

Addressing the Unmet Needs of
**Refractory
Chronic Cough**



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Disclosures:

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Learning Objectives

1. Summarize the steps in the diagnostic evaluation and overall patient work up to identify refractory chronic cough (RCC)
2. Identify the underlying neurologic mechanisms that contribute to cough hypersensitivity and their basis as treatment targets for RCC
3. Assess how ongoing developments in clinical research may help address current limitations in the management of RCC





Chronic cough in the adult population is defined as a cough for lasting greater than:



Which of the following best describes the mechanisms contributing to cough hypersensitivity and their role as treatment targets for refractory chronic cough?



Which research trend is most likely to improve management of refractory chronic cough (RCC)?

Why Do We Cough?

- Protects the lungs from infection and inflammation
- Removes mucus and debris that can obstruct airflow
- Helps expel foreign objects that may have entered the airways



Weinberger SE, UpToDate; Accessed [March 2025]. <https://www.uptodate.com/contents/causes-and-epidemiology-of-subacute-and-chronic-cough-in-adults>



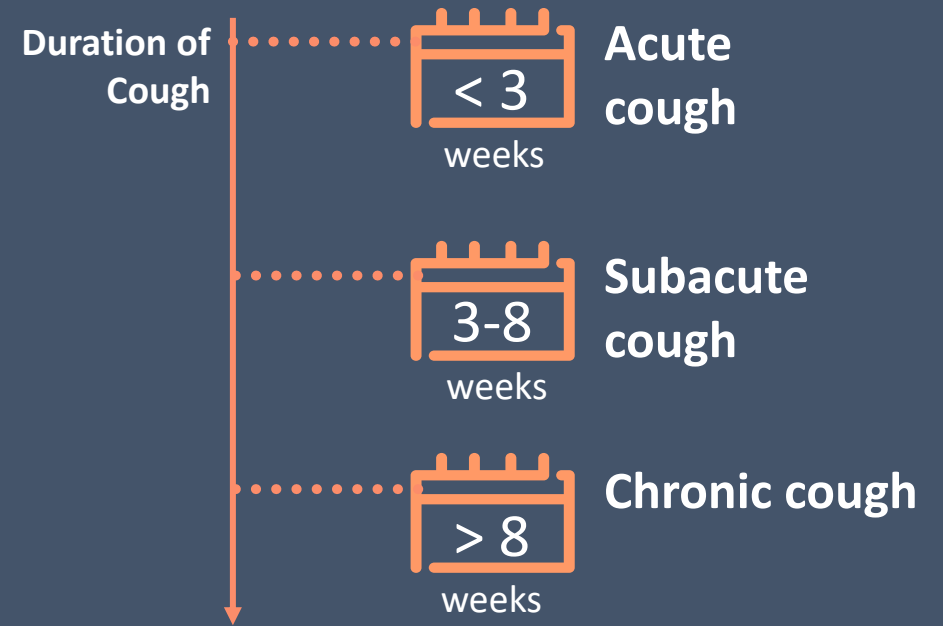
What Is Chronic Cough?

- Classifying cough by **duration** can help diagnose patients and guide treatment decision-making¹

Refractory chronic cough (RCC) occurs when cough persists despite thorough evaluation and treatment of underlying etiologies^{2,3}

- Also referred to as **unexplained chronic cough (UCC)**
- **More common in women than men**
- **Highest incidence seen in 50's and 60's**

CHEST Classification of Cough as a Symptom in Adults¹



Note: the definition of chronic cough varies globally, with some studies using 3 months as the cut-off criterion

1. Irwin RS, et al. *Chest*. 2018;153(1):196-209; 2. Morice AH, et al. *Eur Respir J*. 2020;55(1):1901136; 3. Visca D, et al. *Eur J Intern Med*. 2020;81:15-21.



Refractory Chronic Cough (RCC)

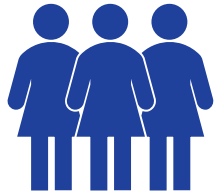
- A chronic cough lasting **more than 8 weeks** that persists despite appropriate treatment of common underlying causes
 - Diagnosis of exclusion
- Often associated with **cough hypersensitivity syndrome**, characterized by heightened neural responses to stimuli



Impact of Chronic Cough



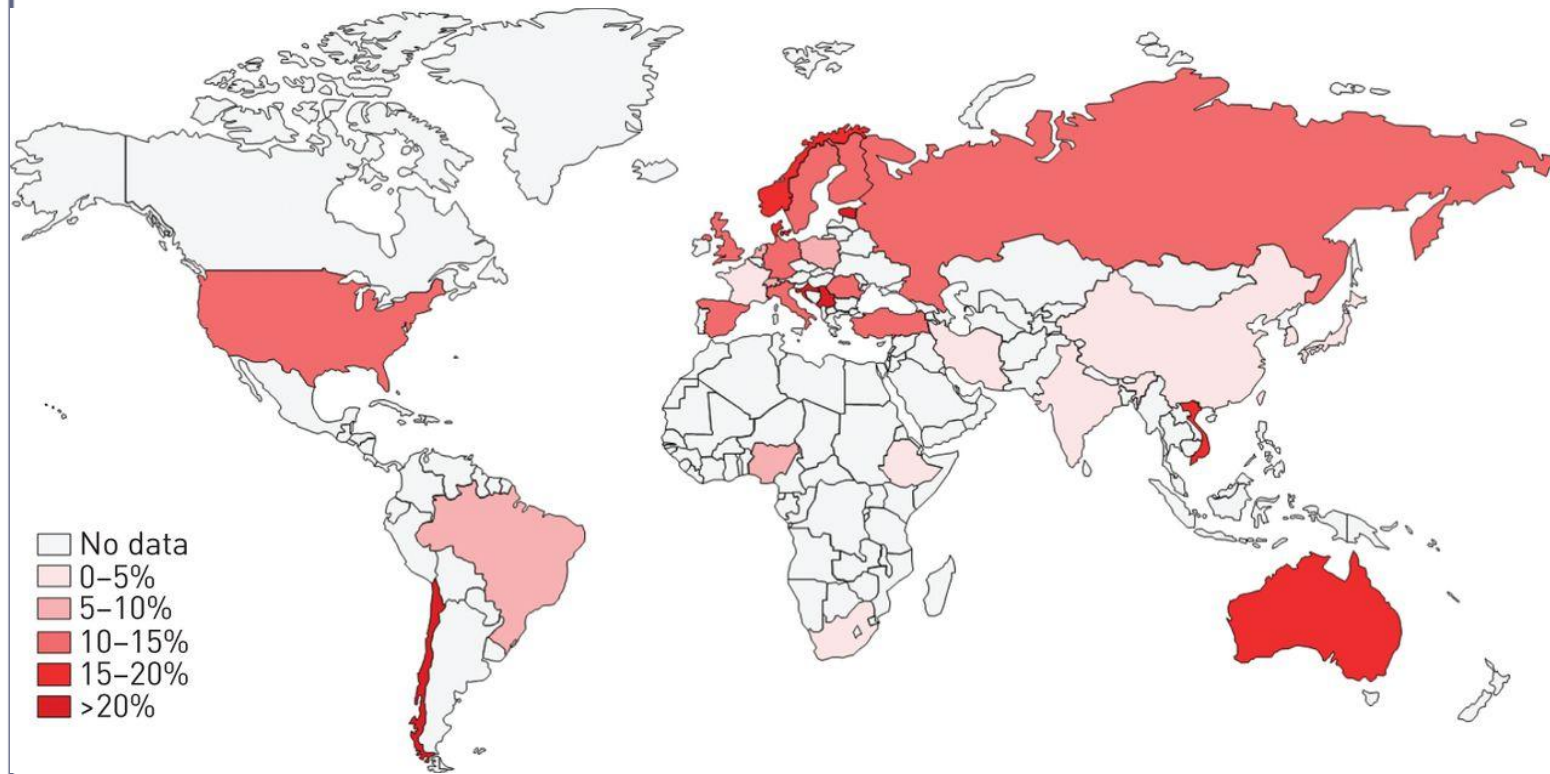
- Approximately 11% of the US general adult population is estimated to suffer from chronic cough²
 - Based on a systematic review and meta-analysis of peer-reviewed journals published between 1980 and 2013²



