

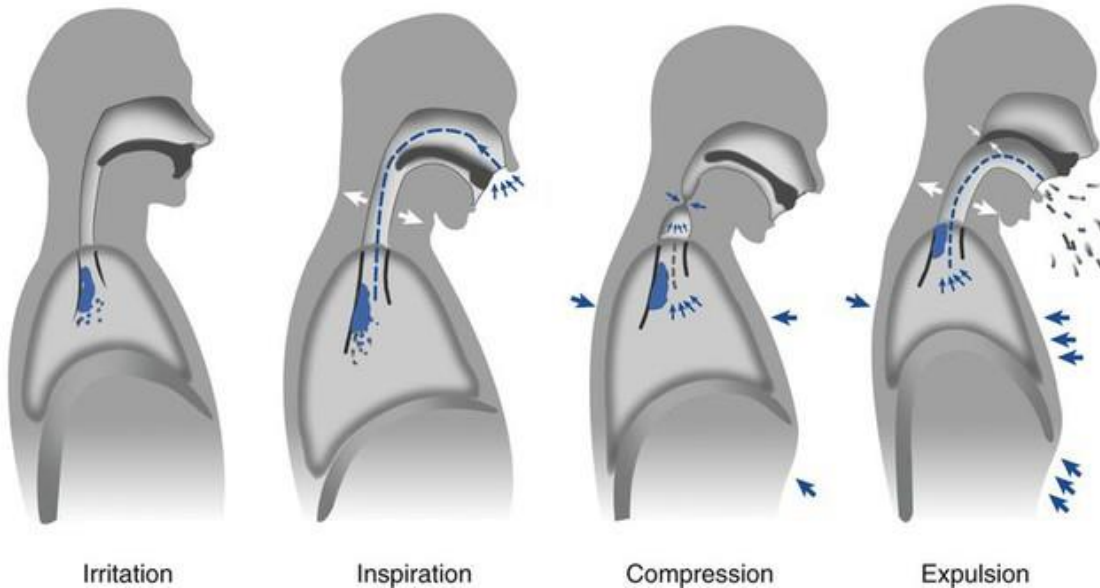
2026 부울경 호흡기 연수강좌

멈추지 않는 기침, 원인별 맞춤 치료전략

부산대학교병원 알레르기내과
조은정



기침은 왜 할까?



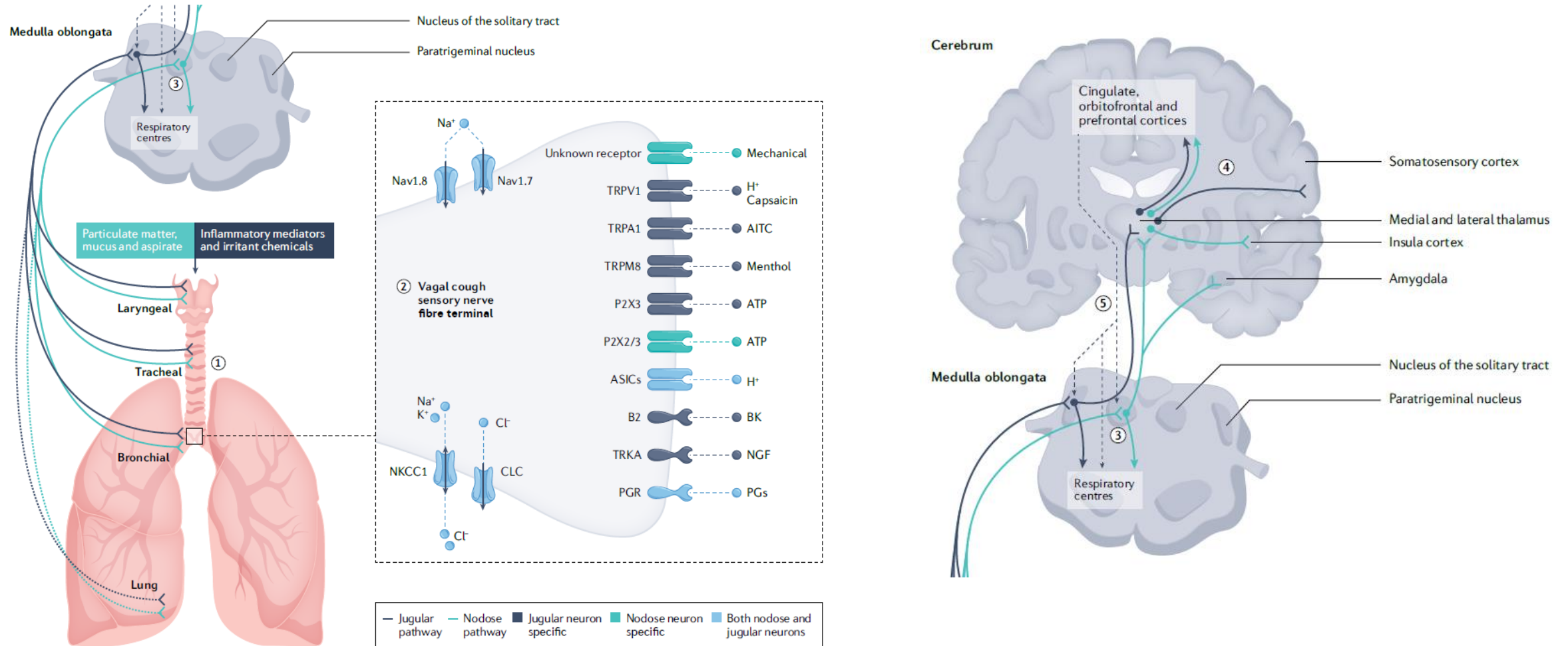
Cough is a vital protective airway reflex

However, when severe or persistent, it becomes among the most common reasons for medical consultation

- **Chronic cough**

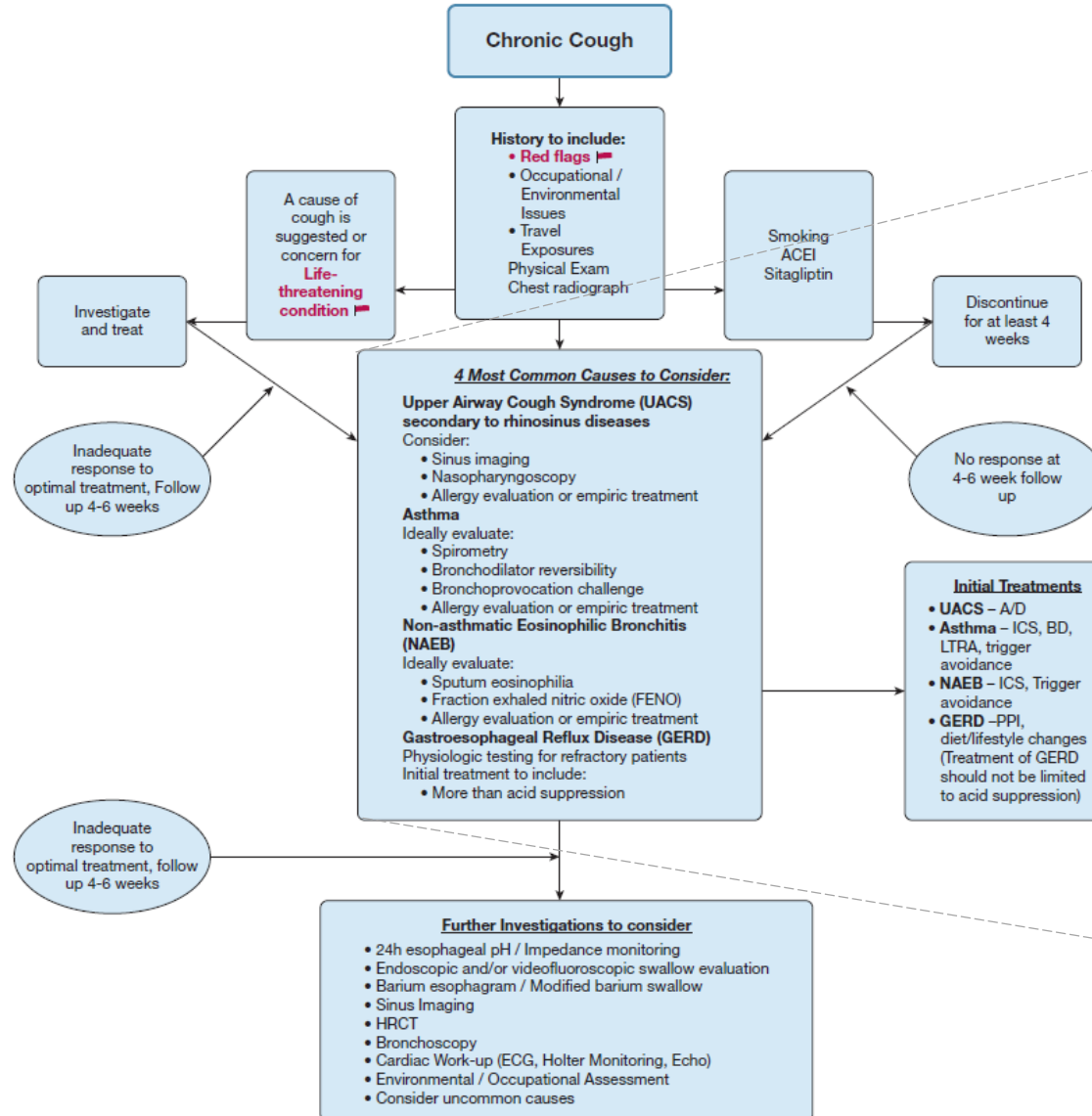
- Definition in clinical guidelines
 - Cough persisting for **>8 weeks in adults**
 - Cough persisting for >4 weeks in children
- Often a long-lasting and burdensome condition

Generation of cough



Anatomic diagnostic protocol (ACCP guideline)

- Red Flags**
- Hemoptysis
 - Smoker > 45 years of age with a new cough, change in cough, or coexisting voice disturbance
 - Adults aged 55-80 years who have a 30 pack-year smoking history and currently smoke or who have quit within the past 15 years
 - Prominent dyspnea, especially at rest or at night
 - Hoarseness
 - Systemic symptoms
 - Fever
 - Weight loss
 - Peripheral Edema with weight gain
 - Trouble swallowing when eating or drinking
 - Vomiting
 - Recurrent pneumonia
 - Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough



4 Most Common Causes to Consider:

Upper Airway Cough Syndrome (UACS) secondary to rhinosinus diseases
Consider:

- Sinus imaging
- Nasopharyngoscopy
- Allergy evaluation or empiric treatment

Asthma
Ideally evaluate:

- Spirometry
- Bronchodilator reversibility
- Bronchoprovocation challenge
- Allergy evaluation or empiric treatment

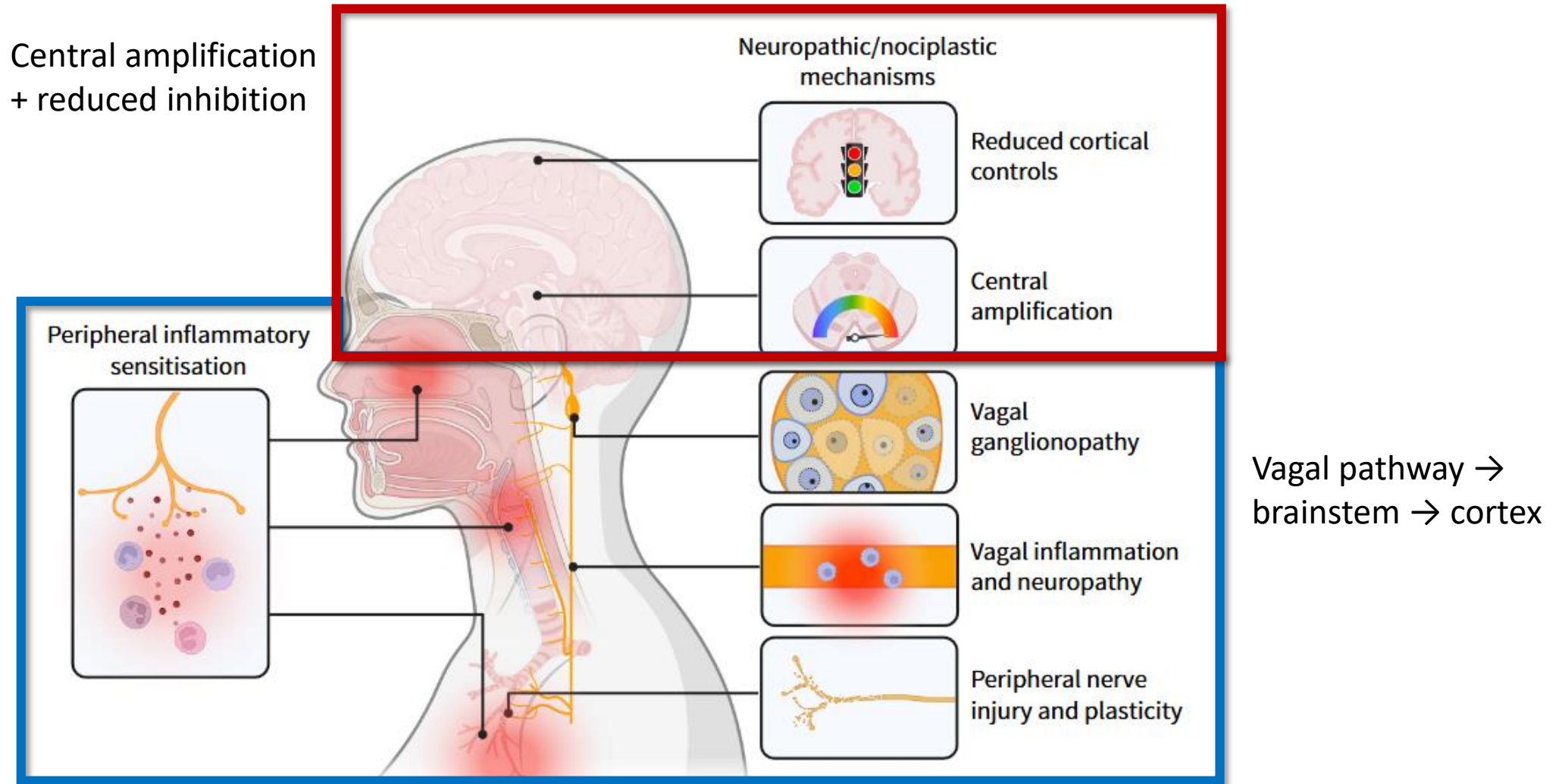
Non-asthmatic Eosinophilic Bronchitis (NAEB)
Ideally evaluate:

- Sputum eosinophilia
- Fraction exhaled nitric oxide (FENO)
- Allergy evaluation or empiric treatment

Gastroesophageal Reflux Disease (GERD)
Physiologic testing for refractory patients
Initial treatment to include:

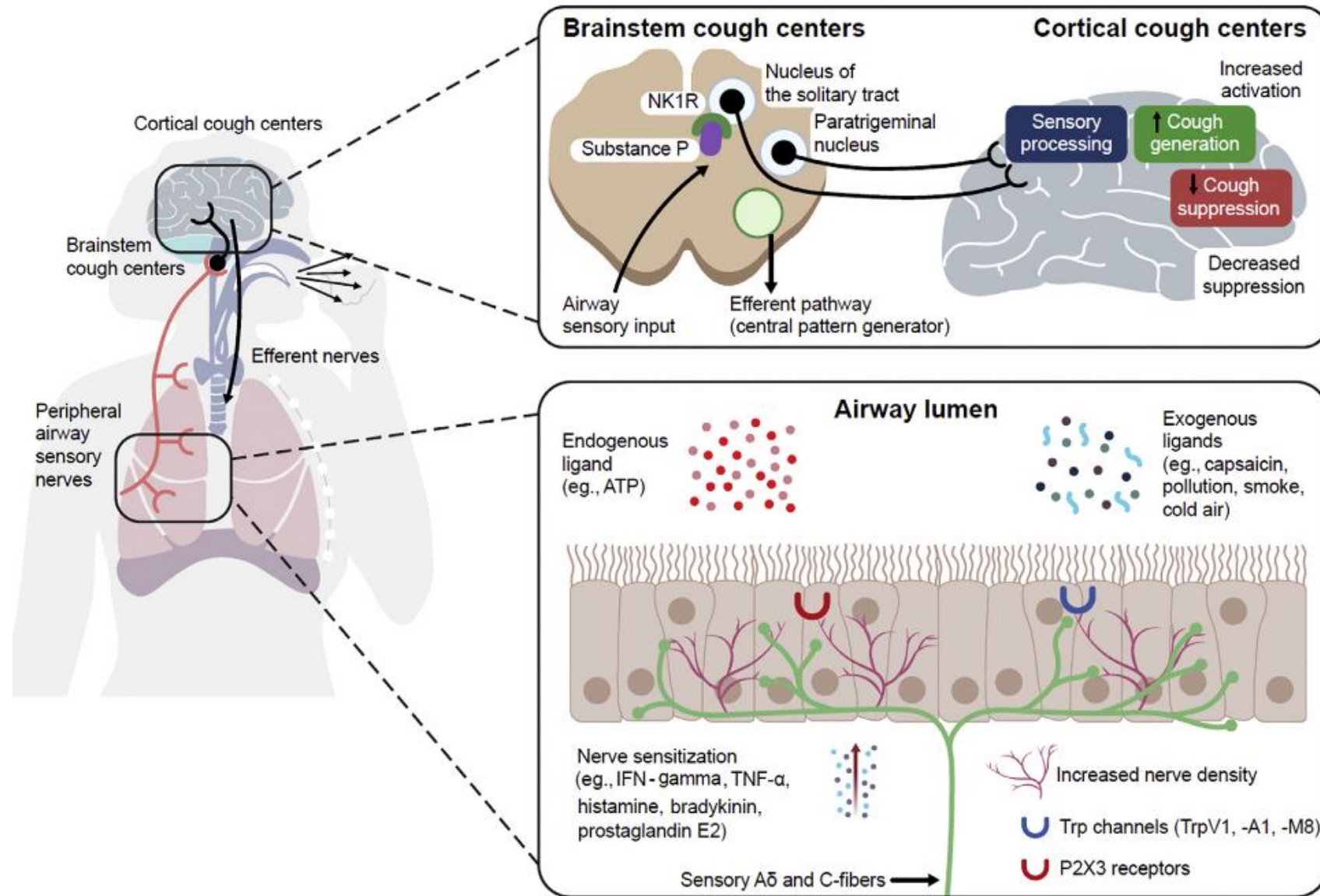
- More than acid suppression

Neural mechanisms contributing to cough hypersensitivity

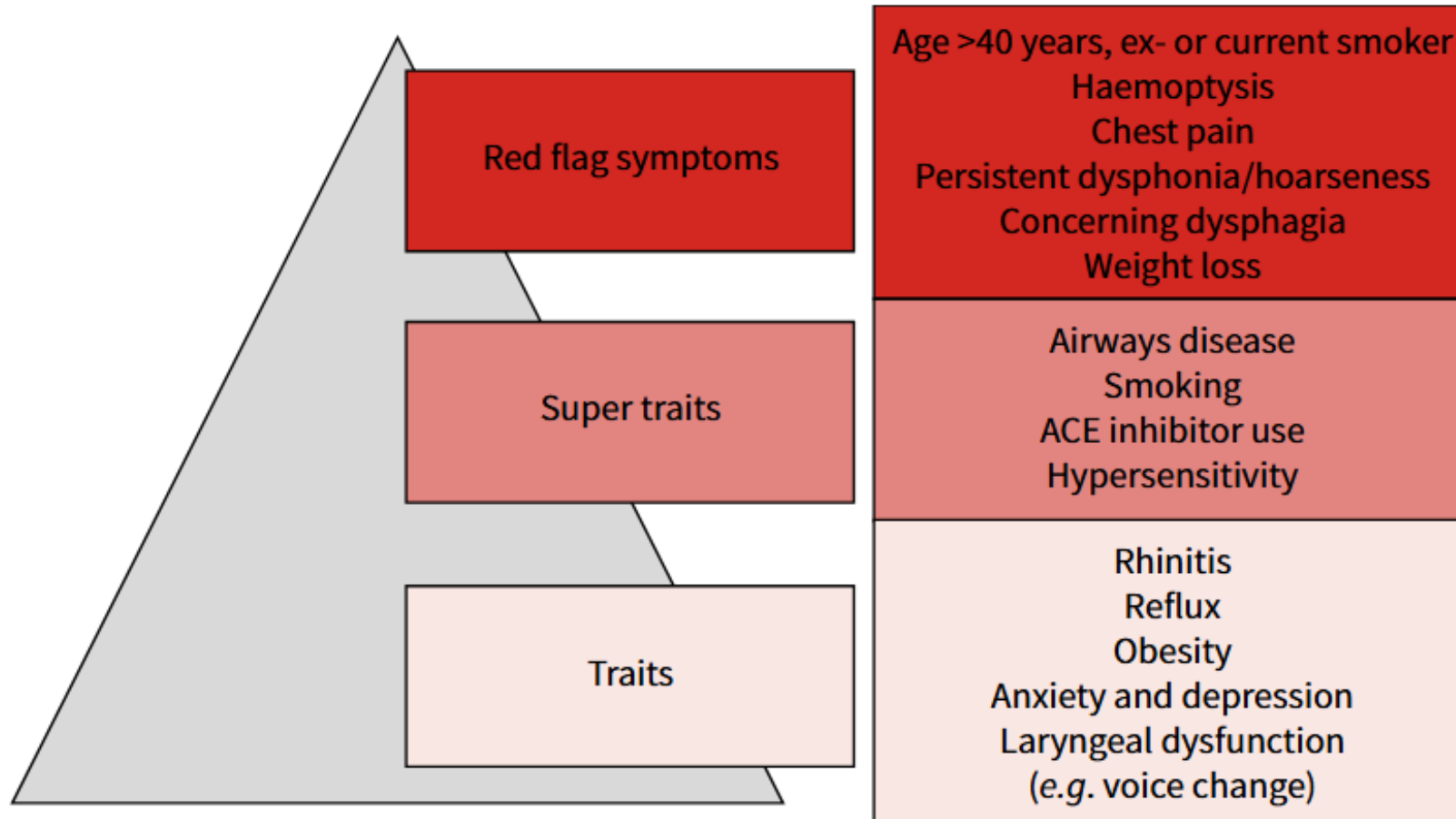


Peripheral inflammation → sensory nerve sensitization

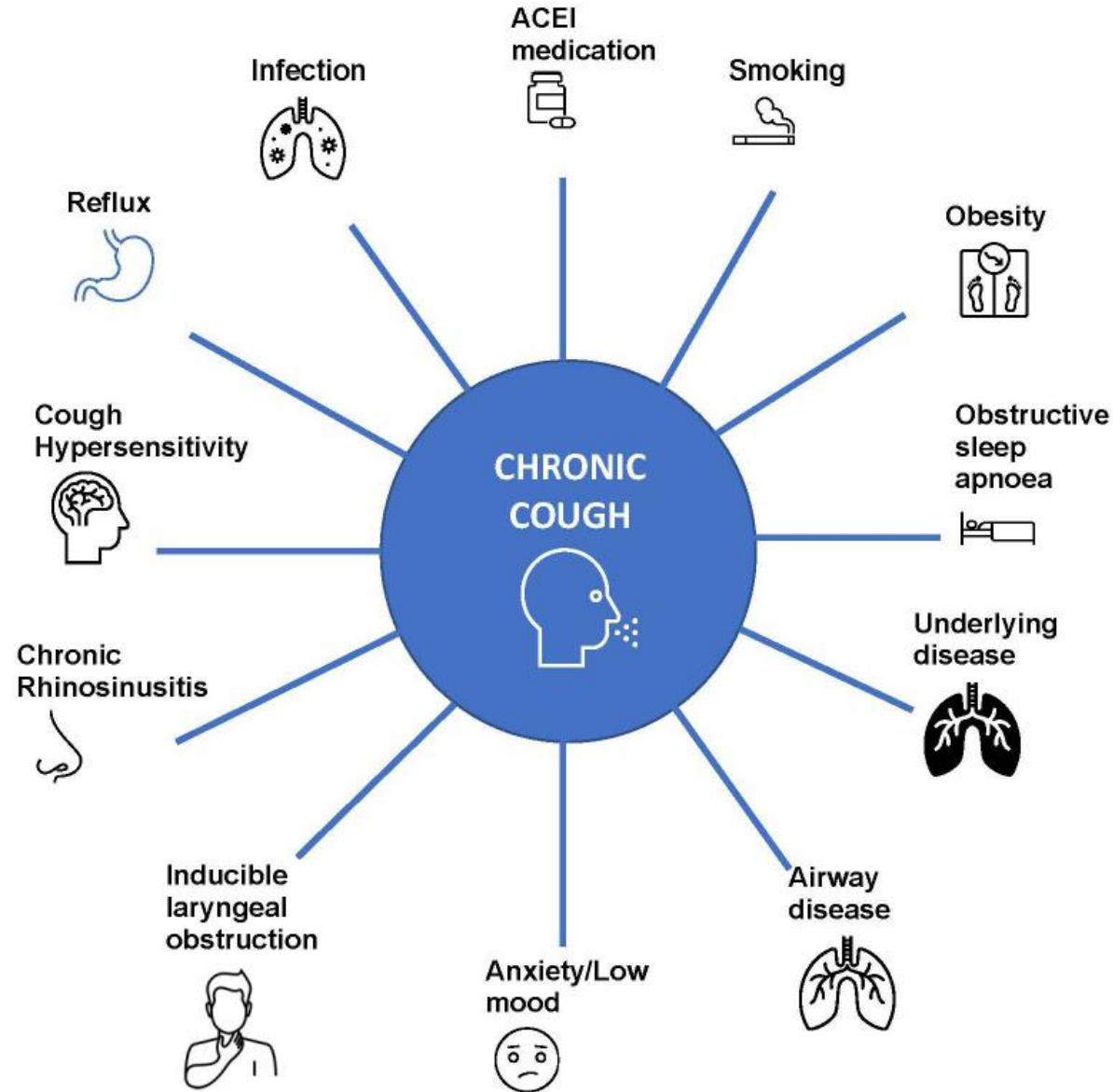
Mechanistic advances in chronic cough



A new approach to cough: treatable trait



Treatable traits of chronic cough (British Thoracic Society guideline)



Airway type 2 (T2) inflammation, eosinophilic airway inflammation

- Approximately 20–50% of adults with chronic cough
- **Cough variant asthma** and **eosinophilic bronchitis**
- **Raised T2 biomarker**
 - Sputum eosinophilia (>3%)
 - Fractional exhaled nitric oxide (FeNO) (≥ 25 ppb)
 - Blood eosinophil count ($\geq 300/\mu\text{L}$)
- **Management: 2–4 weeks trial of inhaled corticosteroids (ICS)**
 - Incomplete response: double dose of ICS or add LTRA or short trial of OCS (oral prednisolone 30 mg)

T2 염증을 확인할 수 없을 때 ICS 써봐도 될까?

Question 3: should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) be used to treat patients with chronic cough?

We suggest a short-term ICS trial (2–4 weeks) in adult patients with chronic cough (conditional recommendation, low-quality evidence).

- Two studies of chronic cough patients (unselected by airway hyperresponsiveness or sputum eosinophilia)
→ Benefits from a 2-week high-dose ICS treatment
- A study of patients with chronic cough + additional respiratory symptom + normal lung function
8-week medium-dose ICS treatment → did not produce a significant improvement
- Two studies of patients with nonasthmatic chronic cough (negative MBPT)
ICS treatment → not superior to placebo

Variable respiratory symptoms in asthma

Feature	Features that support the diagnosis
Wheeze, shortness of breath, chest tightness and/or cough	<ul style="list-style-type: none">• Symptoms occur <u>variably</u> over time and vary in intensity.• Symptoms are often <i>worse at <u>night</u> or on <u>waking</u></i>.• Symptoms are often triggered by <u>exercise, laughter, allergens, cold air</u>.• Symptoms are worsen <u>after end-exercise</u> (very distinctive).• Symptoms often appear or worsen with <u>viral infections</u>.

Airway hyperresponsiveness or reversible airflow obstruction

- **Chronic cough** + accompanied by **breathlessness, wheezing, or baseline airflow limitation**
- Bronchial provocation or bronchodilator response testing
- Management: **bronchodilators** may be trialed in selected individuals – modest benefit

Fenoterol: This short-acting beta₂-agonist is not recommended because of its higher risk of adverse effects (including hypokalemia and cardiovascular effects), and its association with increased asthma mortality.⁴¹¹

Oral bronchodilators: Oral SABA and theophylline have a higher risk of side-effects than inhaled SABA and are not recommended. For clinicians in regions without access to inhaled therapies, advice on minimizing the frequency and dose of these oral medications has been provided elsewhere.²⁵ No long-term safety studies have been performed to assess the risk of severe exacerbations associated with oral SABA or theophylline use in patients not also taking ICS.

