. Increased neuropeptides → inflammatory cell recruitment

Lancet Respir Med 2021; 9: 533–44

Neuronal mechanisms of hypersensitivity



Neuro-inflammation

→Direct injury/infection

Neuro-immunemodulation

→Indirect injury

Lancet Respir Med 2021; 9: 533–44

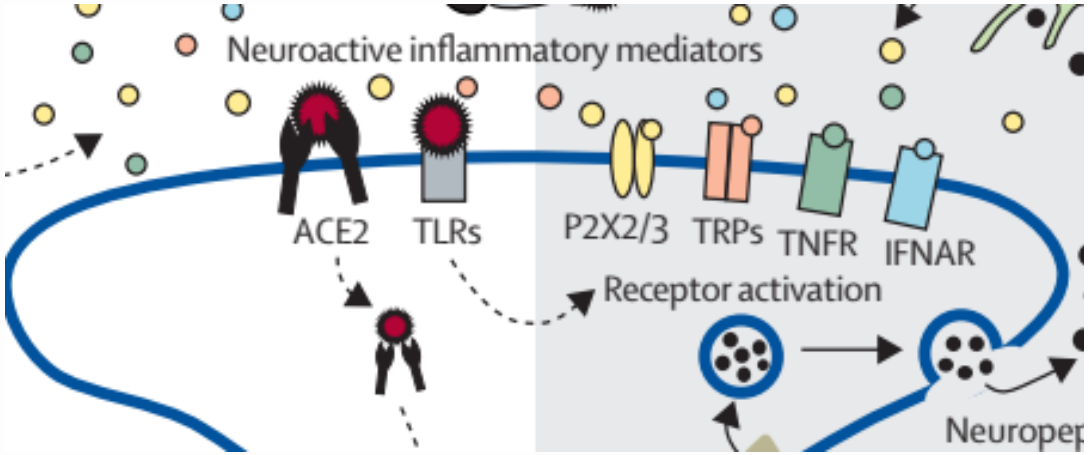
Management? Suggestion of management of chronic cough

1. Treat as you know
2. Neuromodulator ; gabapentin, pregabalin
3. Novel agent – no trials in COVID19
    1. ~~Inhibitors of TRP channels~~
    2. ATP-gated P2X3 receptor antagonist
    3. Neurokinin-1 receptors (NK1Rs) antagonist
    4. Sodium channel blocker.

Lancet Respir Med 2021; 9: 533–44

Novel agent for management of chronic cough

2. ATP-gated P2X3 receptor antagonist



sensory C fibers of the vagus nerve

	24–h cough frequency, % reduction (95% CrI)	Cough severity VAS, mm (95% CrI)	LCQ total score, points (95% CrI)	Taste disturbance, absolute risk difference per 100 patients (95% CrI)	AEs related to treatment, absolute risk difference per 100 patients (95% CrI)	Discontinuation due to AEs, absolute risk difference per 100 patients (95% CrI)	Serious AEs, absolute risk difference per 100 patients (95% CrI)
No. of participants† (No. of trials)	4,113 (14)	4,255 (14)	4,107 (13)	4,897 (16)	4,870 (16)	4,897 (16)	4,897 (16)
Effects and risks in placebo‡	33.1%	–20.6 mm	2.7 points	5 per 100	19 per 100	3 per 100	3 per 100
	Effects and risks in addition to placebo effect						
Camlipixant	14.7 (5.4 to 26.0)	–12.6 (–23.6 to –2.8)	0.3 (0.1 to 0.5)	2 more (1 to 6 more)	5 more (3 to 10 more)	4 more (2 to 10 more)	0 more§ (0 to 3 more)
Eliapixant	14.3 (5.4 to 25.1)	–4.0 (–8.3 to –0.8)	0.1 (0.02 to 0.1)	3 more (1 to 7 more)	5 more (3 to 10 more)	6 more (2 to 28 more)	1 more (0 to 2 more)
Filapixant	22.2 (8.1 to 39.0)	–12.0 (–19.9 to –5.1)	0.4 (0.01 to 0.8)	4 more (1 to 13 more)	23 more (10 to 55 more)	6 more§ (5 to 25 more)	0 more§ (0 to 15 more)
Gefapixant	28.1 (21 .0 to 35.6)	–11.1 (–14. 7 to –8.0)	0.9 (0.6 to 1.2)	38 more (27 to 51 more)	40 more (30 to 53 more)	14 more (7 to 24 more)	1 more (1 to 2 more)
Sivopixant	5.8 (–5. 1 to 17. 7)	–2.1 (–7.1 to 3.0)	0.2 (–0.1 to 0.4)	6 more (2 to 16 more)	9 more (5 to 17 more)	7 more (2 to 23 more)	1 more (0 to 3 more)

Confidence rating of CINeMA	Important benefit	Nonimportant difference	Important harm
High certainty			
Moderate certainty			
Low certainty			
Very low certainty			

Novel agent for management of chronic cough

2. ATP-gated P2X3 receptor antagonist

Gefapixant, a P2X3 receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase 2b trial

*Jaclyn A Smith, Michael M Kitt, Alyn H Morice, Surinder S Birring, Lorcan P McGarvey, Mandel R Sher, Yu-Ping Li, Wen-Chi Wu, Zhi Jin Xu, David R Muccino, Anthony P Ford, on behalf of the Protocol 012 Investigators**