- Chronic cough affects both men and women, but the typical patient is a female in her 50s¹



Global Impact of Chronic Cough



Region	Prevalence
Overall	9.6% (95% CI 7.6-11.7%)
Oceania	18.1% (95% CI 9.8-27.2%)
Europe	12.7% (95% CI 10.4-15.2%)
America	11.0% (95% CI 7.8-14.4%)
Asia	4.4% (95% CI 1.8-7.4%)
Africa	2.3% (95% CI 0.0-6.7%)

Meltzer EO, et al. *J Allergy Clin Immunol Pract.* 2021;9(11):4037-4044.e2; Song WJ, et al. *Eur Respir J.* 2015;45(5):1479-1481..



Chronic Cough Persists for Years

A cohort of adult patients diagnosed with chronic cough by a pulmonologist, gastroenterologist, allergist, or otolaryngologist reported:



**Average duration
of cough (n=560)**

8.6 years

Standard deviation

±10.5 years



Patient Perspectives: Impact of CC

- Burdens experienced by >50% of patients^{1,2}
 - Hindered communication
 - Embarrassment
 - Frustration
 - Worry
 - Reduced quality of life (QoL)
- Only 40% report improved symptoms with medication³
- Most (70%) are frustrated by the persistence of their condition and lack of effective treatments³

“Theres no ability to stop [coughing] or control it; it’s like it takes over, it just takes over your body and until that cough is out...”

“I have not slept well for many years...the coughing spells start at night.”

“It can get so severe that I literally have to go to the sink just to hold on just to keep my body up.”

“At times it’ll get bad enough, where I black out, or feel like I’m going to black out.”

1. Bali V, et al. *Ther Adv Respir Dis*. 2024 Jan-Dec;18:17534666241236025; 2. Hirons B, et al. *ERJ Open Res*. 2024;10:00923 2023; 3. Kum e, et al. *ERJ Open Res*. 2022;8:00667-2021.



Patient Burden of Refractory Chronic Cough^{1,2}



Clinical

- Urinary incontinence
- Dizziness and headaches
- Sleep disruption
- Exhaustion
- Can cause an exacerbation of underlying diseases



Social

- Conversation/speech interruption
- Avoidance of activities
- Disruption of family, friends, and coworkers



Psychological

- Depression
- Anxiety
- Self-consciousness and embarrassment
- Concerns about serious underlying condition

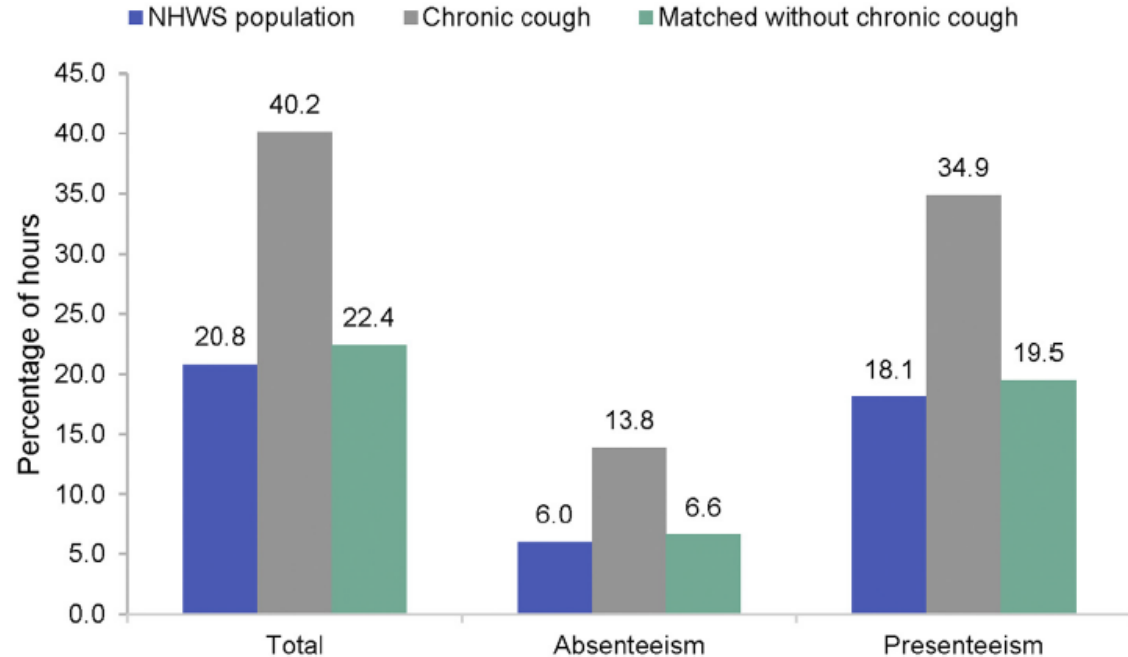


Economic

- Impaired productivity
- More emergency department visits and hospitalizations



Economic Burden of Chronic Cough



Impacts healthcare costs (increased physician visits, diagnostic testing, medication use) and lost productivity and work absenteeism¹