Anticholinergic agents in the absence of ICS: In adults, inhaled short-acting muscarinic antagonists (SAMA) like ipratropium are potential alternatives to SABA for routine relief of asthma symptoms; however, these agents have a slower onset of action than inhaled SABA. Like SABAs (p.87) they should not be used without ICS. Use of long-acting muscarinic antagonists (LAMA) in asthma without concomitant ICS is associated with an increased risk of severe exacerbations.⁴¹²

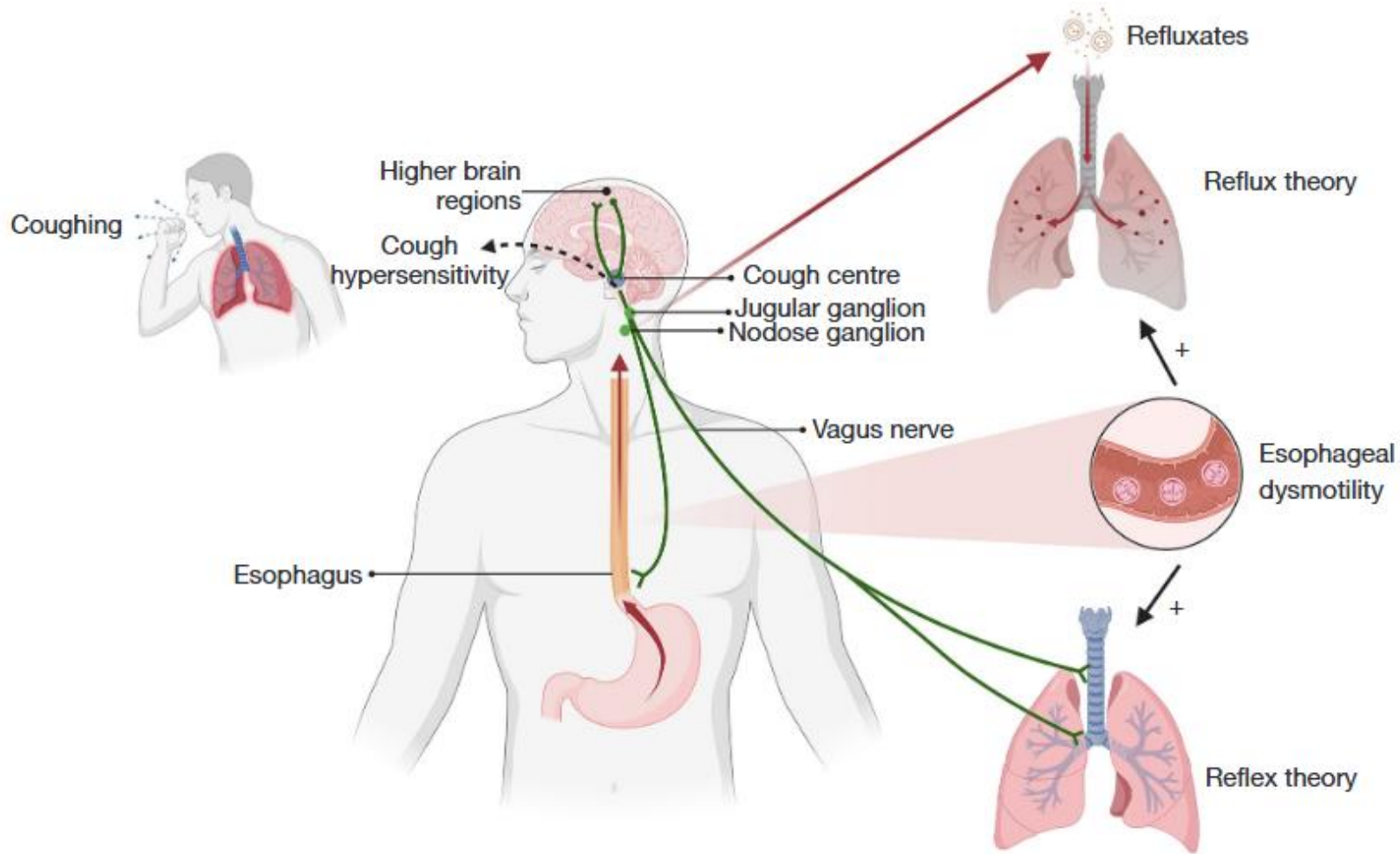
Formoterol without ICS: The rapid-onset LABA, formoterol, is as effective as SABA as a reliever medication in adults and children,⁴¹³ and reduces the risk of severe exacerbations by 15–45%, compared with as-needed SABA,^{337,414,415} but use of regular or frequent LABA without ICS is strongly discouraged because of the risk of exacerbations (Evidence A).^{158,416}

Global Initiative for Asthma 2025

Mucus hypersecretion (productive cough)

- **Persistent sputum production**
 - Provoke cough through mechanical stimulation and sustained airway inflammation
- **Sputum color:** key indicator of airway inflammation
 - Yellowish or green color of sputum → typically in patients with bronchiectasis during clinical exacerbations
- Consider low-dose **macrolide** therapy
 - for example, azithromycin 250 mg three times/week initially, titrating up to 500 mg three times/week depending on clinical response
- European Respiratory Society 2025 Bronchiectasis Guidelines acknowledge
 - Patients with a dry cough + mucus plugging on chest CT scans → benefit from **airway clearance techniques**

GERD-associated cough mechanism



Direct mechanism

reflux → airway irritation → cough

Indirect mechanism

distal esophagus → vagal reflex → cough

Neural sensitization

reflux → cough reflex ↑ → cough

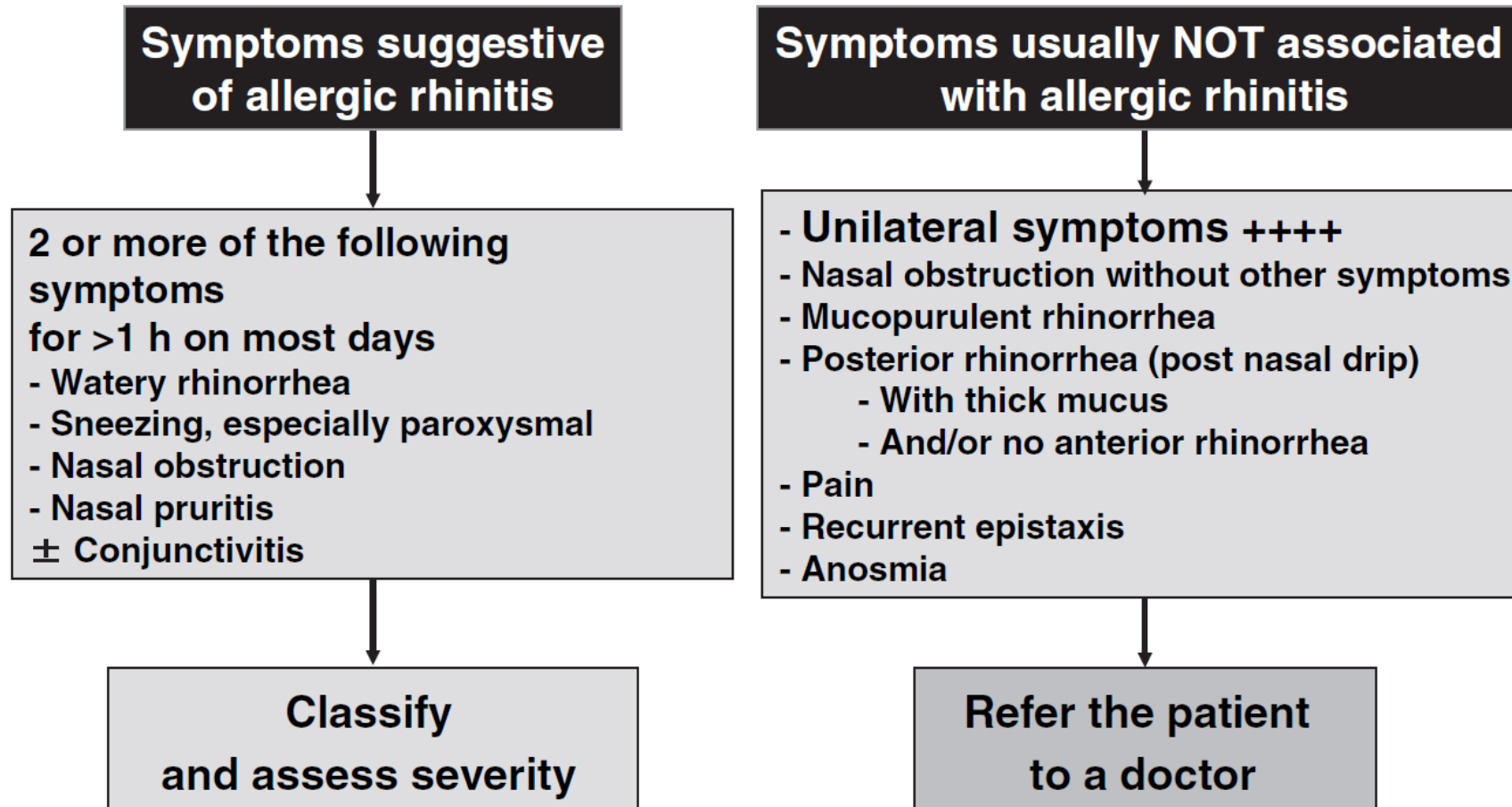
Reflux

- Frequently associated with chronic cough
- Reflux can be acidic or non-acidic.
- Diagnosis
 - Gastroendoscopy and barium swallow - cannot reliably diagnose
 - Esophageal manometry, impedance monitoring, esophageal pH monitoring
- **Proton pump inhibitors**
 - Heartburn or other definitive evidence of acid reflux
 - Acid suppression is **not recommended** in the **absence of symptoms** or objective **evidence** of acid reflux
- **Airway reflux (micro-aspiration of non-acidic gaseous gastric contents) and esophageal dysmotility**
 - Play a significant role
 - **Prokinetic** agents may help manage non-acid reflux

Upper airway diseases

- Allergic rhinitis and chronic rhinosinusitis - frequently associated with chronic cough
- **Allergic rhinitis**
 - Rhinorrhea, nasal congestion, sneezing, and postnasal drip
 - Positive skin prick tests or allergen-specific IgE
- **Chronic rhinosinusitis**
 - Generally diagnosed through typical symptoms
 - Combined with nasal endoscopy or sinus imaging
- **Treatment options**
 - **Intranasal corticosteroids**
 - **Antihistamines**
 - Saline nasal irrigation
 - Allergen-specific immunotherapy (where indicated)

Symptoms of allergic rhinitis



Inducible laryngeal obstruction (ILO) or laryngeal dysfunction

- Also known as vocal cord dysfunction or paradoxical vocal fold movement
- Inappropriate, transient, reversible narrowing of the larynx in response to external triggers
- Increasingly recognized as common comorbidities and potentially treatable traits in chronic cough.
- As with cough hypersensitivity, ILO symptoms are often localized to the larynx
- These conditions often present with **episodic dyspnea**, **throat tightness**, or **voice changes** and commonly coexist with **chronic cough**
- Diagnosis typically requires a specialized laryngoscopic examination with provocation testing.

기침이 throat symptoms을 주로 동반할 때..

- Laryngeal dysfunction and hypersensitivity are common in CC.
- PPIs are not beneficial for throat symptoms.
- **Voice issues/dysphonia**
 - Talking: often a trigger for coughing
 - Due to phonotrauma following coughing bouts
 - More chronic in presentation due to engrained muscle tension
 - Marker of underlying laryngeal hypersensitivity or vagal dysfunction
- **Globus pharyngeus**
 - Throat clearing to alleviate the feeling → leading to further laryngeal irritation and tension
 - Globus sensation: commonly reported in patients with CC and ILO.

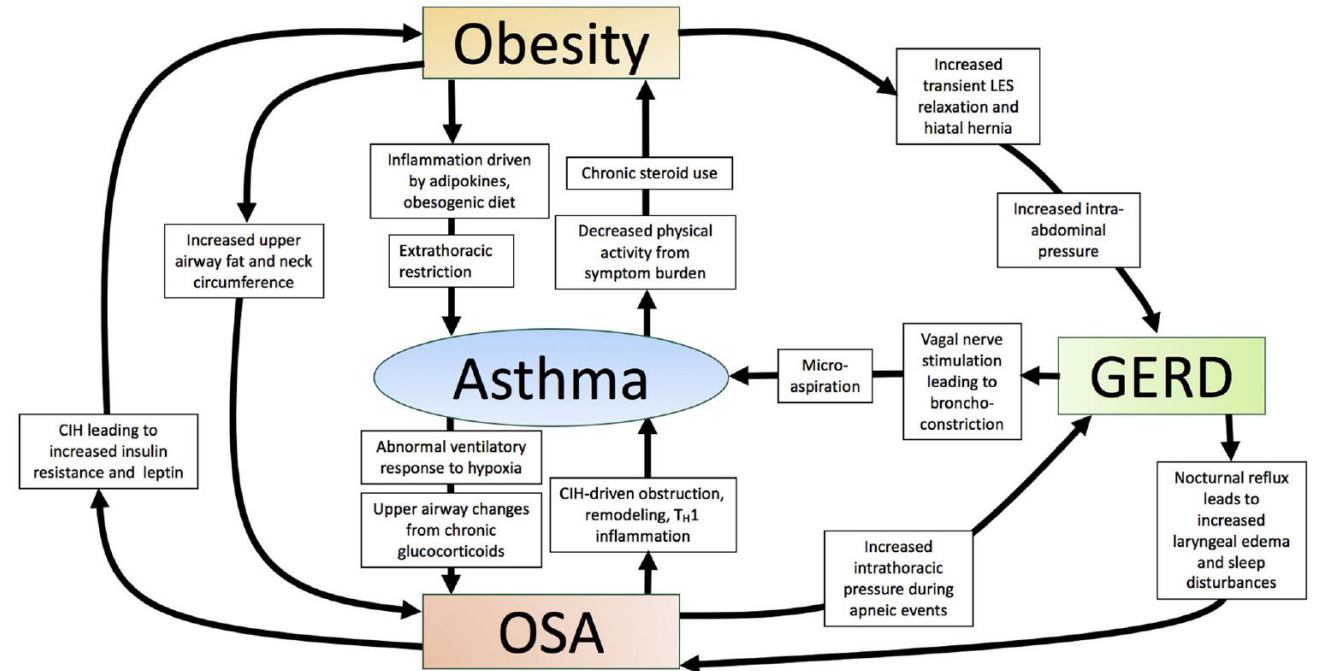
Obstructive sleep apnea (OSA) and obesity

- **OSA**

- Characterized by snoring, daytime fatigue
- Potential treatable trait in refractory cough
- **Continuous positive airway pressure therapy** has been shown to improve cough in affected individuals.