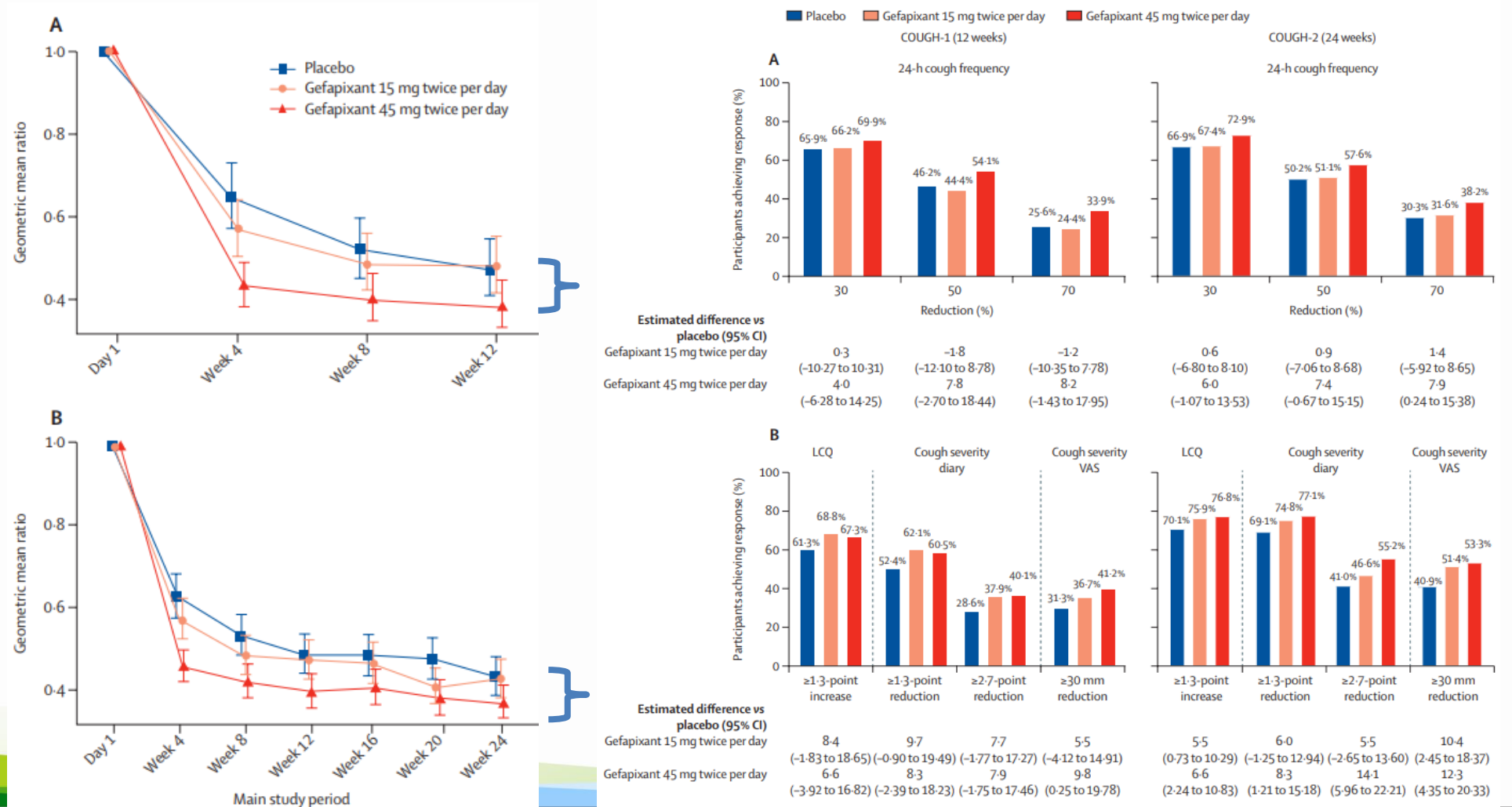
Efficacy and safety of gefapixant, a $P2X_3$ receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials

*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**

Lancet Respir Med 2020; 8: 775–85
Lancet 2022; 399: 909–23

Novel agent for management of chronic cough

2. ATP-gated P2X3 receptor antagonist



Lancet Respir Med 2020; 8: 775–85
Lancet 2022; 399: 909–23

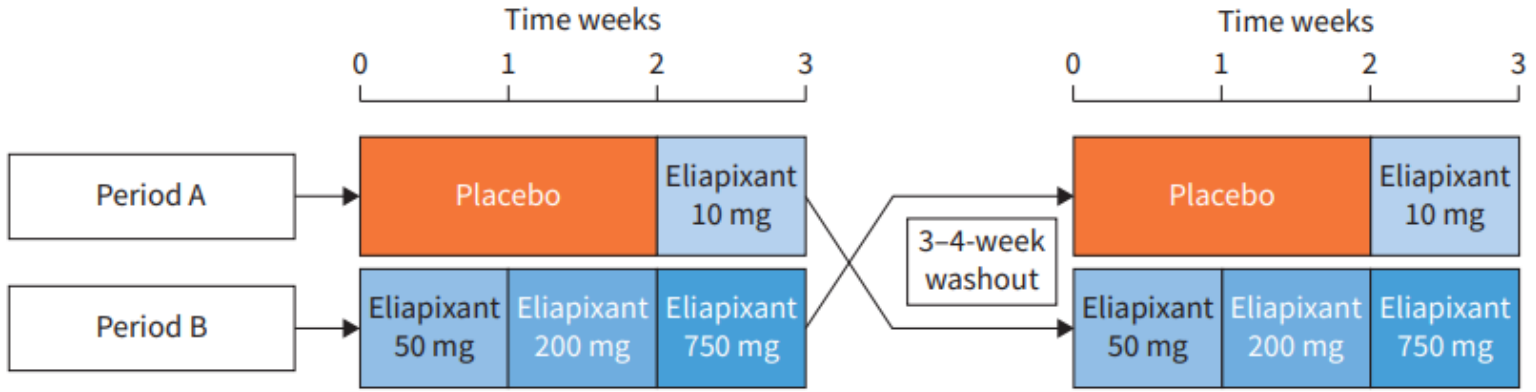
Novel agent for management of chronic cough