Chronic cough is associated with high healthcare resource utilization (HCRU) due to challenges in diagnosis and treatment and is anticipated to have a substantial economic impact.²

Work productivity among employed respondents over the past week. $P < .001$ for all comparisons of chronic cough vs. matched controls. Propensity score matched to chronic cough sample on age, gender, and modified Charlson Comorbidity Index.

1. Meltzer EO, et al. *J Allergy Clin Immunol Pract.* 2021;9(11):4037-4044.e2; 2. Bali V, et al. *BMC Pulm Med.* 2023;23(1):416.



Initial Assessment of Chronic Cough

Clinical History

- Cough duration and characteristics
- Cough triggers
- Family history
- Risk factors (e.g., smoking, use of ACE inhibitors, occupational exposure)
- Red flags that indicate a life-threatening cause for cough

Routine Evaluations

- Physical examination
- Chest radiography
- Pulmonary function test

Cough-Specific Measures

- Cough severity assessment
 - Numerical questionnaire
 - Visual analog scale

Red Flags

- Hemoptysis
- Smoker aged > 45 years with a new cough, change in cough, or 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, particularly at rest or at night
- Hoarseness
- Systemic symptoms (eg, fever, weight loss, peripheral edema)
- Dysphagia
- Vomiting
- Recurrent pneumonia
- Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough

CHEST Guidelines and Expert Panel Report

ACE = Angiotensin-Converting Enzyme

Irwin RS, et al. *Chest*. 2018;153(1):196-209; Morice AH, et al. *Eur Respir J*. 2020;55(1):1901136; Chung KF, et al. *Nat Rev Dis Primers*. 2022;8(1):45.



Process of Refractory Chronic Cough Assessment and Diagnosis

Algorithm from
CHEST Guidelines
and Expert Panel
Report

Initial
investigations



**Risk factor
management**

Discontinue:

- Smoking
- ACE inhibitors

4-6
weeks

Underlying conditions

**Optimally treat underlying
conditions:**

- UACS (antihistamine/
decongestant)
- NAEB (ICS, trigger
avoidance)
- Asthma (ICS, bronchodilator,
LTRA, trigger avoidance)
- GERD (PPI, dietary/lifestyle
changes beyond acid suppression)

4-6
weeks

Consider further investigations:

- 24-h esophageal pH/impedance
monitoring
- Endoscopic and/or video
fluoroscopic swallow
evaluation
- Barium esophagram/modified
barium swallow
- Sinus Imaging
- HRCT scan
- Bronchoscopy
- Cardiac work-up (ECG, Holter
monitoring, echocardiogram)
- Environmental/occupational
assessment
- Consider uncommon causes



**If cough persists after underlying conditions have been
optimally treated and/or no further investigations
remain, a diagnosis of refractory chronic cough is given**

UACS = Upper Airway Cough Syndrome; NAEB = Nonasthmatic Eosinophilic Bronchitis; ICS = Inhaled Corticosteroid; LTRA = Leukotriene Receptor Antagonist; PPI = Proton Pump Inhibitor; HRCT = High-Resolution Computed Tomography; ECG = Electrocardiography

Irwin RS, et al. *Chest*. 2018;153(1):196-209; Morice AH, et al. *Eur Respir J*. 2020;55(1):1901136.



The "Big 3" Common Causes of Chronic Cough

These 3 conditions account for most cases of chronic cough in immunocompetent, nonsmoking patients with normal chest radiographic findings:

- 1. Upper Airway Cough Syndrome (UACS)**
Postnasal drip, allergic rhinitis, sinusitis
- 2. Asthma & Non-Asthmatic Eosinophilic Bronchitis (NAEB)**
- 3. Gastroesophageal Reflux Disease (GERD)**



Evaluation of the “Big 3”

Upper Airway Cough Syndrome (UACS) secondary to Sino-nasal diseases

Consider:

- Sinus imaging
- Nasopharyngoscopy
- Allergy evaluation or empiric treatment

Asthma & Non-asthmatic Eosinophilic Bronchitis (NAEB)

Ideally evaluate:

- Spirometry
- Bronchodilator reversibility
- Bronchoprovocation challenge
- 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:

- Acid suppression with medications
- Lifestyle changes to reduce reflux



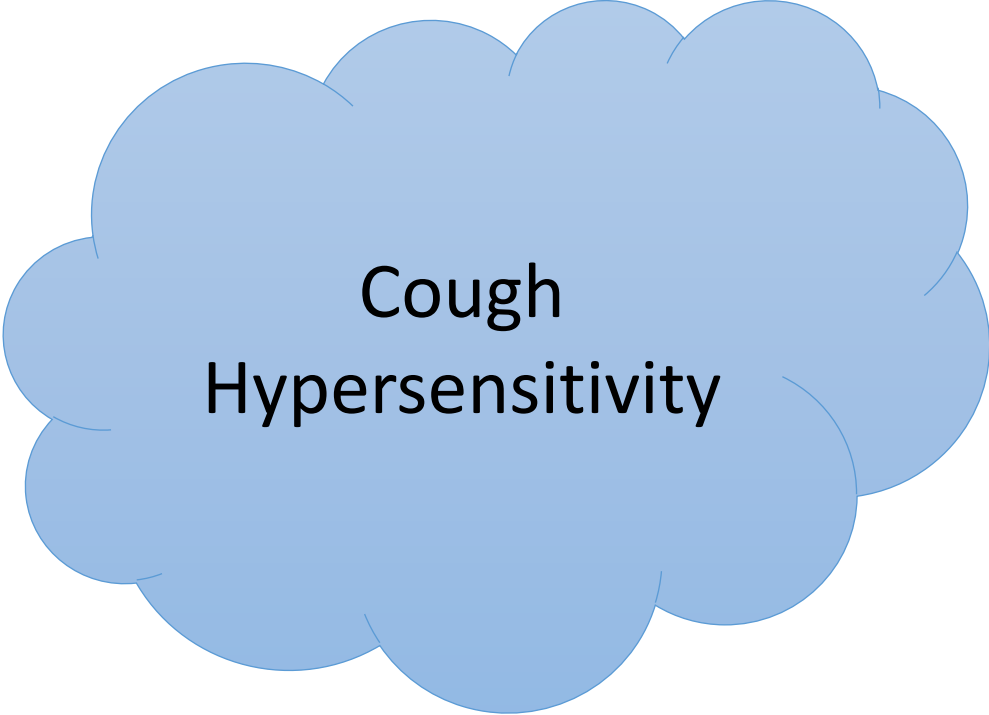
Diagnostic Criteria for RCC

- Diagnosis of exclusion
- **Cough lasting > 8 weeks**
- No identifiable cause (rule out asthma, GERD, upper airway cough syndrome)
- Normal or non-diagnostic findings
 - Normal chest x-ray
 - Normal pulmonary function tests
 - Laryngoscopy and bronchoscopy normal
- Failure to respond to therapy targeted at common causes



Cough Hypersensitivity

Central Role in Refractory Chronic Cough



Cough
Hypersensitivity

Common Features

- Exquisite sensitivity to inhaled irritants
- Innocuous stimuli trigger coughing
- Sensations of tickling in the throat
- Urge to cough



Chronic Cough >8 Weeks With Cough

Associated / underlying medical conditions are identified and treated per guidelines, but cough persists

Refractory
Chronic Cough (RCC)

Associated / underlying medical conditions are not identified by the investigator

Unexplained
Chronic Cough (UCC)

"In addition, there is a unique epidemiology with two-thirds of patients being female and the peak prevalence in the fifties and sixties." — *European Respiratory Society (ERS) Guidelines on the Diagnosis and Treatment of Chronic Cough in Adults*