- **Obesity**

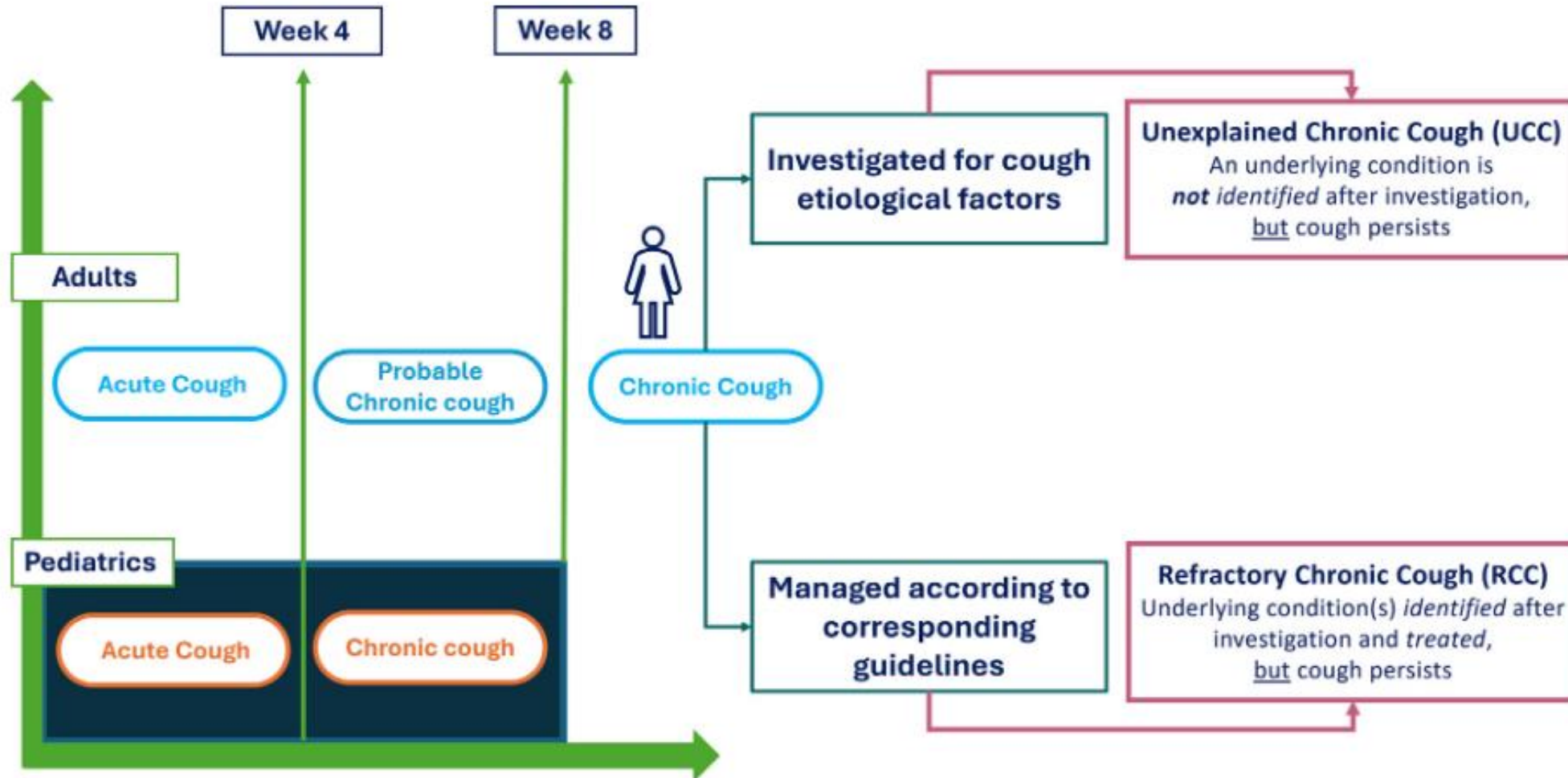
- Elevated body mass index
- Additional risk factor, and **weight-reduction** interventions may improve cough symptoms



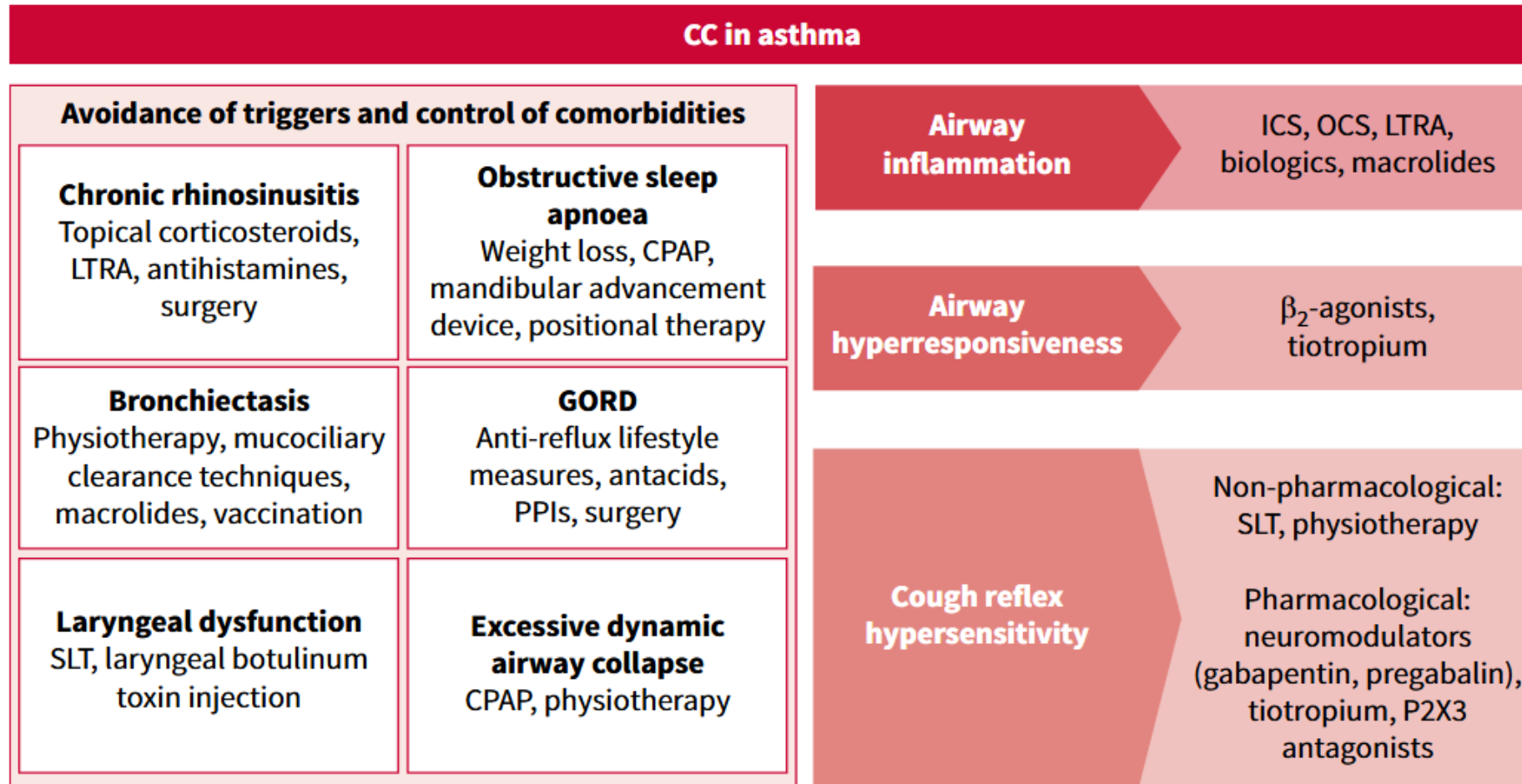
Anxiety and depression

- Interaction between psychological and physiological processes → amplify or sustain chronic cough
- **Comorbid** conditions such as anxiety and depression → persistence and exacerbation of **cough** symptoms
- Patients experience numerous unpleasant symptoms; throat discomfort, chest pain, exhaustion, dizziness, syncope and urinary incontinence.
- **Concerns** around serious underlying illness are common.

Classification of chronic cough

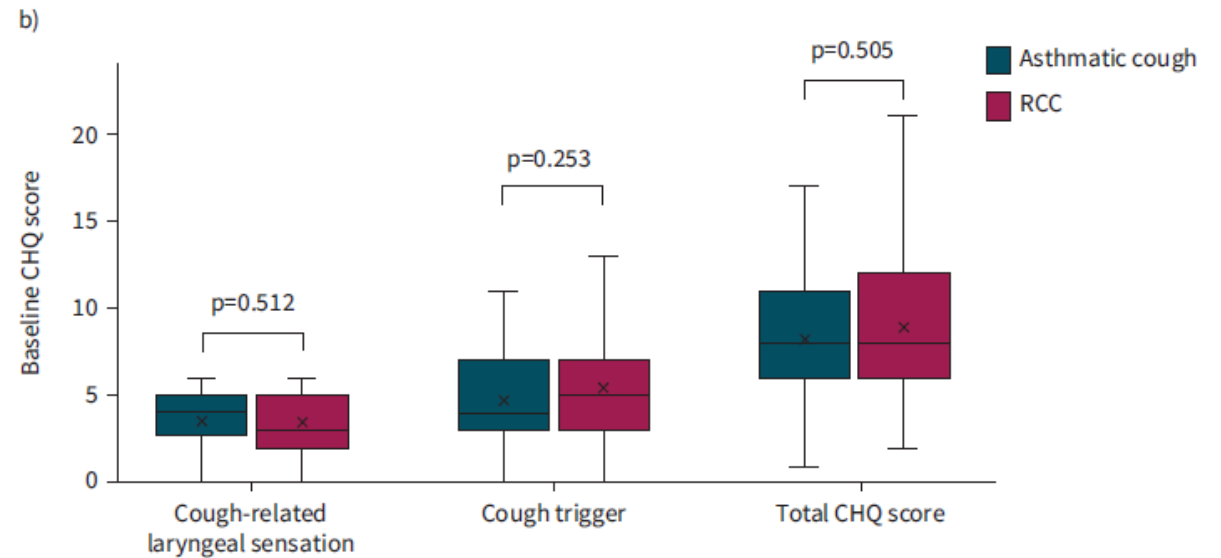
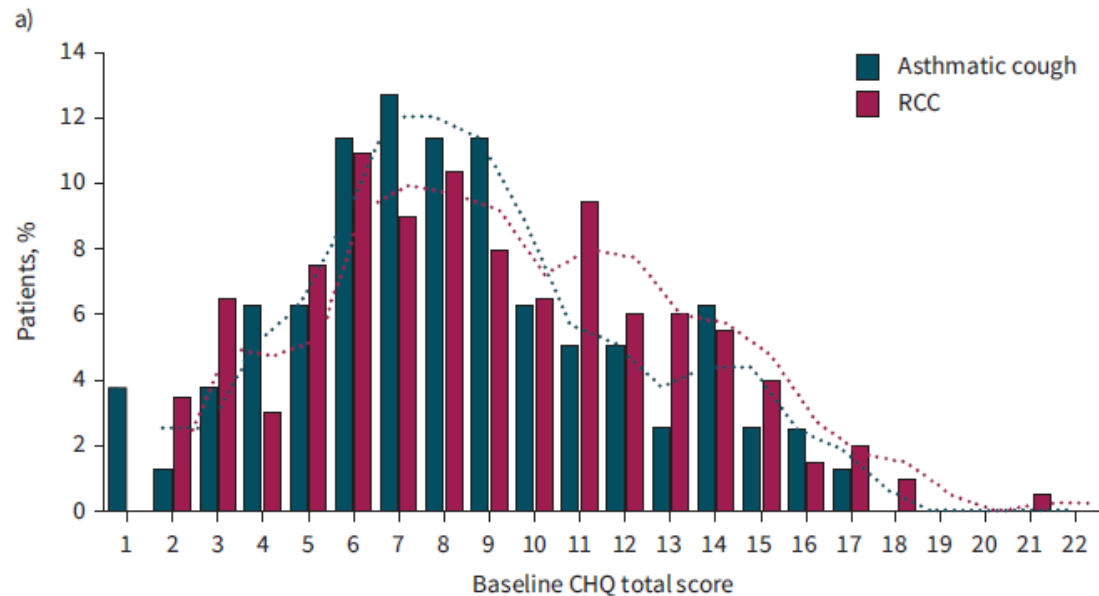


Treatable traits associated with CC in asthma and possible therapeutic approaches

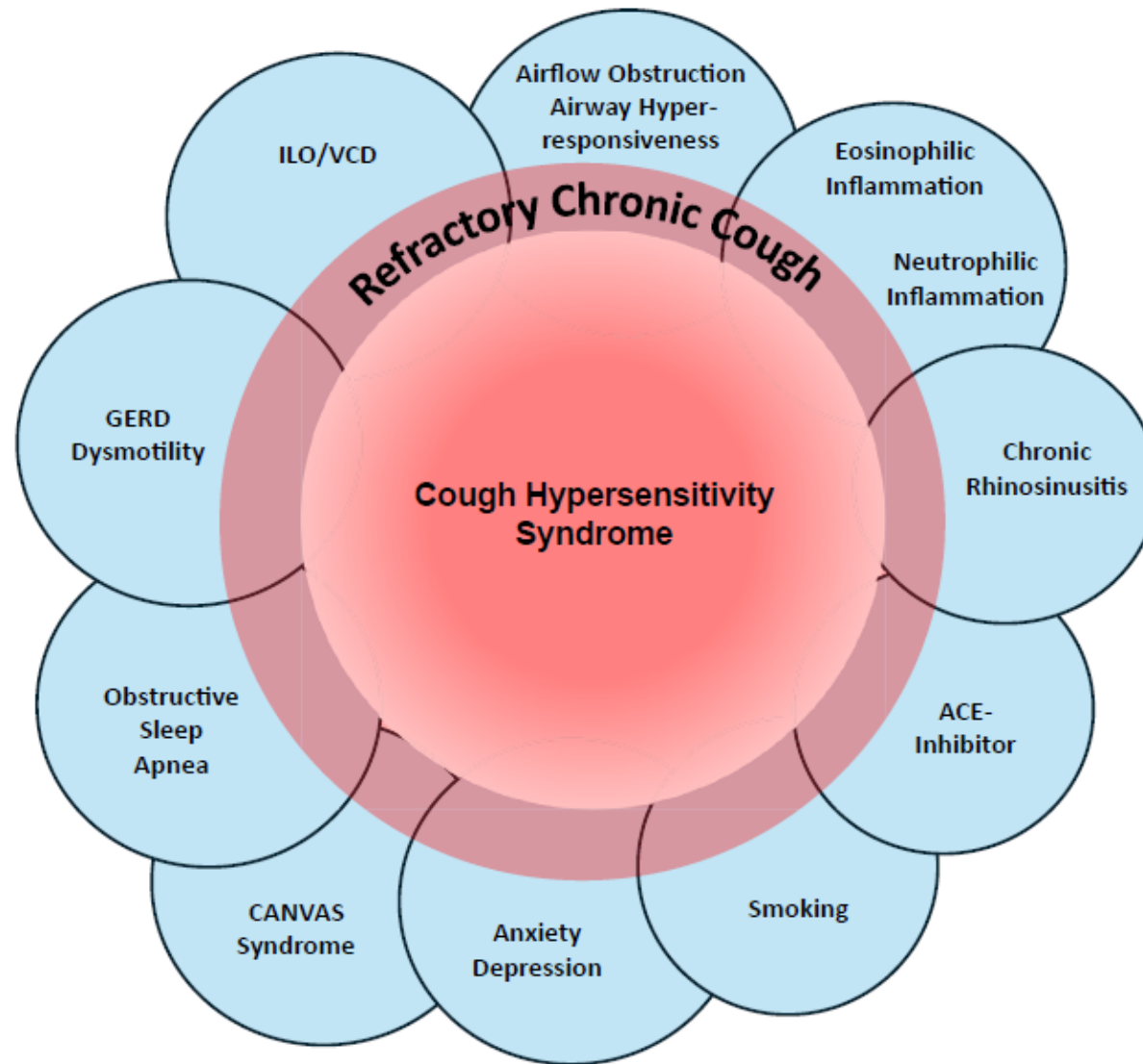


A shared mechanism with distinct treatable traits

- Korean Chronic Cough Registry
- 280 pts (asthmatic cough=79 and RCC=201) who attended the 6-month follow-up
- Cough hypersensitivity questionnaire (CHQ) score
 - Asthmatic cough: 8.3 ± 3.7 vs RCC: 8.9 ± 3.9 , $p=0.215$