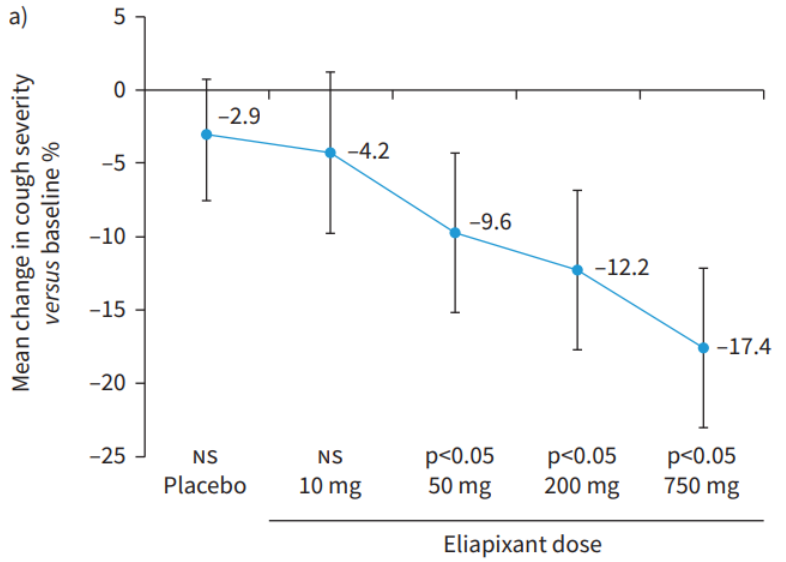
2. ATP-gated P2X3 receptor antagonist

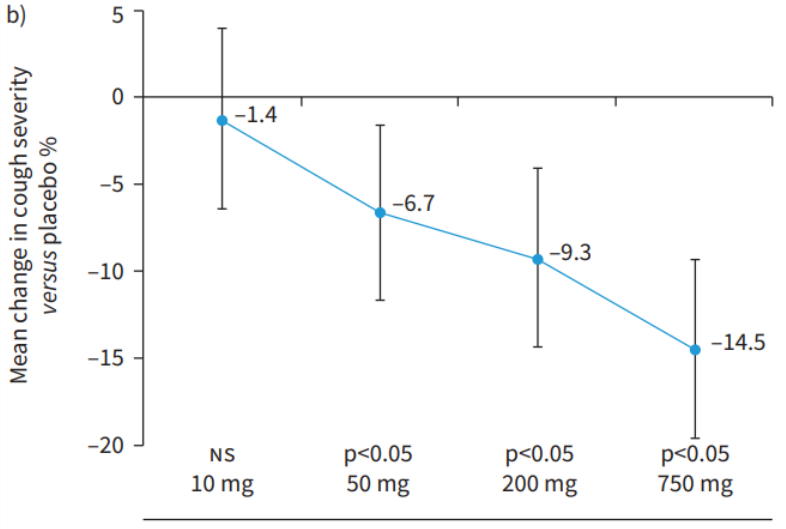
EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
A. MORICE ET AL.

Eliapixant (BAY 1817080), a P2X3 receptor antagonist, in refractory chronic cough: a randomised, placebo-controlled, crossover phase 2a study

Alyn Morice[1], Jaclyn A. Smith[2], Lorcan McGarvey[3], Surinder S. Birring[4], Sean M. Parker[5], Alice Turner[6], Thomas Hummel[7], Isabella Gashaw[8], Lueder Fels[8], Stefan Klein[8], Klaus Francke[8] and Christian Friedrich[8]







Eur Respir J Nov 2021;58(5) 2004240

Novel agent for management of chronic cough

2. ATP-gated P2X3 receptor antagonist

Pharmaceutical Technology

FDA rejects MSD's gefapixant for chronic cough

Despite approvals in Europe and Japan, the FDA rejected the oral drug, citing a lack of substantial evidence for treatment effectiveness.

2023. 12. 21.

FierceBiotech

Merck, with GSK in its rearview, suffers second FDA rejection of cough drug gefapixant

Merck received its first FDA rejection for gefapixant, a P2X3 receptor antagonist designed to treat chronic cough, at the start of last year.

2023. 12. 21.

BioSpace

Merck's Chronic Cough Drug Fails to Secure FDA Approval for Second Time

Pharmaphorum

Bayer's pipeline takes a hit as it drops eliapixant

Bayer has abandoned development of its investigational P2X3 receptor antagonist eliapixant, despite promising efficacy data in clinical...

2022. 2. 7.

The Pharma Letter

Bayer discontinues clinical development of eliapixant

Bayer discontinues clinical development of eliapixant.

2022. 2. 4.

BioSpace

P2X3 Receptor Antagonist Field Murkier as Bayer Abandons Program

After reviewing available data, Bayer decided to abandon its Phase II development of eliapixant as the benefit-risk profile was not...

2022. 2. 7.

FierceBiotech

Bayer ends work on cough med that passed phase 2b weeks after FDA rejected Merck's drug

Novel agent for management of chronic cough

2. ATP-gated P2X3 receptor antagonist

European Respiratory Journal
https://erj.ersjournals.com › content › suppl_66

Efficacy in SOOTHE, A Phase 2b Trial of BLU-5937 In ...

SS Birring 저술 · 2022 · 10회 인용 — Here we characterize the TDAEs and impact on efficacy in SOOTHE, a phase 2b trial of the selective P2X3 antagonist **BLU-5937** in the treatment of RCC.

European Respiratory Journal
https://erj.ersjournals.com › content › suppl_66

Improvements in Awake Cough Frequency in SOOTHE, A ...