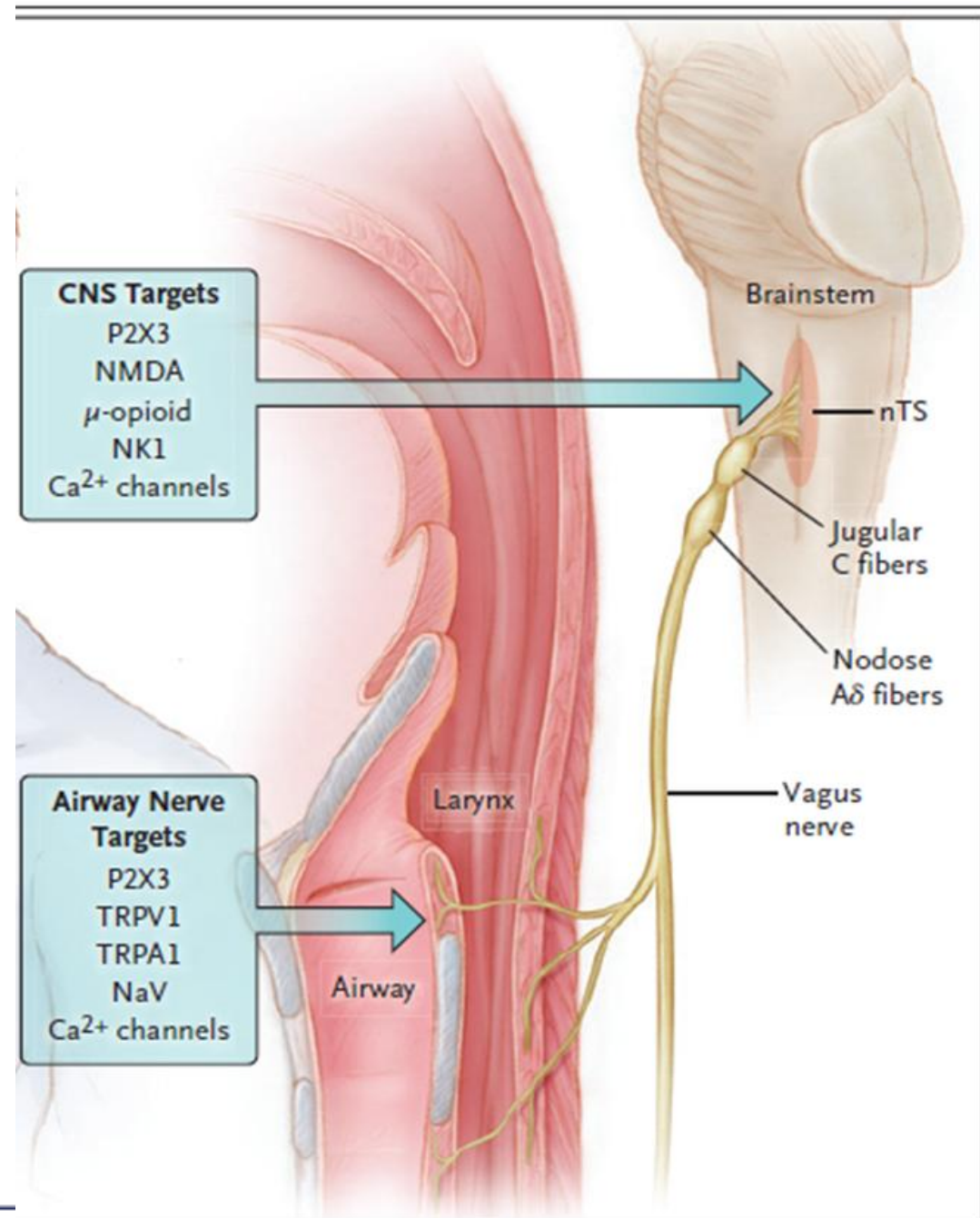


Peripheral & Central Neural Pathway Targets

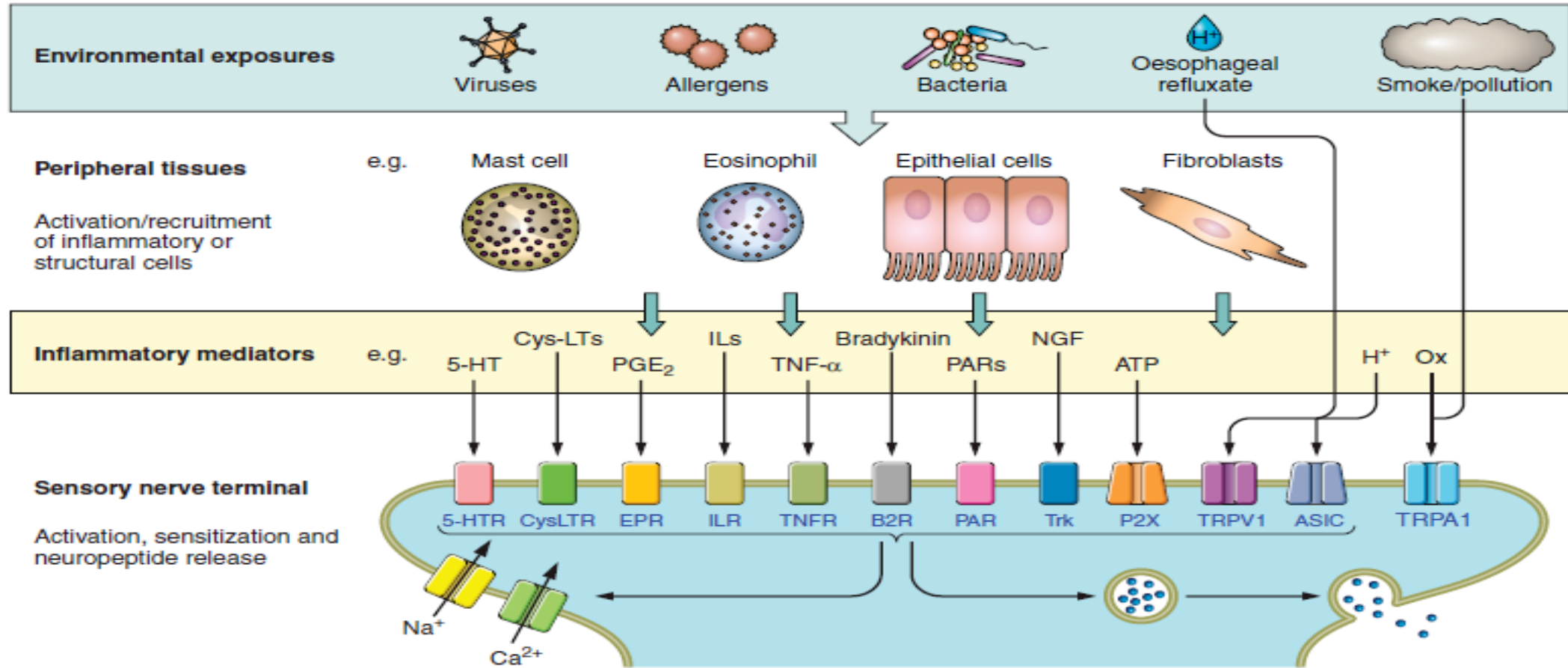
- Vagal afferents transmit stimuli from airways to the nTS and Para V in brain stem
- Neuronal signals to the somatosensory cortex via thalamus which causes throat irritation, causing the urge to cough
- Leads to cough via activation of spinal motor neurons

nTS= nucleus of solitary tract; aMCC=anterior mid-cingulate cortex; Para V=Paratrigeminal nucleus

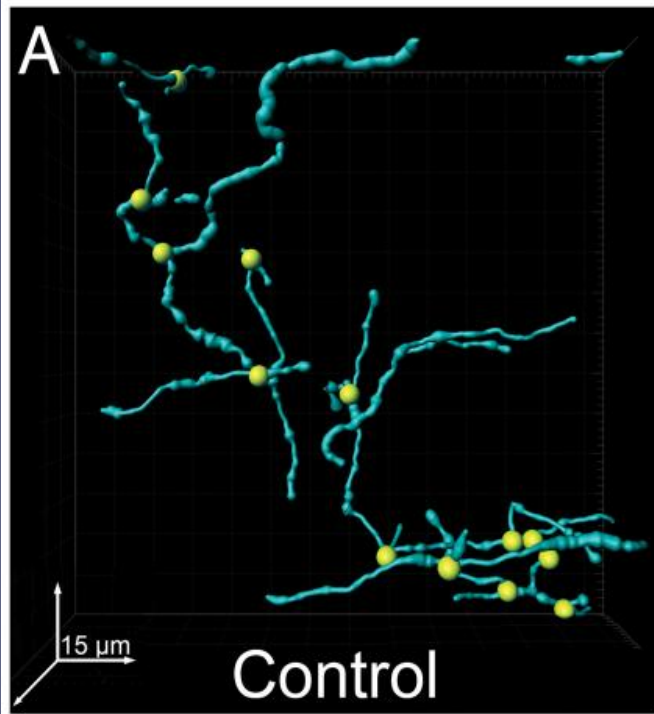
Smith JA, et al. *N Engl J Med.* 2016;375(16):1544-51.



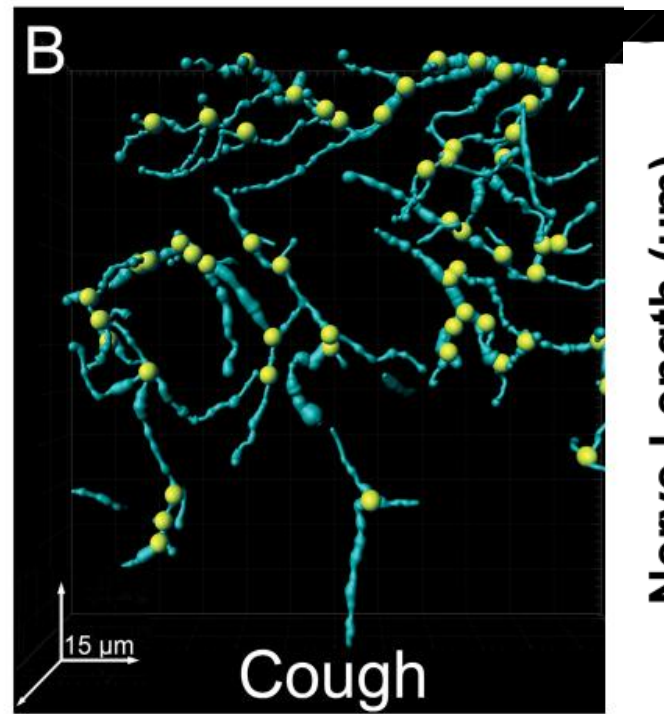
Mechanisms of Sensory Involvement in Respiratory Disease