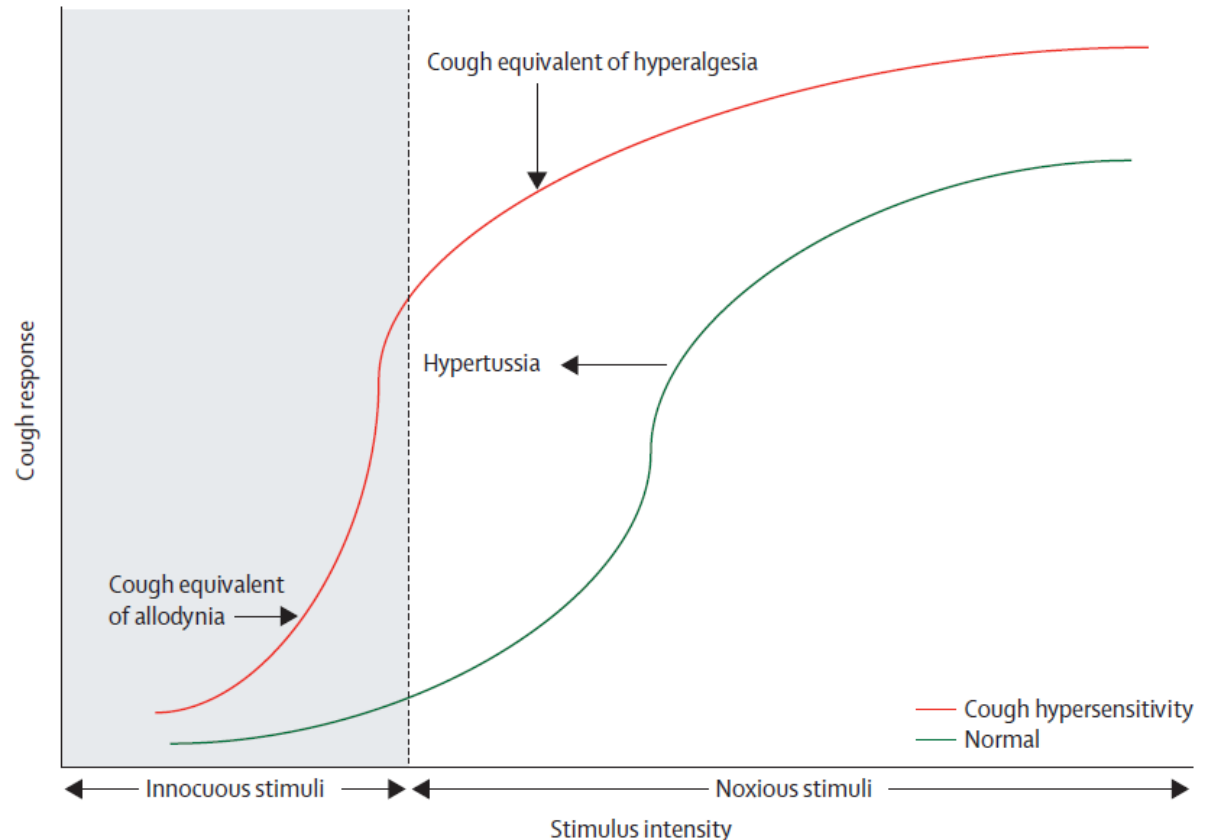


Cough hypersensitivity as a treatable trait

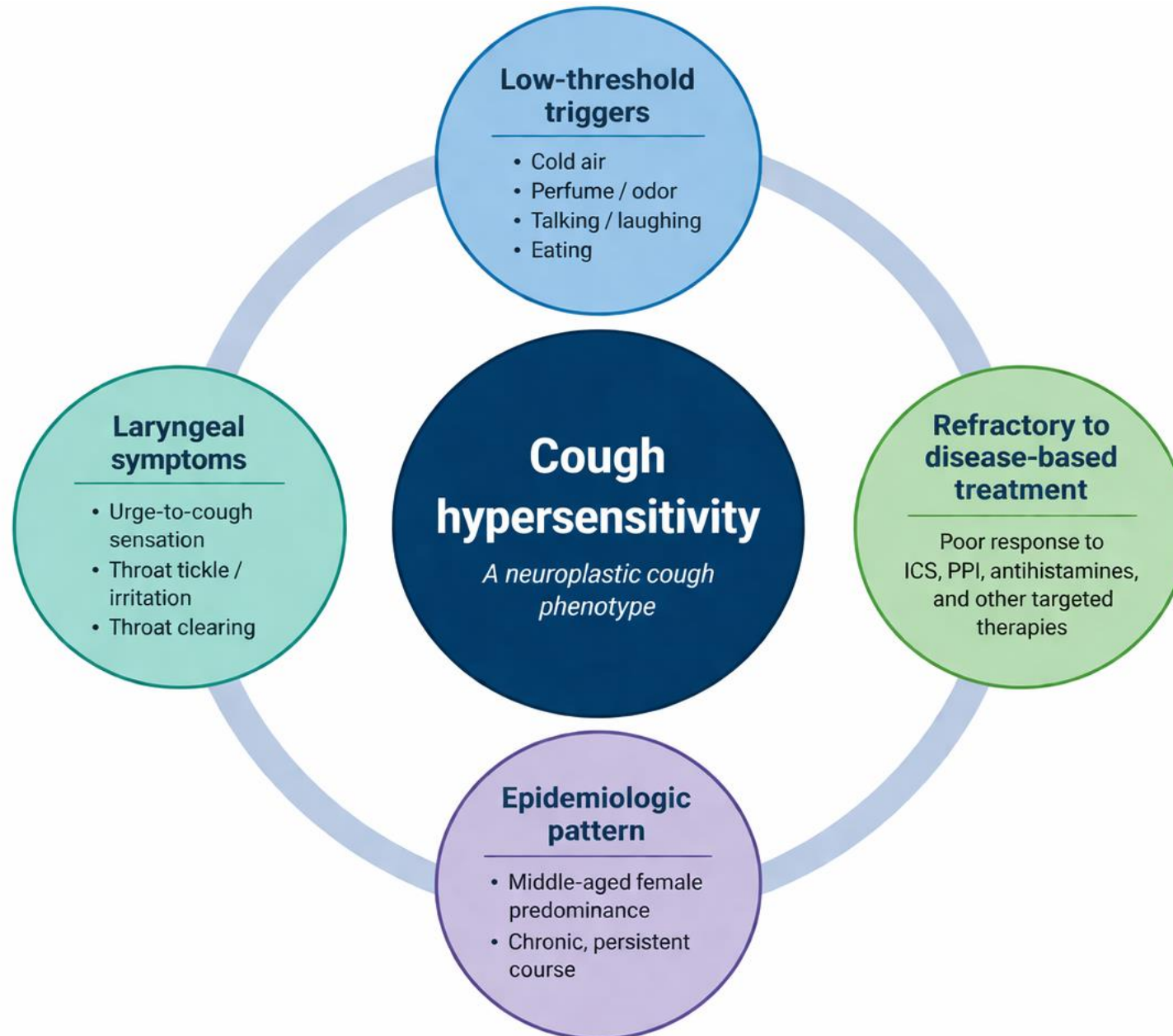


Paradigm shift toward the concept of cough hypersensitivity

- **Cough hypersensitivity**
 - defined as troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure
 - now considered a unifying feature in CC, irrespective of the aetiology
- **Allotussia**
 - cough triggered by innocuous stimuli such as talking, eating and perfumes
- **Hypertussia**
 - heightened cough sensitivity to known cough stimuli such as smoke, fumes and bleach
- **Laryngeal paresthesia**
 - Tickle or itch in throat, Urge-to-cough

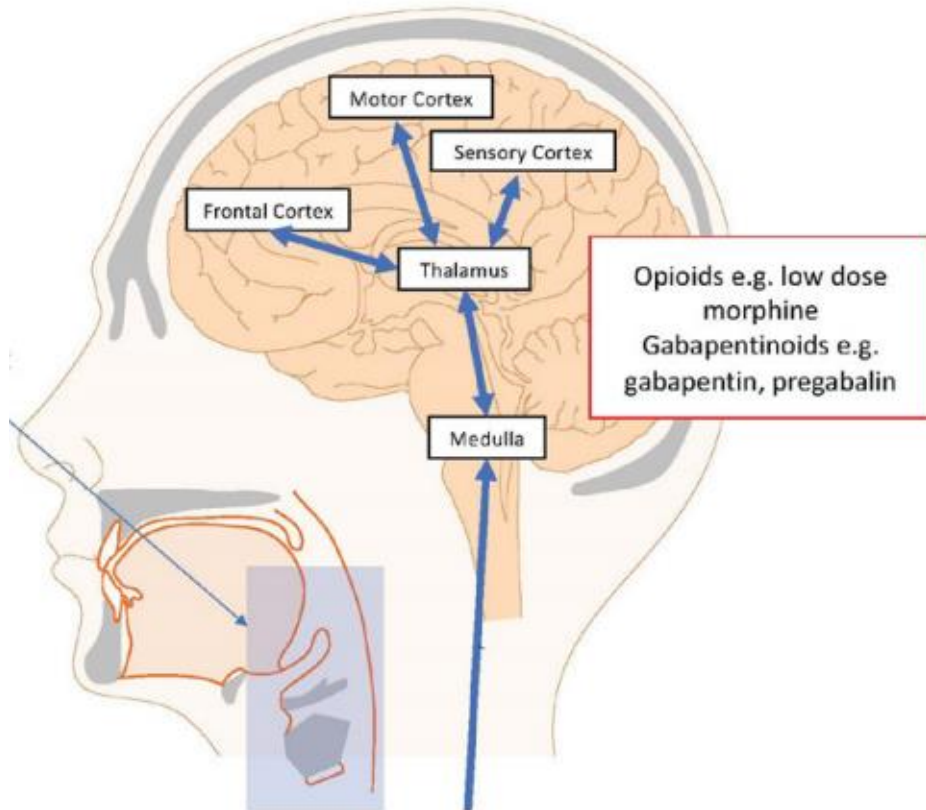


Cough hypersensitivity is a clinical diagnosis.

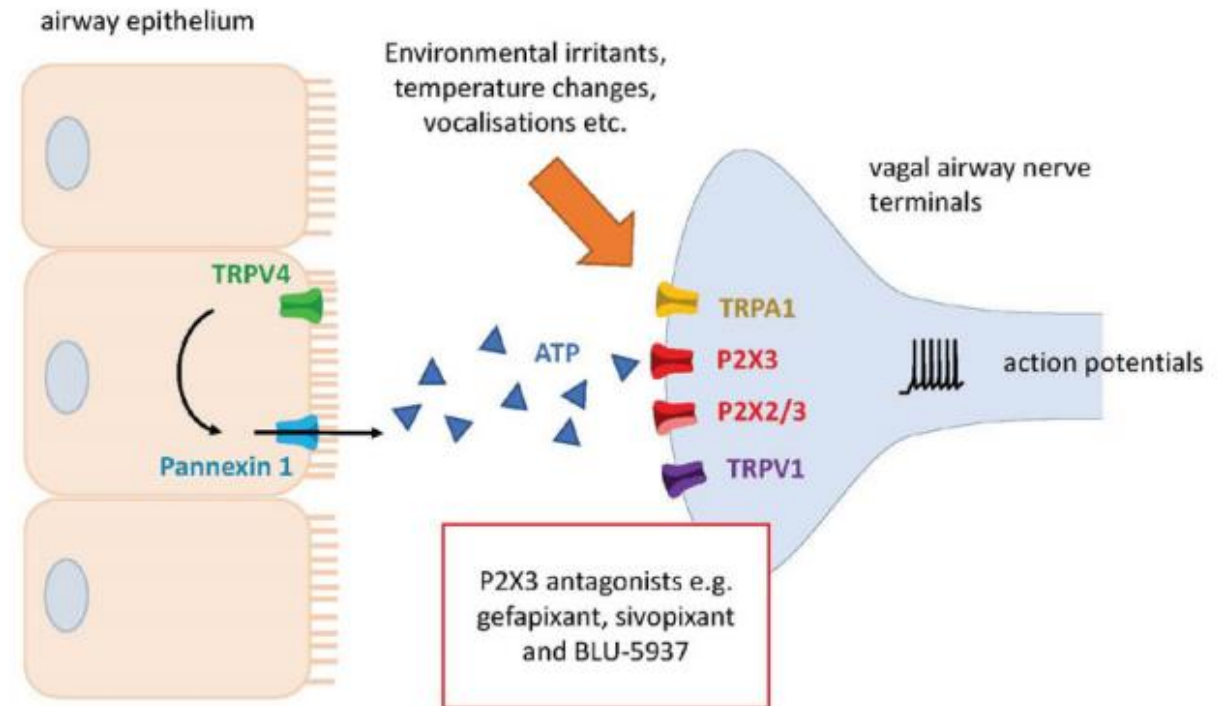


Treatment options for cough hypersensitivity

Central acting treatment



Peripheral acting treatment



Opiate Therapy in Chronic Cough

Alyn H. Morice¹, Madhav S. Menon¹, Siobhan A. Mulrennan¹, Caroline F. Everett¹, Caroline Wright¹, Jennifer Jackson¹, and Rachel Thompson¹

¹Department of Academic Medicine (Chest), University of Hull, Castle Hill Hospital, Hull, East Yorkshire, United Kingdom

Randomized double-blind placebo-controlled study

- 27 chronic cough patients (females n=18, mean age 55±10.6)
- 4 wks of **slow-release morphine sulfate** (MST) 5 mg twice daily
- 4 wks of placebo

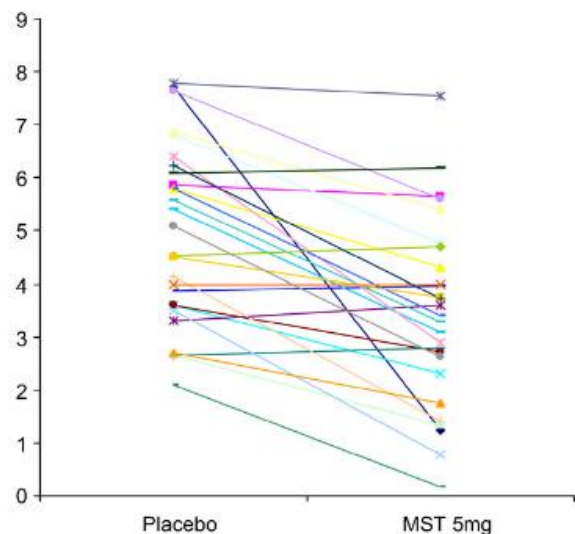
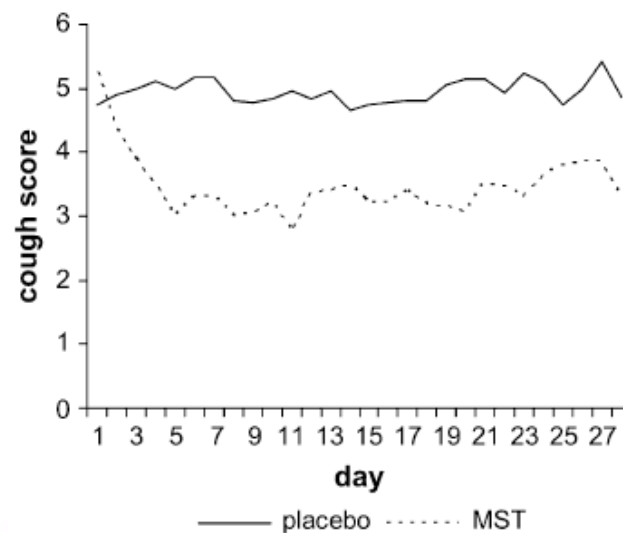


Figure 1. Daily cough severity scores on a scale of 0 to 9. MST = slow-release morphine sulfate.