JA Smith 저술 · 2022 · 4회 인용 — SOOTHE was a phase 2b, dose-finding trial of **BLU-5937** in participants diagnosed with RCC, that demonstrated clinically and statistically significant…

European Respiratory Journal
https://erj.ersjournals.com › content › suppl_66

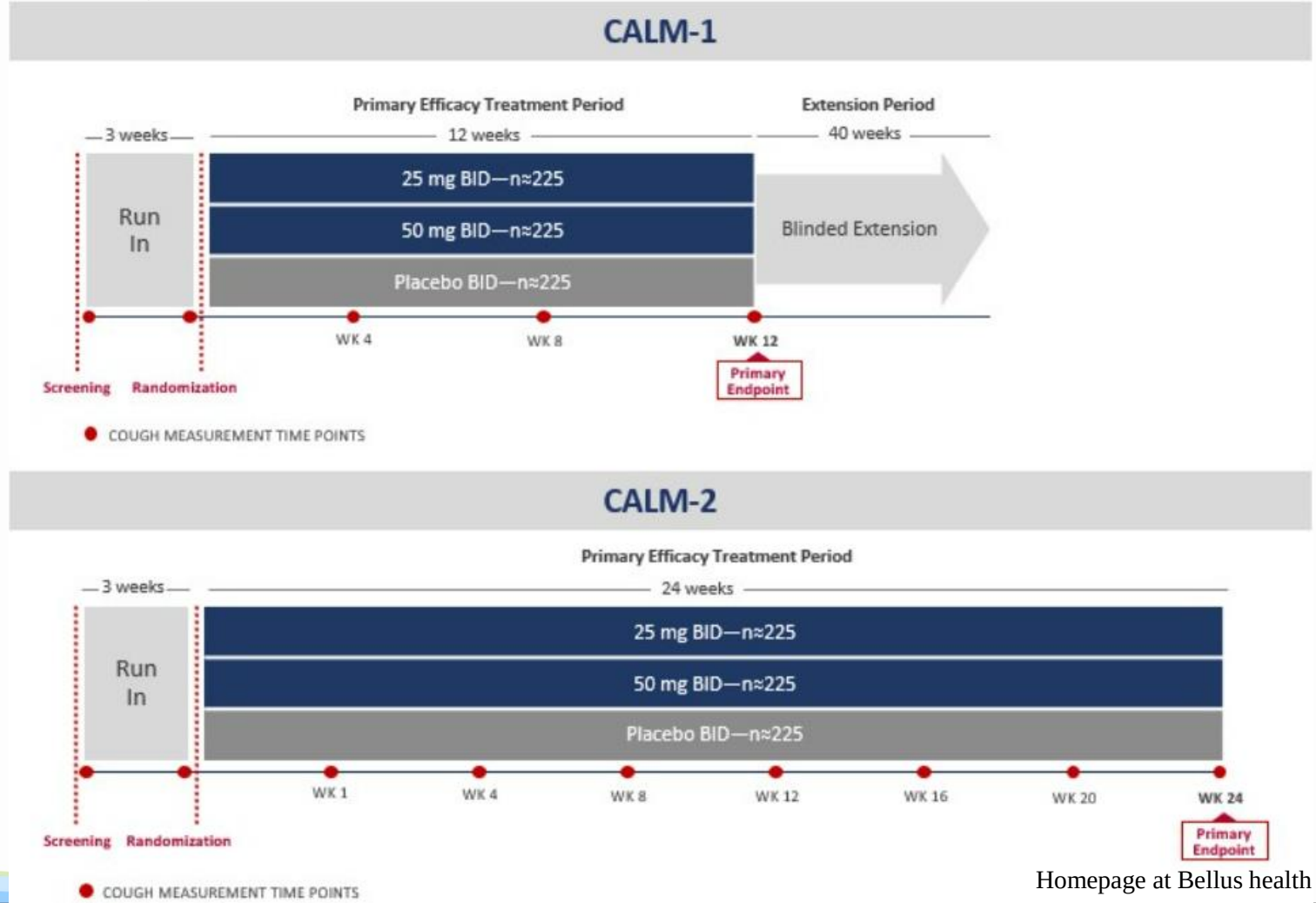
Characteristics of Participants with Refractory Chronic Cough ...

AH Morice 저술 · 2022 · 2회 인용 — The SOOTHE study assessed the safety and efficacy of **BLU-5937** in a refractory chronic cough (RCC) population enriched for cough frequency.

European Respiratory Journal
https://erj.ersjournals.com › content › suppl_65

Improvements in cough severity and cough-related quality of ...

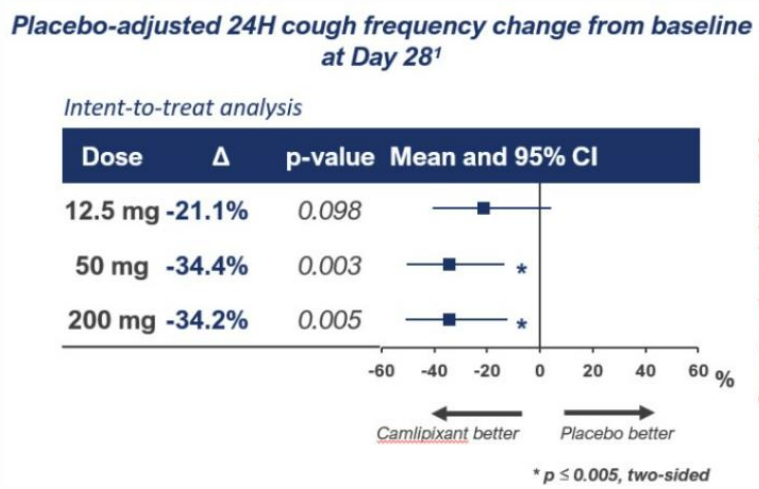
SS Birring 저술 · 2021 · 5회 인용 — Over a 16-day treatment period, cough severity and QoL improvements in RELIEF favored **BLU-5937**, with greater benefits in subgroups that…