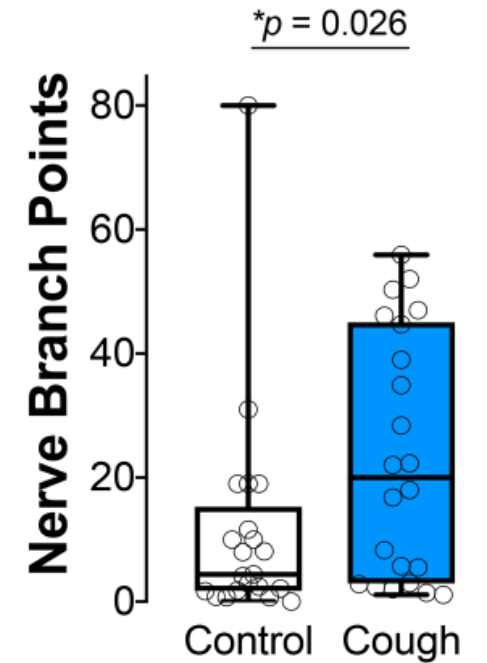
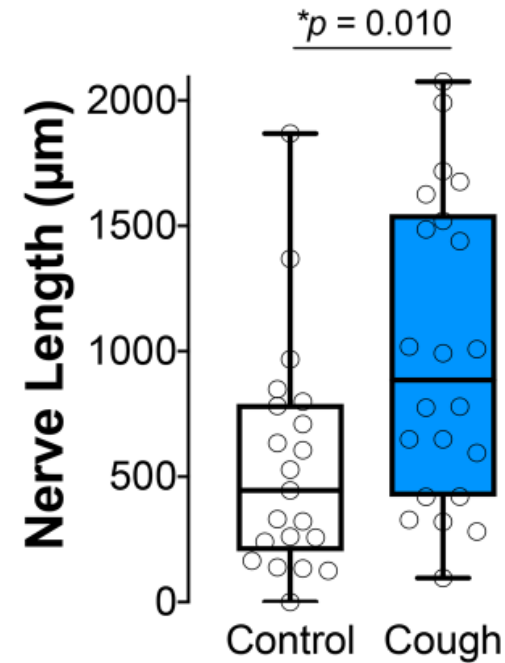
Airway Sensory Nerve Density



Healthy Volunteer



Chronic Cough



Goals of Treating Refractory Chronic Cough

After refractory chronic cough is diagnosed, the goal of treatment changes from identification/treatment of underlying causes to **suppressing the cough reflex**.^{1,2}

In the United States, no pharmacotherapies are approved for management of refractory chronic cough.

Guidelines recommend the following treatment strategies:

- Off-label pharmacotherapies^{1,2}
- Behavioral cough suppression therapy by a speech-language pathologist^{1,2}

Pharmacotherapies commonly used off-label in the US

Neuromodulators	<ul style="list-style-type: none">• Amitriptyline• Gabapentin• Pregabalin
Opioids	<ul style="list-style-type: none">• Morphine• Codeine• Hydrocodone

Sequential therapeutic trials may provide insight to the patient's most treatable traits.

Length of trial should be determined by the pharmacotherapy .

1) Dicipinigaitis, PV. *J Precis Respir Med.* 2023;6(1):10-13; 2) Morice AH, et al. *Eur Respir J.* 2020;55(1):1901136.



Neuromodulators for Refractory Chronic Cough: Gabapentin

Gabapentin improved cough-related QoL, severity, and frequency¹

- Improvements were not sustained after treatment discontinuation

AEs: included nausea, fatigue, and blurred vision

RCT comparing gabapentin (maximum tolerable daily dose of 1800 mg) or placebo in 62 patients with refractory chronic cough¹

Outcome	Gabapentin-placebo difference from baseline to treatment period* (95% CI)	P value
Mean LCQ score	1.80 (0.56 to 3.04)	.004
Mean cough severity VAS score, mm	-12.23 (-23.22 to -1.25)	.029
Cough frequency, coughs/h	-27.31 (-51.75 to -2.88)	.028

*8 weeks; LCQ=Leicester Cough Questionnaire



Neuromodulators for Refractory Chronic Cough: Amitriptyline & Pregabalin

Amitriptyline shown to improve cough in patients with vagal neuropathy.¹

- Tricyclic antidepressants with neuromodulator properties.
- Shown to reduce cough frequency and neural sensitivity in upper airway
- Dosing between 10-25 mg at bedtime to minimize SE

When combined with SPT, **pregabalin** shown to improve cough reduction greater than SPT alone.²

- Targets cough hypersensitivity via central neural pathways.
- SPT addresses behavioral and laryngeal control strategies
- Synergistic approach leads to greater cough reduction

SE=Side Effects; SPT = Speech Pathology Treatment

1. Jeyakumar A, et al. *Laryngoscope*. 2006;116(12):2108-2112; 2. Vertigan AE, et al. *Chest*. 2016;149(3):639-648.



Low-Dose Morphine for Refractory Chronic Cough

RCT comparing slow-release morphine (5 mg, escalated up to 10 mg twice daily) or placebo in 27 patients with refractory chronic cough

LCQ domain	Mean value for placebo at week 4	Mean value for morphine at week 4	Placebo vs. morphine 95% CI (P value)
Physical	4.8	5.3	-1.1 to -4.3 (<.04)
Psychological	4.6	5.1	-1.1 to -3.9 (<.04)
Social	4.2	5.1	-1.7 to -3.0 (<.05)

Results: Morphine improved cough-related QoL and cough frequency

AEs: constipation and drowsiness

Clinical Concern: Dependence remains a concern with opiate therapy



Non-Pharmacologic RCC Treatments

- Non-pharmacologic treatment goals: reduce cough frequency and severity
 - **Speech therapy**
 - » Control laryngeal function & reduce cough reflex sensitivity
 - » Breathing exercises & vocal hygiene
 - **Behavioral modifications**
 - » Cough trigger awareness, controlled breathing exercises, vocal rest
 - » Dietary adjustments (avoid acidic/spicy foods)
 - **Cognitive behavioral therapy (CBT) for cough suppression**
 - » Manage anxiety-driven triggers, distraction, relaxation
 - **Integrative approach**
 - » Multiple therapies and approaches
 - » Mindfulness & breathing exercises