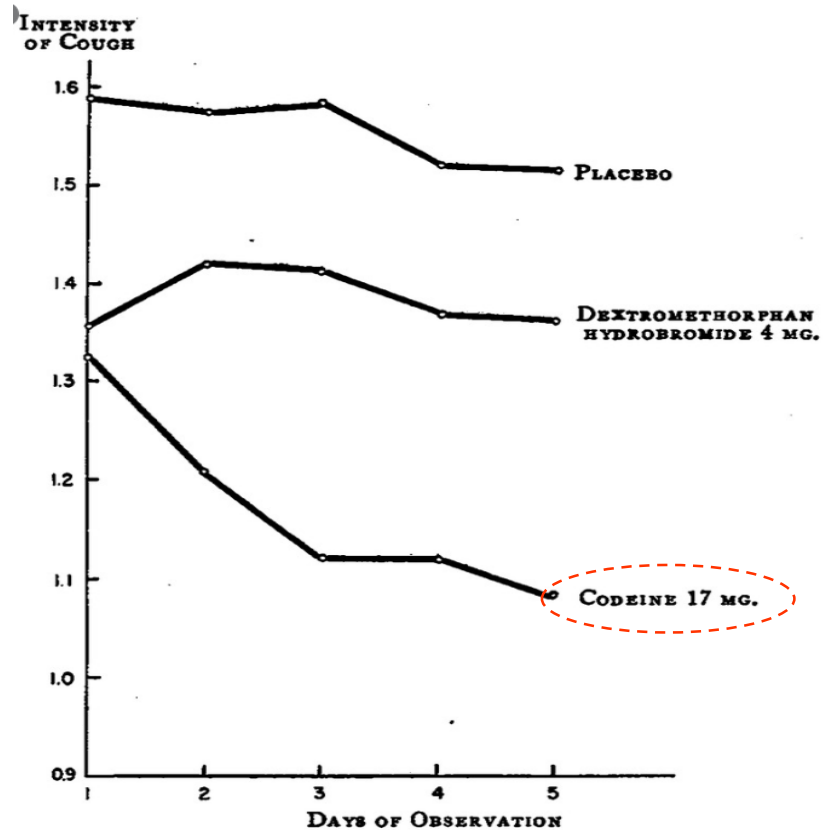
Mean of daily diary cough scores.

LCQ Domain	Mean Value at Baseline	Mean value for Placebo	Mean value for Morphine	95% Confidence Interval Placebo vs. Morphine
Physical	4.0	4.8	5.3	-1.1 to -4.3, p < 0.04
Psychological	4.1	4.6	5.1	-1.1 to -3.9, p < 0.04
Social	3.7	4.2	5.1	-1.7 to -3.0, p < 0.05

Adverse effects: constipation (40%), and drowsiness (25%)

Codeine

- 65 patients with persistent cough
- Codeine 17 mg qid for 5 days



Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease

Jaclyn Smith, MD, PhD,^a Emily Owen, MPhil,^a John Earis, MD,^b and Ashley Woodcock, MD^a
Manchester and Liverpool, United Kingdom

- 21 patients with stable COPD (FEV1 30-75% pred) who complained of cough
- Codeine phosphate 60 mg or matched placebo

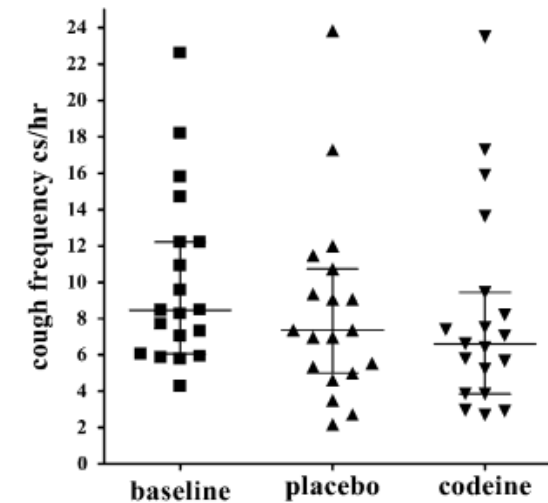
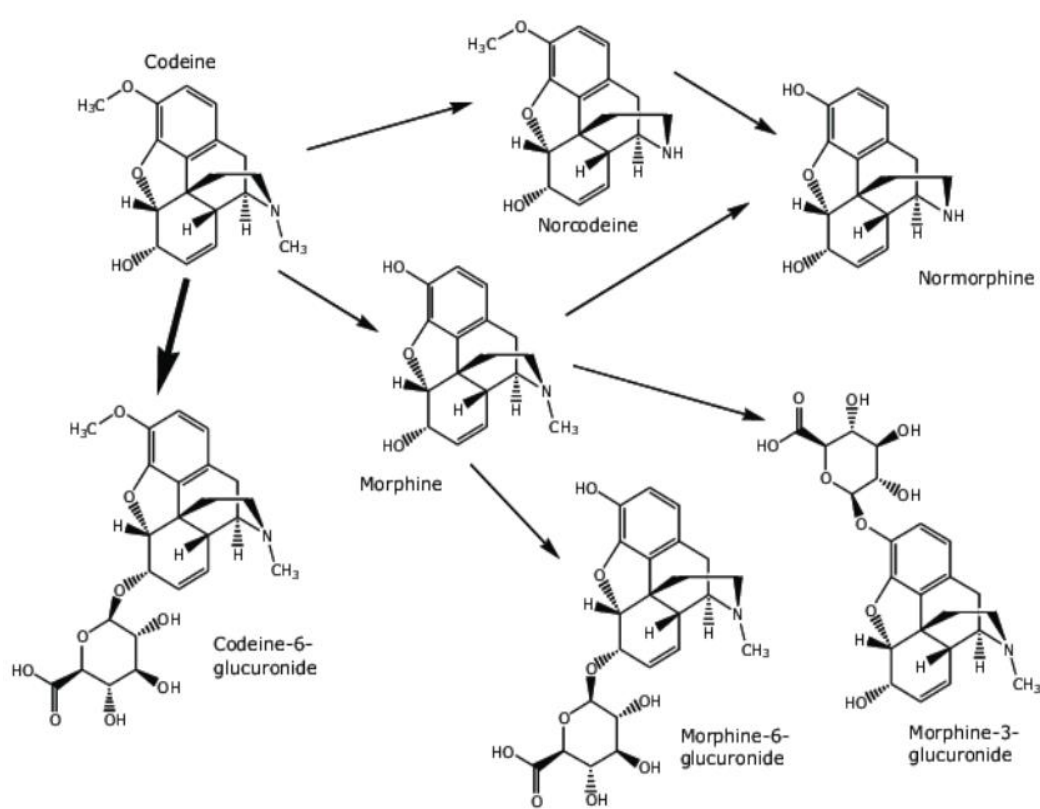
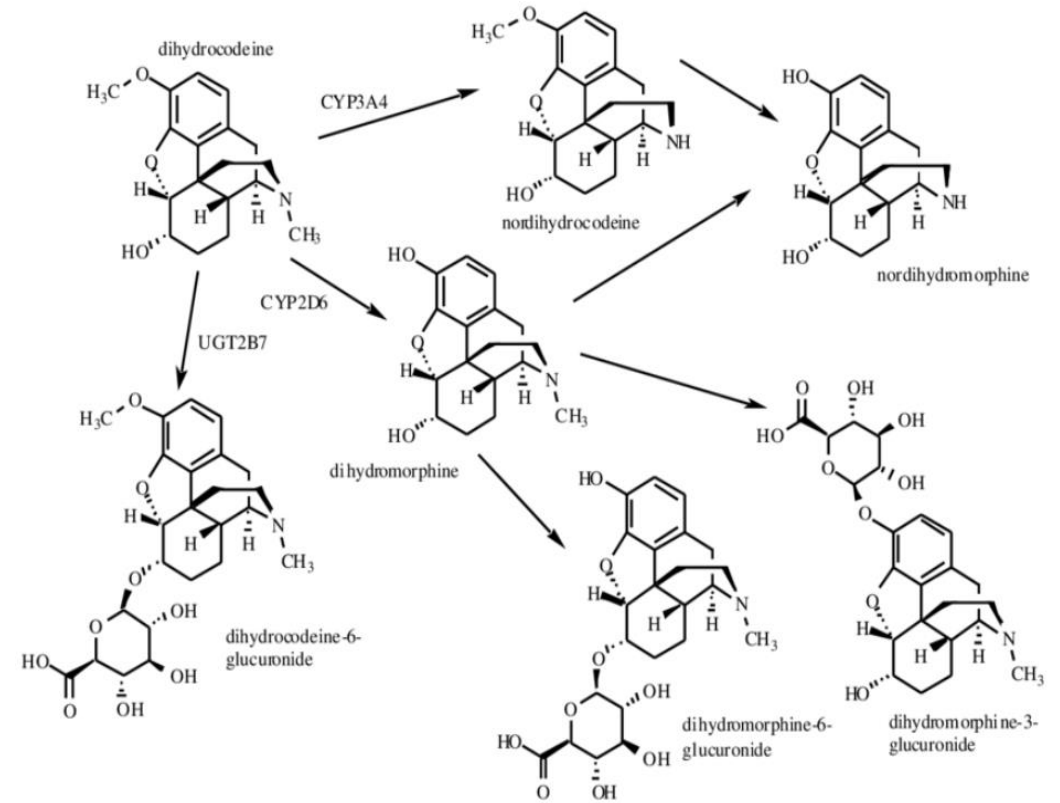


FIG 1. Time spent coughing on baseline study day and after treatment with codeine and placebo. Horizontal lines represent median time spent coughing and error bars the IQR.

Influence of CYP2D6 genetics on opioid kinetics, metabolism and response



The chemical structures of codeine and its major metabolites



Metabolic pathways of dihydrocodeine and enzymes contributing to the metabolism

Currently-available drugs in patients with RCC; opioids

	Effect	Limitation	Adverse effects	Strength of recommendation		
				국내 (2018)	ERS (2019)	ACCP (2015)
Morphine	Improvement of <u>LCQ</u> , cough <u>severity</u> score, and cough <u>frequency</u>	No significant difference in citric acid cough challenge	Constipation, drowsiness, sedation, dry mouth, dizziness, nausea, headache	B	Strong	Not mentioned
Codeine	Improvement of cough intensity (<i>Cass et al. 1953</i>)	No significant effect on cough frequency (<i>Smith et al. 2006</i>)		B	Not mentioned	Not mentioned