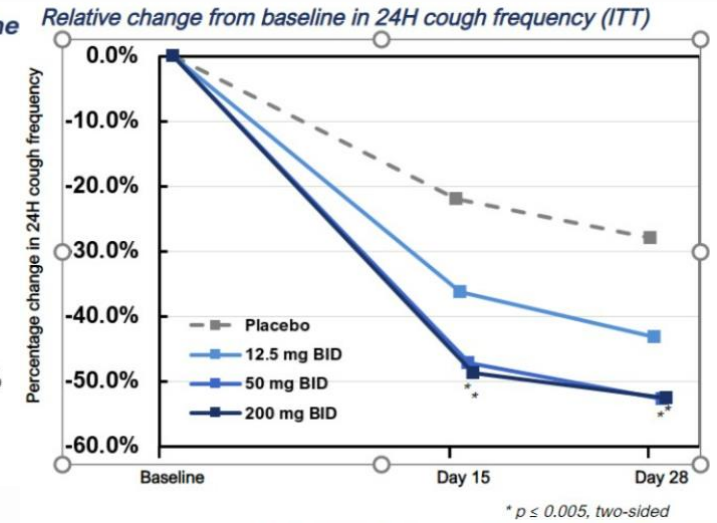


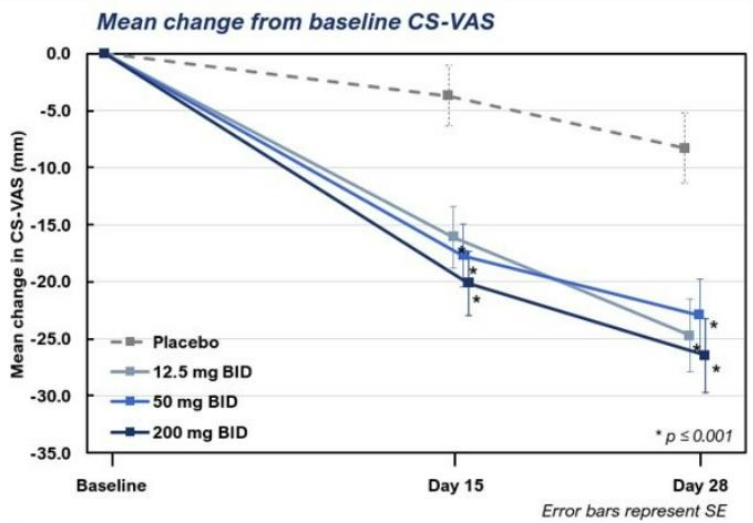
Homepage at Bellus health

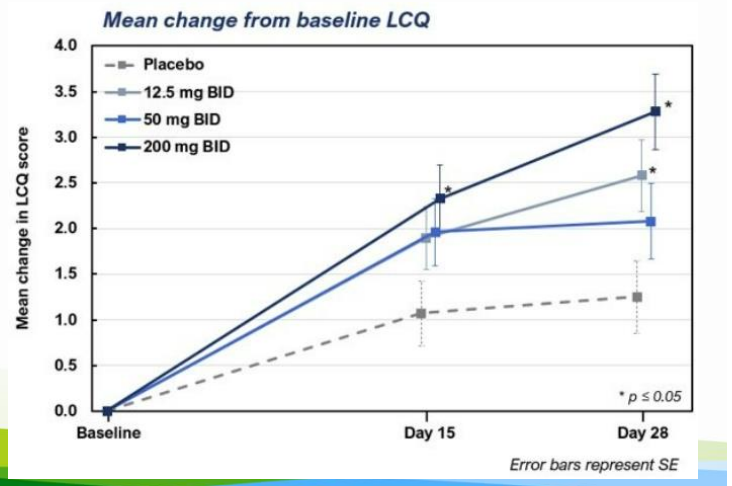
Novel agent for management of chronic cough