Emerging RCC Pharmacological Treatments

- **P2X3 Receptor Antagonists**
 - Gefapixant (not approved in US)
 - Camlipixant (Phase 3)
- **Neurokinin Receptor Antagonists**
 - Orvepitant (Phase 2)
- **Sodium Channel Blockers**
 - Taplucainium (Phase 2b)
 - XEN-D0501 (Phase 2)
 - GSK2339345 (Phase 1)
- **NMDA Receptor Antagonists**
 - Ifenprodil (Phase 2)
 - Dextromethorphan/Quinidine (Phase 2)
- **TRPM8 Agonists**
 - AX-8 (Phase 2)
- **TRP Channel Modulators**
 - SB-705498 (Phase 2)
 - NAL-NL001 (Preclinical)
 - Mavatrep (Phase 1)
- **Opioid analgesic/Mixed agonist-antagonist**
 - Nalbuphine (Phase 2)
 - Agonist at κ -opioid receptors (kappa)
 - Antagonist at μ -opioid receptors (mu)



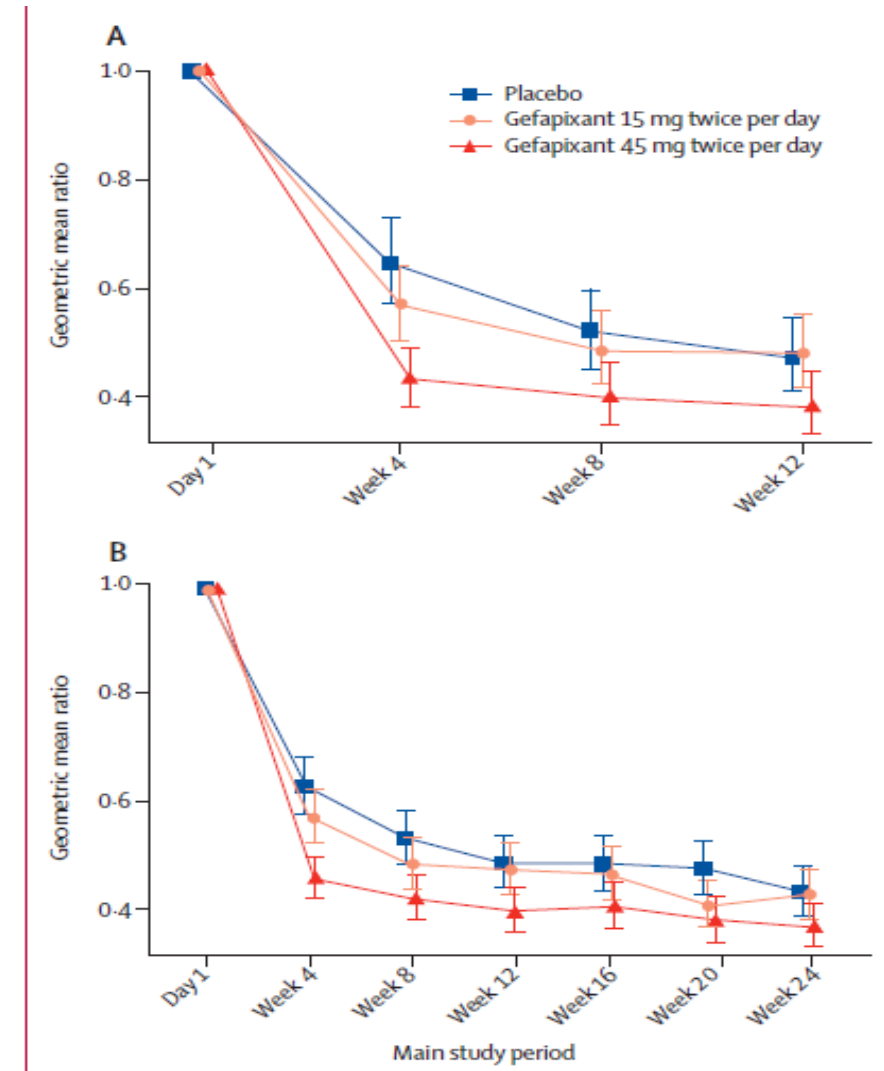
P2X3 Receptor Antagonists

Gefapixant

Mechanism of Action: P2X3 receptor antagonist that reduces cough hypersensitivity by inhibiting ATP-mediated signaling in airway sensory nerves

- **Status:** Phase 3 trials → FDA complete response letter (2023) questioned efficacy (vs. safety). Merck determining next steps
 - » Approved in Japan, Switzerland, and Europe
- **Clinical Trials:** COUGH-1 & COUGH-2^{1,2}
 - » **Key Result:** 45 mg BID reduced 24-hour cough frequency more than placebo
 - » **Side effects:** Taste alteration in 12.7%-68%
 - Nearly 1/3 of patients experienced taste-related adverse events (30% discontinued medication)^{1,2}

1) Dicipinigitis PV, et al. *Lung*. 2020;198(5):609-616; 2) McGarvey. *Lancet*. 2022;399:909



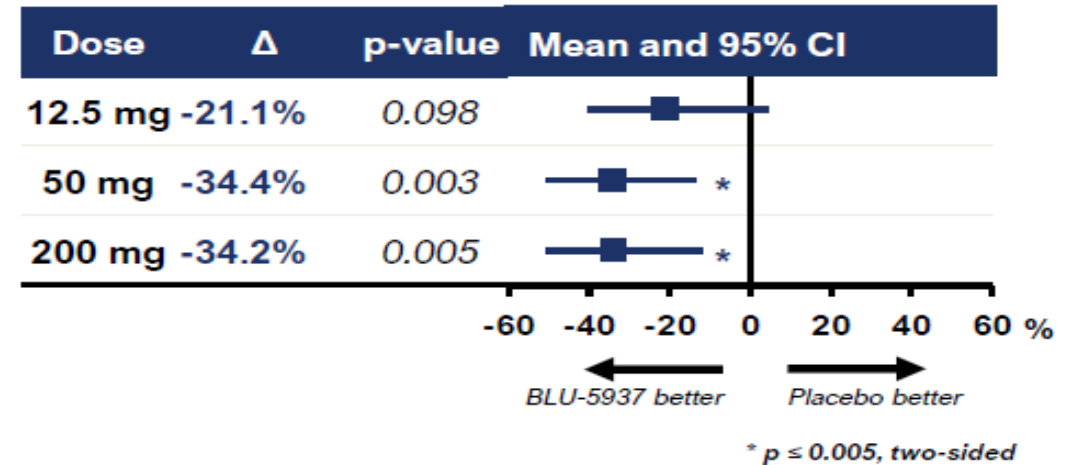
P2X3 Receptor Antagonists

Camlipixant

Mechanism of Action: Selective P2X3 receptor antagonist with improved tolerability over gefapixant