대한천식알레르기학회 만성기침 진료지침

권고등급 정의

A 치료나 검사의 편익이 그로 인한 위험, 부담, 비용을 명백히 상회하는 경우

B 치료나 검사의 편익이 그로 인한 위험, 부담, 비용을 상회하나 불확실한 경우

Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial

Nicole M Ryan, Surinder S Birring, Peter G Gibson

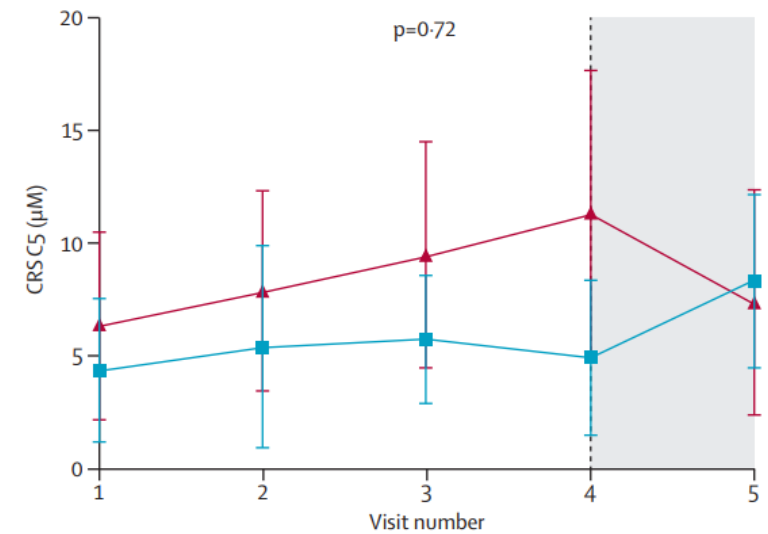
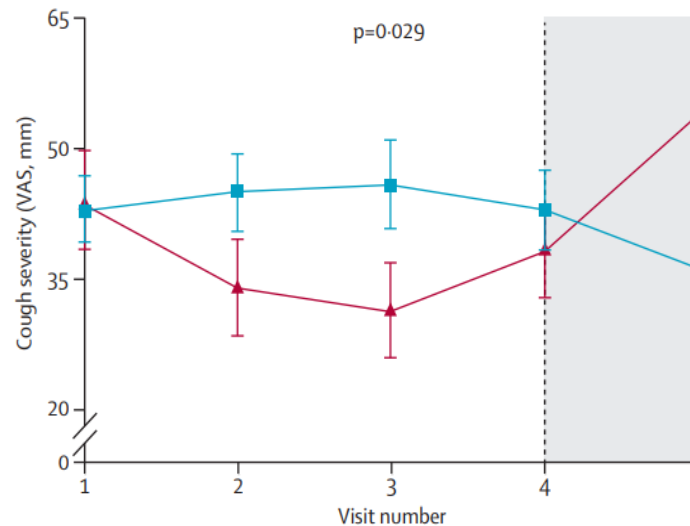
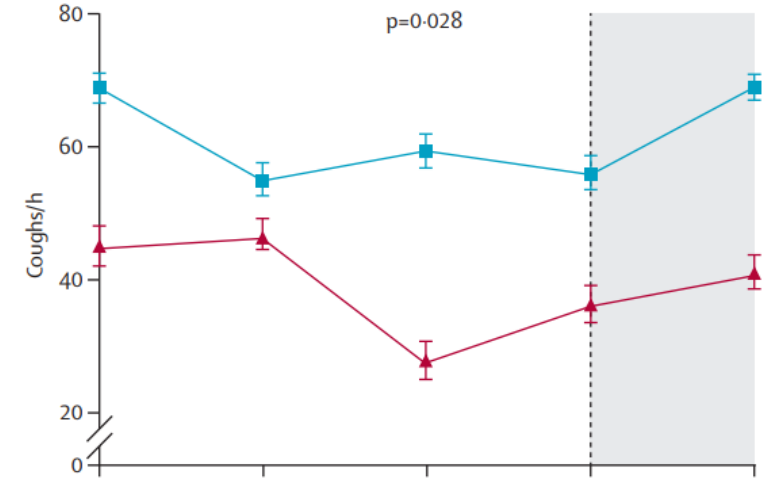
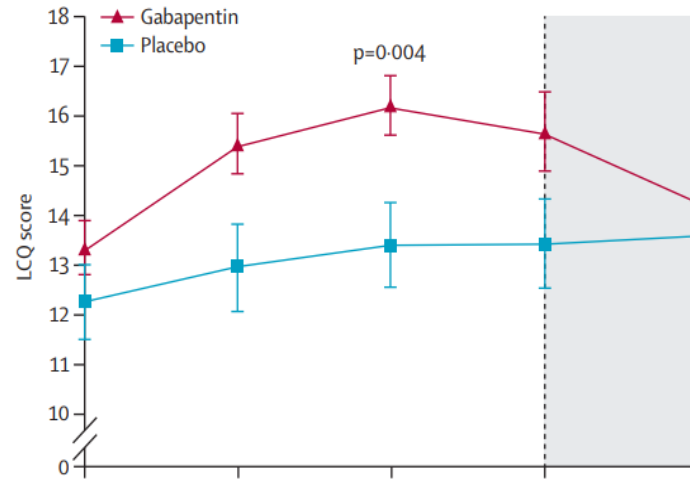
Randomised, double-blind, placebo-controlled trial

62 pts with RCC

- Gabapentin (max 1800 mg) for 10 wks
- Placebo for 10 wks

10 pts withdrew before the study end

Mean difference in LCQ
= 1.8 (95% CI 0.56-3.04, p=0.04)



Pregabalin and Speech Pathology Combination Therapy for Refractory Chronic Cough

A Randomized Controlled Trial

Anne E. Vertigan, PhD; Sarah L. Kapela, BSpPath; Nicole M. Ryan, PhD; Surinder S. Birring, MB, ChB (Hons), MD;
Patrick McElduff, PhD; and Peter G. Gibson, MBBS (Hons)

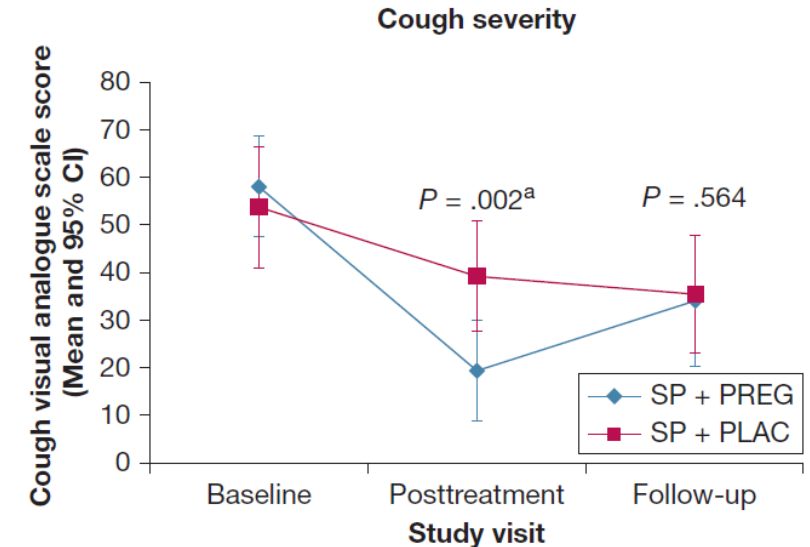
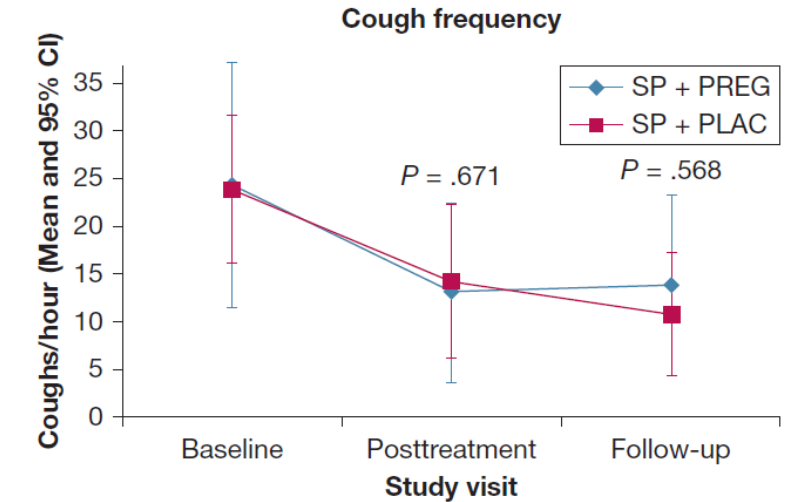
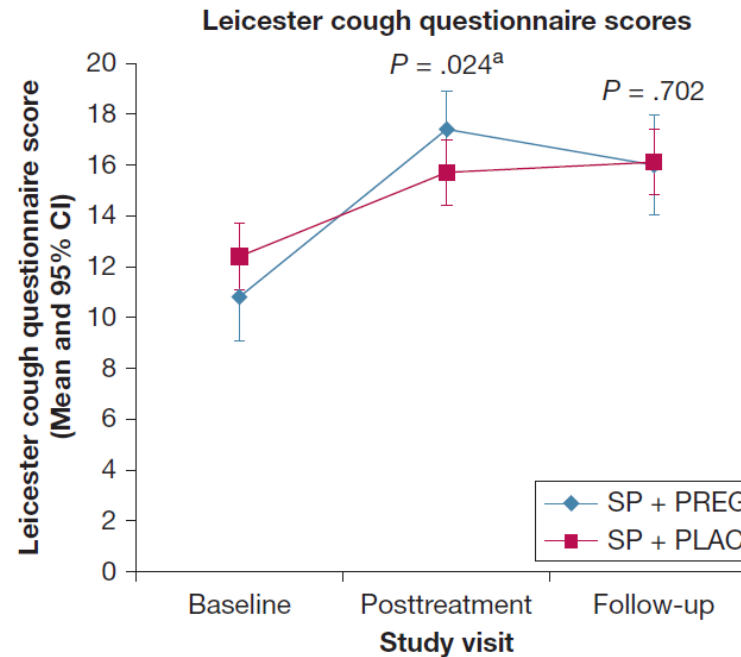
Randomized, double-blind, placebo (PLAC)-controlled trial

40 pts with RCC

- Speech pathology (SP) + pregabalin (PREG, max 300 mg/day)
- SP + placebo (PLAC) for 14 weeks

Mean difference in LCQ
= 3.5 (95% CI 1.1-5.8)

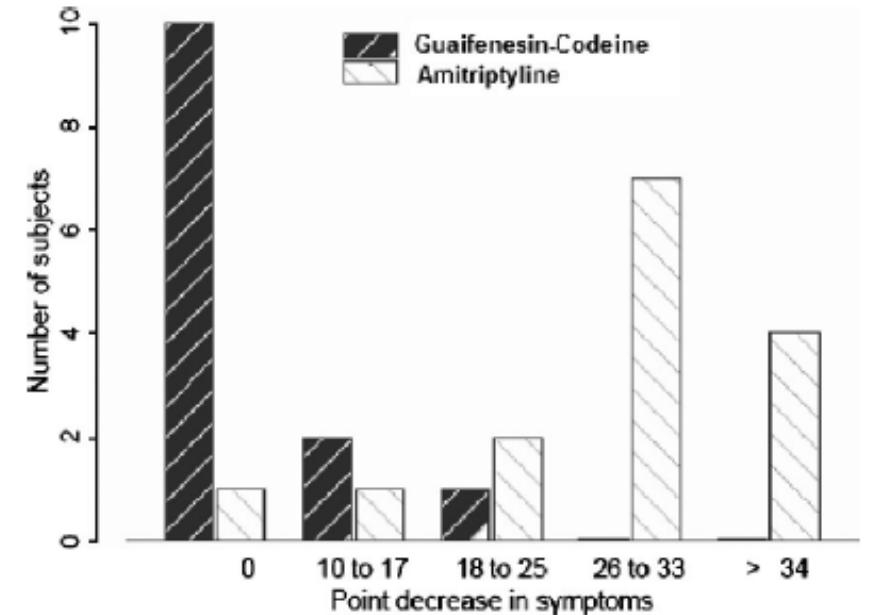
Mean difference in cough VAS
= 25.1 (95% CI 10.6 to 39.6)



Effectiveness of Amitriptyline Versus Cough Suppressants in the Treatment of Chronic Cough Resulting From Postviral Vagal Neuropathy

Anita Jeyakumar, MD; Todd M. Brickman, MD; Michael Haben, MD, MSc

- 28 patients with nonproductive chronic cough
 - h/o Postviral vagal neuropathy
 - precipitated by throat tickle, dry sensation, laughter, or speaking
- 10 mg **amitriptyline**
vs. 10-100 mg/ 5, 10 mL codeine/guaifenesin
every 6 hours standing dose



Difference in response rates between amitriptyline and codeine/guaifenesin in pre- and **posttreatment cough quality of life**

Currently-available drugs in patients with RCC; neuromodulator

	Effect	Limitation	Adverse effects	Recommendation		
				국내	ERS	ACCP
Gabapentin	Improvement of <u>LCQ</u> , cough <u>severity</u> , and cough <u>frequency</u>	No significant difference in <u>capsaicin cough sensitivity</u> , urge-to-cough, laryngeal dysfunction score. LCQ score was <u>not sustained after treatment withdrawal</u>	blurred vision, disorientation, dizziness, dry mouth, fatigue and nausea	B	Conditional	2C
Pregabalin	Improvement of <u>LCQ</u> and cough <u>severity</u>	No significant difference in <u>capsaicin cough sensitivity</u> , cough <u>frequency</u> , and <u>urge-to-cough</u>		B	Conditional	
Amitriptyline	<u>QoL</u> ≥ 50% response (vs. codeine/guaifenesin)	Objective cough frequency was not measured.		B		

Efficacy and safety of gefapixant, a P2X₃ 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*

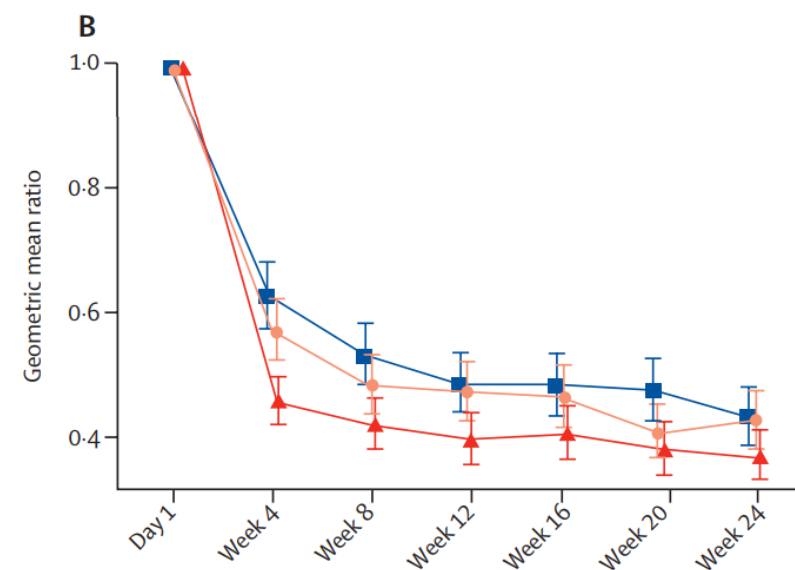
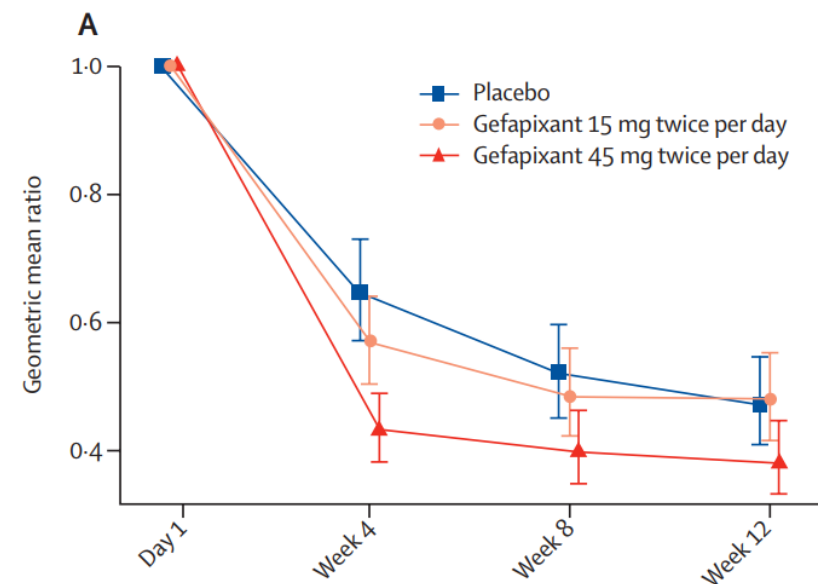
COUGH-1 and COUGH-2: double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials

730 pts (female 74.2%, mean age 59.0±12.6) with RUCC in COUGH-1
1314 pts (female 74.9%, mean age 58.1±12.1) with RUCC in COUGH-2

- Placebo
- Gefapixant 15 mg twice per day
- Gefapixant 45 mg twice per day

Gefapixant 45 mg twice per day

- significant reductions in 24-h cough frequency compared with placebo at week 12 in COUGH-1 = 18.5% (95% CI 32.9–0.9, p=0.041)
at week 24 in COUGH-2 = 14.6% (95% CI 26.1–1.4, p=0.031)



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

Oral Nalbuphine in Idiopathic Pulmonary Fibrosis–Associated Cough

The CORAL Randomized Clinical Trial

Philip L. Molyneaux, MD, PhD; Nesrin Mogulkoc, MD; Hakan Gunen, MD; Anna Doboszyńska, MD; Michael Kreuter, MD; Blue Neustifter, PhD; Vandana Mathur, MD; James Cassella, PhD; for the CORAL Study Group

Nalbuphine

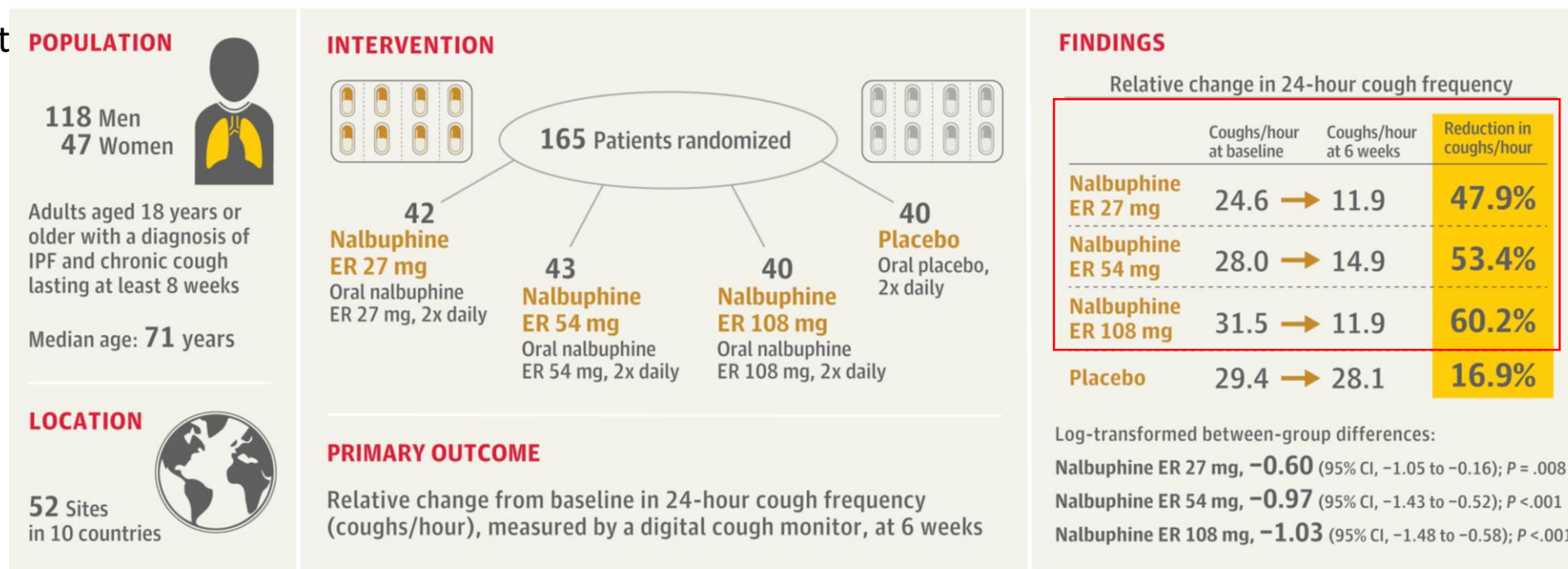
: κ opioid receptor agonist and μ-opioid receptor antagonist

- respiratory depression ↓
- abuse potential ↓
- central + peripheral modulation

QUESTION In patients with chronic cough caused by idiopathic pulmonary fibrosis (IPF), does nalbuphine extended release (ER) reduce cough and improve patient-reported outcomes?

CONCLUSION For patients with IPF-associated chronic cough, treatment with nalbuphine ER reduced cough frequency and improved patient-reported outcomes at 6 weeks.

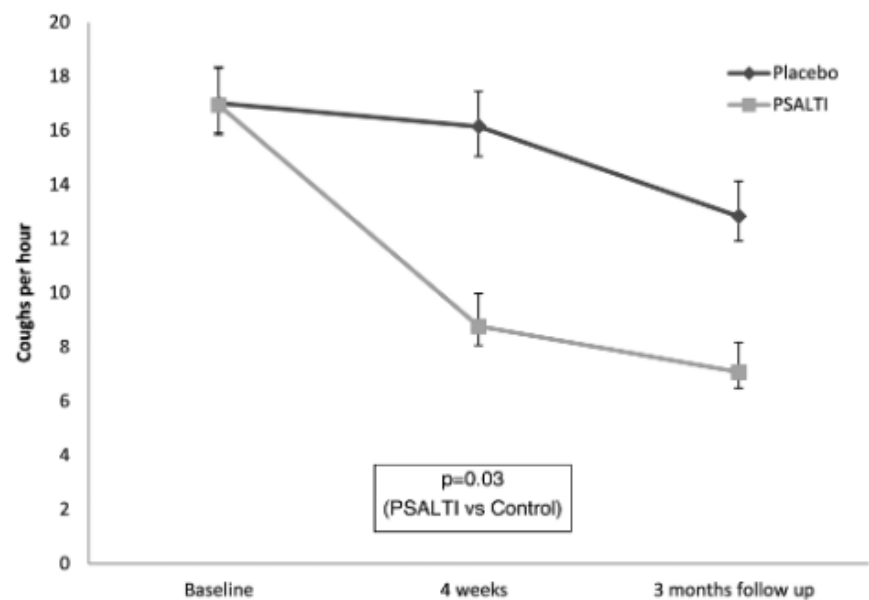
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Molyneaux PL, Mogulkoc N, Gunen H, et al; CORAL Study Group. Oral nalbuphine in idiopathic pulmonary fibrosis-associated cough: the CORAL randomized clinical trial. *JAMA*. Published online January 22, 2026. doi:10.1001/jama.2025.26179

Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised controlled trial

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Data presented as Geometric Mean (log 95%CI) coughs per hour. PSALTI: physiotherapy speech and language therapy intervention.

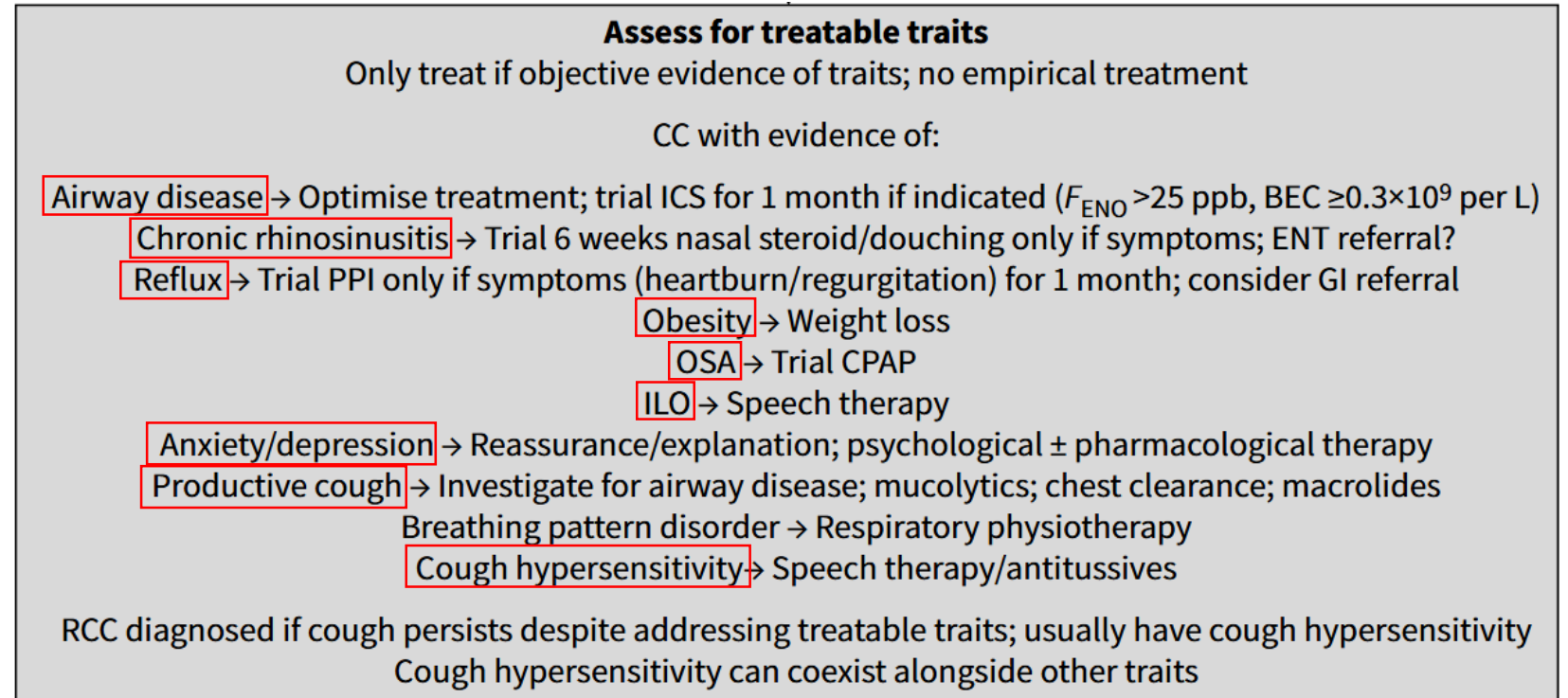
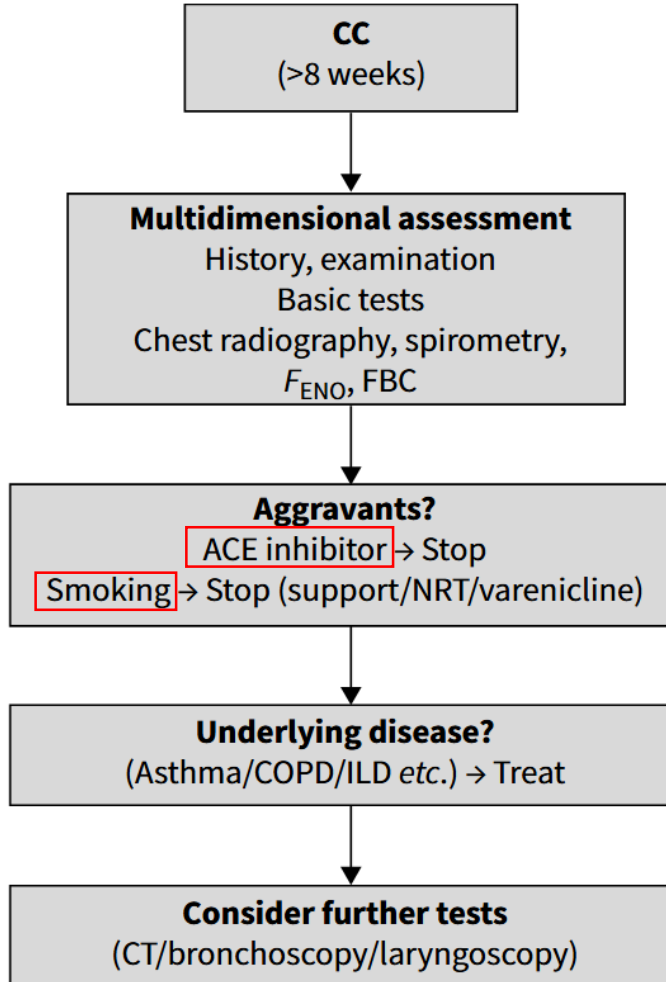
Figure 2 Change in objective cough frequency in physiotherapy, and speech and language therapy intervention (PSALTI) and control groups.

PSALTI component	Technique
Education	Educate patients on the cough reflex, chronic cough and cough reflex hypersensitivity. Explain the negative effects of repeated coughing. Educate patients on voluntary control of cough.
Laryngeal hygiene and hydration	Increase frequency and volume of water and non-caffeinated drinks. Reduce caffeine and alcohol intake. Promote nasal breathing.
Cough control	Teach patients to identify their cough triggers. Teach patients to use cough suppression or distraction techniques at the first sign or sensation of the need or urge to cough. These cough-suppression/distraction techniques include: forced swallowing, sipping water and sucking sweets.
LCQ total	Teach patients breathing exercises: breathing pattern re-education promoting relaxed abdominal breathing pattern technique; pursed lip breathing to use to control cough.
Cough frequency (CF/hour)	
VAS severity	Psychoeducational counselling Motivate patients, reiterate the techniques and the aims of therapy. Behaviour modification: to try to reduce over-awareness of the need to cough. Stress and anxiety management

다면적 기침억제행동요법

내용	치료목표	예시
교육	<ul style="list-style-type: none"> · 반복하는 기침이 이점이 없으며, 부정적인 영향을 미칠 수 있다는 인식 마련 · 기침을 스스로 조절할 수 있다는 인식을 만들어 줌 	<ul style="list-style-type: none"> · 목에 무언가 걸린 것 같은 느낌으로 기침을 반복하는 것을 중단함. · 반복적인 기침이 후두의 손상을 초래하고, 후두의 자극으로 기침이 지속될 수 있음을 교육.
기침억제요법	<ul style="list-style-type: none"> · 자극에 대한 기침의 억제 	<ul style="list-style-type: none"> · 입술 오므리고 숨쉬기(pursed lip breathing) · 복식호흡 · 발살바(Valsalva) 법을 활용한 침 삼키기 · 물 마시기 · 입에 얼음 물고 있기 · 껌 씹기
음성위생법	<ul style="list-style-type: none"> · 후두 자극의 감소 · 수분공급 	<ul style="list-style-type: none"> · 직접흡연 및 간접흡연 회피 · 구강호흡 회피 · 술이나 카페인, 기침을 진정시키는 것으로 알려진 약물성 사탕은 오히려 후두를 건조시킬 수 있어 사용을 제한함 · 위식도역류에 대한 생활습관 관리 · 물을 자주 마시거나 증기를 흡입 · 비약물성 사탕으로 침 생성을 유도하여 수분을 공급
심리교육상담		<ul style="list-style-type: none"> · 특별성 기침은 치료가 어렵다는 것을 강조 · 기침조절이 외부의 원인보다 자극에 대한 반응이 문제됨을 강조 · 치료의 현실적인 목표를 세움.

Management of CC





경청해 주셔서 감사합니다.