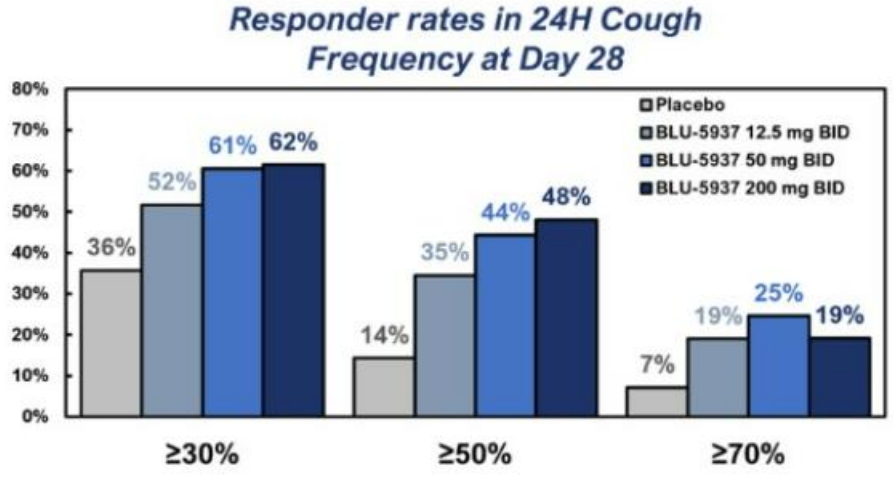
2. ATP-gated P2X3 receptor antagonist











Homepage at Bellus health

Novel agent for management of chronic cough

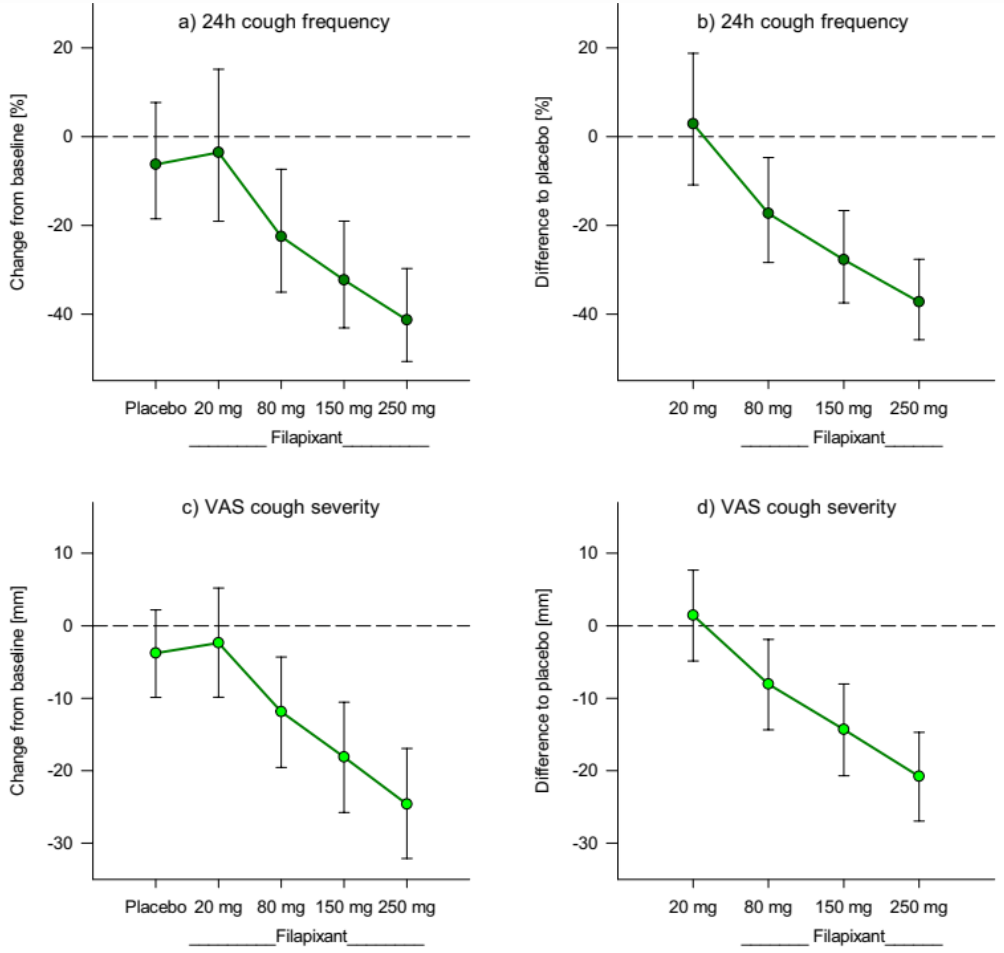
2. ATP-gated P2X3 receptor antagonist

RESEARCH Open Access

The P2X3 receptor antagonist filapixant in patients with refractory chronic cough: a randomized controlled trial

Christian Friedrich[1*], Klaus Francke[1], Surinder S. Birring[2], Jan Willem K. van den Berg[3], Paul A. Marsden[4], Lorcan McGarvey[5], Alice M. Turner[6], Pascal Wielders[7], Isabella Gashaw[1], Stefan Klein[1] and Alyn H. Morice[8]

Substantially higher in vitro selectivity for P2X3 over P2X2 (data on fle, Bayer).



Respir Res 24, 109 (2023)

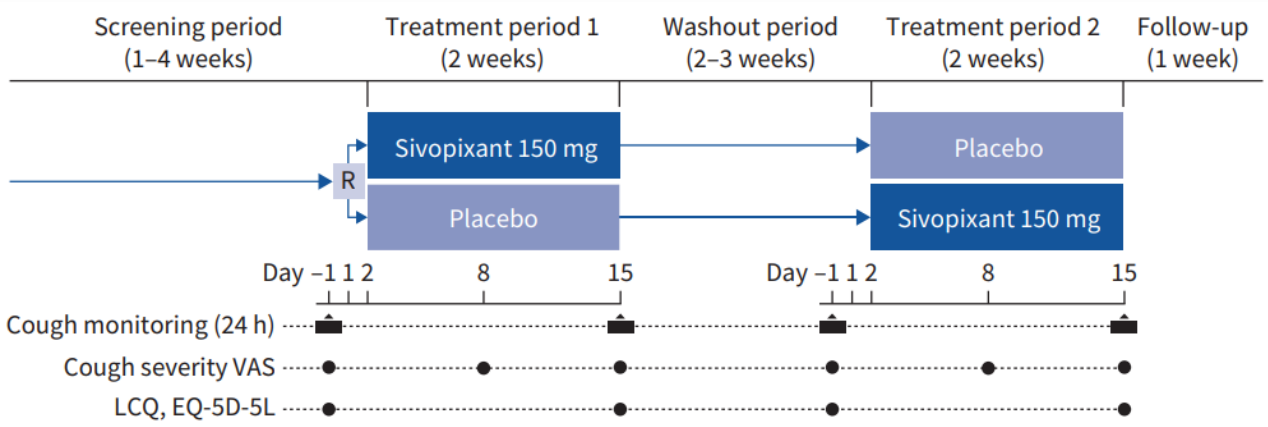
Novel agent for management of chronic cough

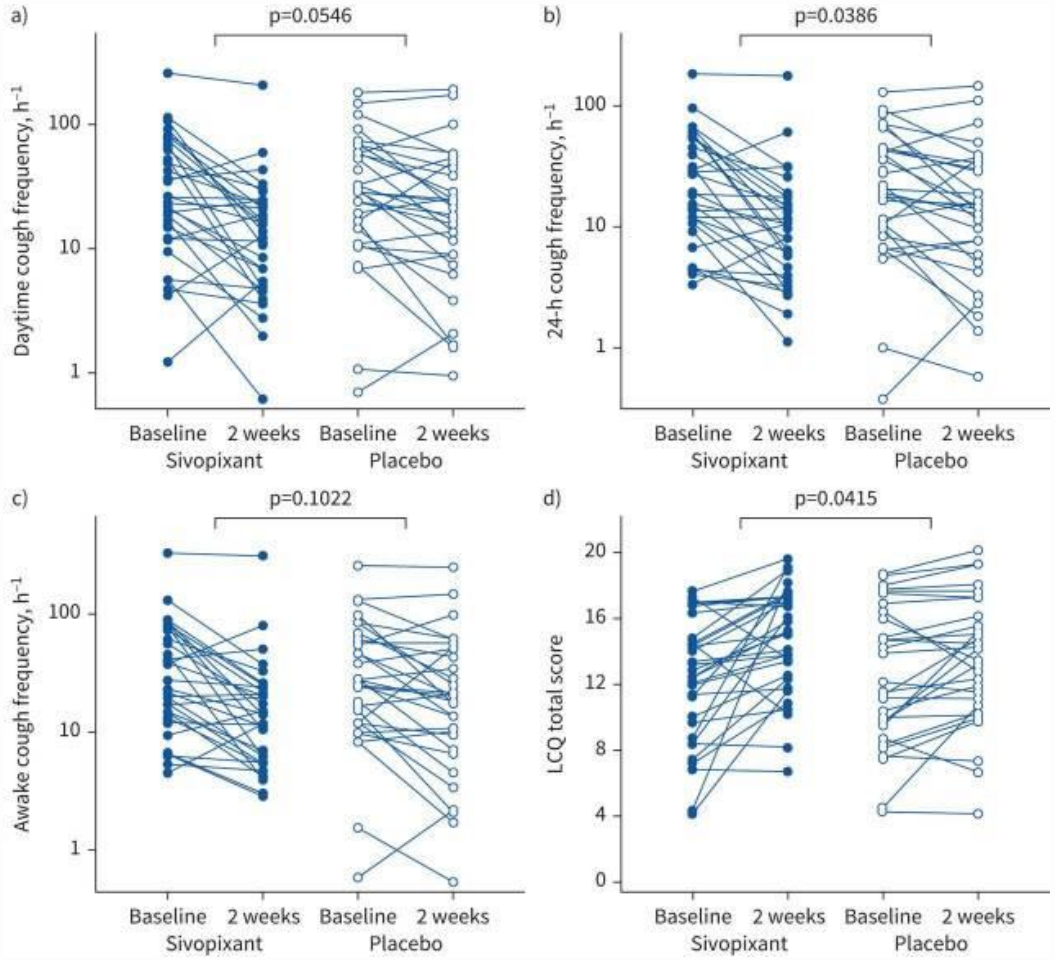
2. ATP-gated P2X3 receptor antagonist

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
A. NIIMI ET AL.

Randomised trial of the $P2X_3$ receptor antagonist sivopixant for refractory chronic cough

Akio Niimi[1], Junpei Saito[2], Tadashi Kamei[3], Masaharu Shinkai[4], Hiroyuki Ishihara[5], Mitsuaki Machida[5] and Sayaka Miyazaki[5]





Eur Respir J. 2022 Jun; 59(6)

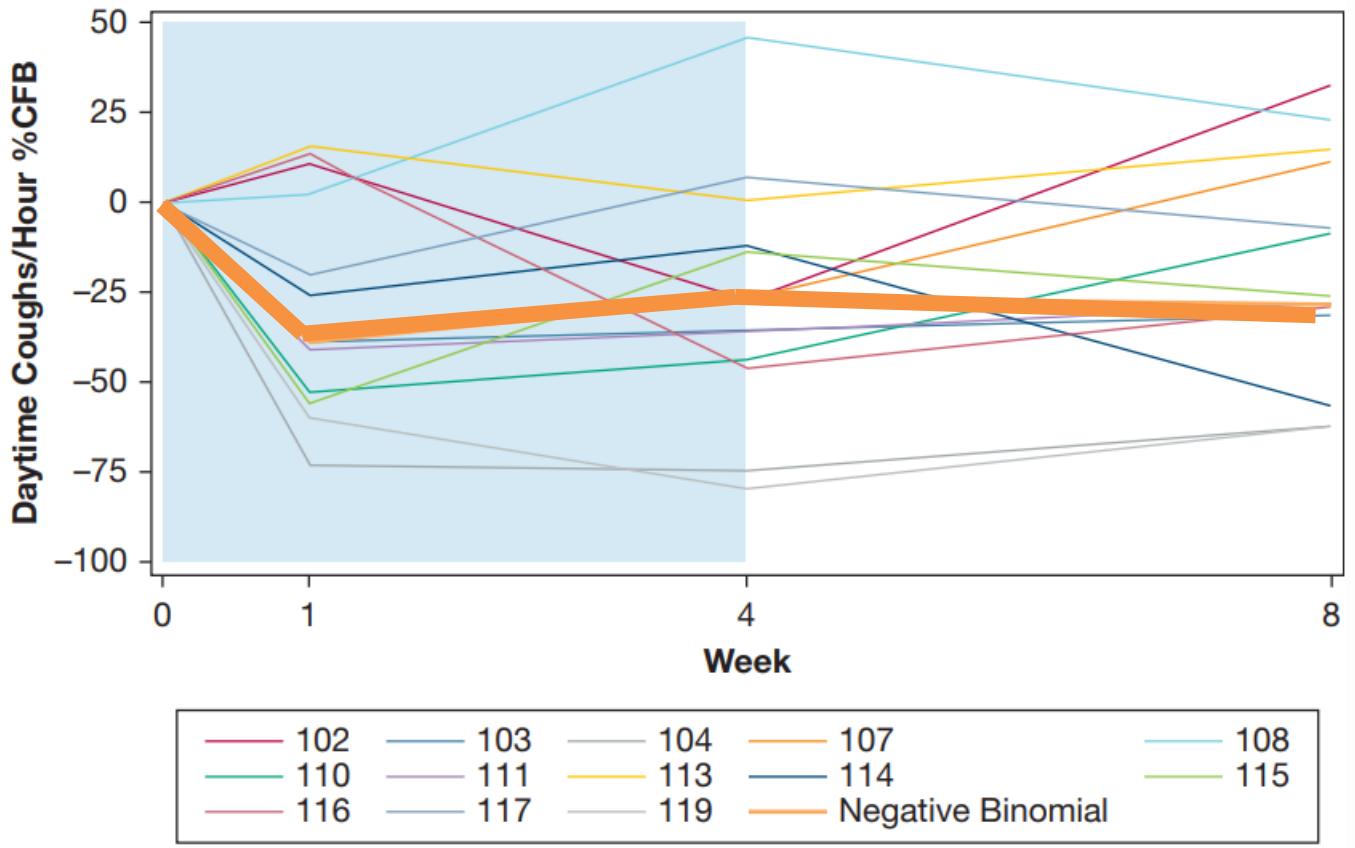
Novel agent for management of chronic cough

3. Neurokinin-1 receptors (NK1Rs) antagonist

The Neurokinin-1 Receptor Antagonist Orvepitant Is a Novel Antitussive Therapy for Chronic Refractory Cough

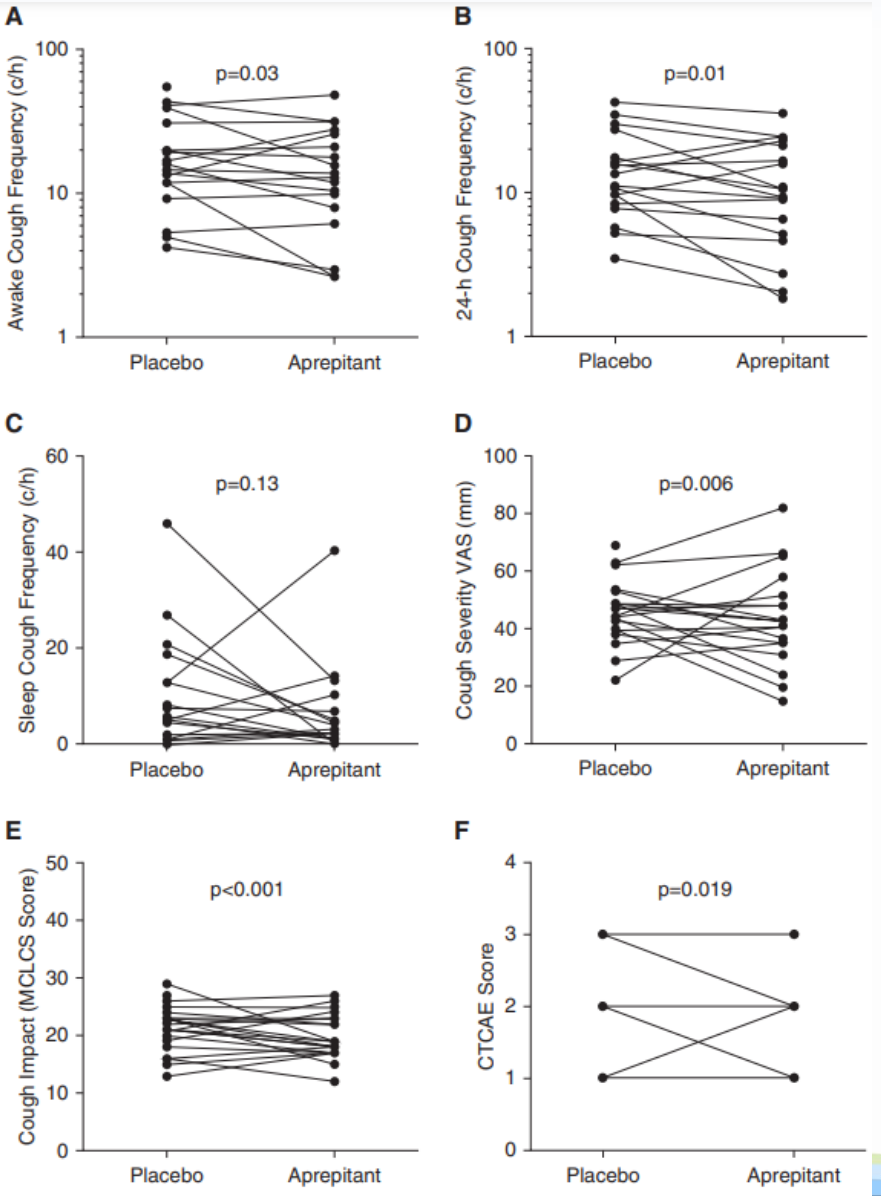
Results From a Phase 2 Pilot Study (VOLCANO-1)

orvepitant 30 mg once daily



CHEST 2020; 157(1):111-118

Novel agent for management of chronic cough



3. Neurokinin-1 receptors (NK1Rs) antagonist

ORIGINAL ARTICLE

Aprepitant for Cough in Lung Cancer

A Randomized Placebo-controlled Trial and Mechanistic Insights

Jaclyn A. Smith[1,2*], Amélie Harle[3,4*], Rachel Dockry[1,2], Kimberley Holt[1,2], Philip Russell[3], Alex Molassiotis[5], Janelle Yorke[3,6], Ryan Robinson[7], Mark A. Birrell[7,8], Maria G. Belvisi[7,8], and Fiona Blackhall[3,4]

Cough frequency improved with aprepitant, reducing by 22.2% (95% confidence interval [CI], 2.8–37.7%) over placebo while awake (P = 0.03), 30.3% (95% CI, 12.7–44.3) over 24 hours (P = 0.002), and 59.8% (95% CI, 15.1–86.0) during sleep (P = 0.081). Patient-reported outcomes all significantly improved.

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Novel agent for management of chronic cough

4. Sodium channel blocker; NTX1175

EudraCT Number: 2020-004715-27	**Sponsor Protocol Number:** NOC100-C-201	**Start Date*:** 2021-02-03
Sponsor Name: Nocion Therapeutics, Inc.		
Full Title: A Phase 2a, Randomised, Double-Blind, Placebo-Controlled, Two-Part Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetic Profiles of Inhaled Doses of NOC-100 in Adult Participants...		
Medical condition: Cough		

Disease:	Version	SOC Term	Classification Code	Term	Level
	20.0	10038738 - Respiratory, thoracic and mediastinal disorders	10011224	Cough	PT

Population Age: Adults, Elderly	**Gender:** Male, Female
Trial protocol: DE *(Completed)*	
Trial results: *(No results available)*	

EuraCT 2020-004715-27

Summary

- Background
  - •PND→UACS
- Recent researches
  - •BTS2023; **multifactorial**, against use of PPI, nonsedating H1 antagonist, ~~편강탕~~
- Post-pandemic (after COVID19)
  - •Neuro-hypersensistivity – neuroleptics, novel agent

THANK YOU
for your
ATTENTION!