- **Status:** Phase 3
- **Phase 2b Clinical Trial:** SOOTHE Trial
- **Key Result:** 34% placebo-adjusted reduction in 24-hour cough frequency at 50 mg and 200 mg BID doses (included cough-related QOL with greater improvement in all arms vs. placebo)
- **Dose Response:** observed between 12.5 mg and 50 mg BID doses

Intent-to-treat analysis



- Low Taste-Related Adverse Events (< 6.5%)
 - No complete or partial loss of taste at any dose
 - No severe taste-disturbance adverse effects



P2X3 Receptor Antagonists

Camlipixant

Ongoing Phase 3 trials are evaluating the efficacy and safety of camlipixant (BLU-5937) in adults with refractory chronic cough (RCC)

A 52-Week Study of the Efficacy and Safety of Camlipixant in Adults With Refractory Chronic Cough (CALM-1)¹

A **Phase 3, 12-Week**, Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm Efficacy and Safety Study With Open-Label Extension of BLU-5937 in Adult Participants With Refractory Chronic Cough, Including Unexplained Chronic Cough (N = 825)

A 24-Week Study of the Efficacy and Safety of Camlipixant in Adults With Refractory Chronic Cough (CALM-2)²

A **Phase 3, 24-Week**, Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm Efficacy and Safety Study With Open-Label Extension of BLU-5937 in Adult Participants With Refractory Chronic Cough, Including Unexplained Chronic Cough (N = 825)

1) Smith JA, et al. *Am J Respir Crit Care Med.* 2025;211(4):A2533; 2) Smith JA, et al. *Am J Respir Crit Care Med.* 2025. Published online March 5, 2025. doi:10.1164/rccm.202409-1752OC



Neurokinin (NK) Receptor Antagonists

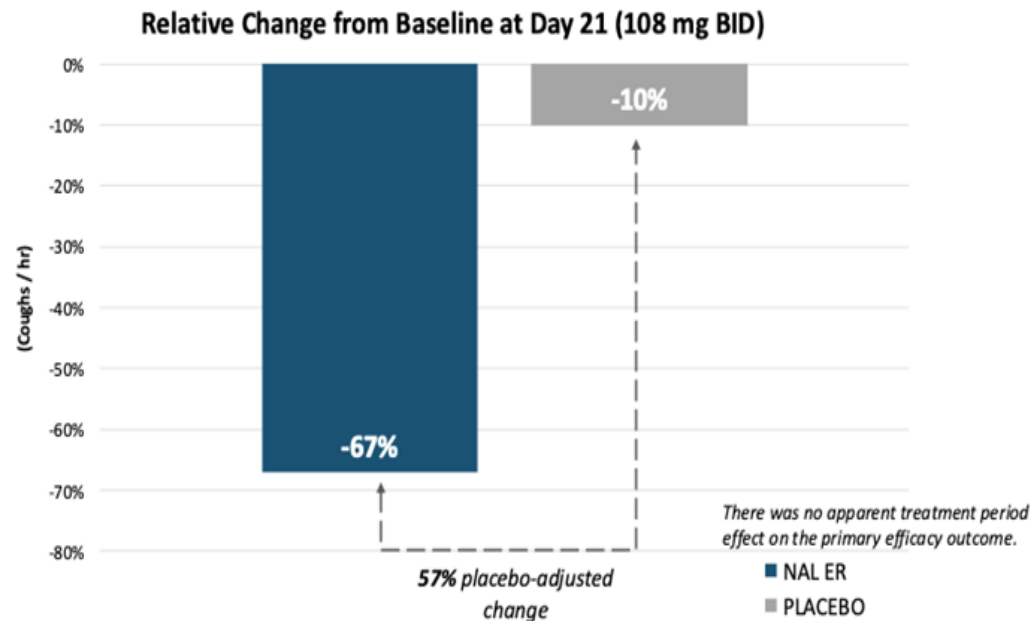
Orvepitant

- **Mechanism of Action:** NK-1 receptor antagonist that modulates neurogenic inflammation and central cough pathways to reduce hypersensitivity
 - **Status:** Phase 2 trials for RCC
 - **Clinical Trials:** VOLCANO-1 (Phase 2a) & VOLCANO-2 (Phase 2b)
 - » **Key Result:** 30 mg once daily x 4 weeks resulted in significant reduction in 24-hour cough count and improvements in QOL, patient-reported outcomes.



Opioid Analgesic/Mixed Agonist-Antagonist

Nalbuphine ER



- **Cross-over Trial Design:** Phase 2a RIVER trial
 - Double-blind, randomized, placebo-controlled, 2-period crossover study
 - 66 participants
- **Criteria:**
 - Diagnosed with RCC for at least 1 year, randomized to subgroups based on pre-treatment cough monitor results
 - 10-19 coughs/hour
 - ≥ 20 coughs/hour
- **Primary endpoint:**
 - Relative change from baseline in cough frequency (coughs/hour) versus placebo at day 21
- **AEs:**
 - somnolence, dizziness, headache, hypoaesthesia, lethargy, nephrolithiasis



Summary: Take-Home Points

- In adults, a chronic cough is defined as a cough lasting **more than 8 weeks**
- If a chronic cough persists despite appropriate treatment of all potential underlying causes, it is classified as “**refractory chronic cough**” (RCC)
- Currently, there are **no FDA-approved therapies for UCC or RCC**
- RCC can persist for many years and **significantly impacts quality of life**
- RCC is believed to be **associated with cough hypersensitivity syndrome**
- Advancing knowledge of the mechanisms underlying cough hypersensitivity syndrome is driving the development of targeted treatments, **such as P2X3 receptor antagonists**





Chronic cough in the adult population is defined as a cough for lasting greater than:



Which of the following best describes the mechanisms contributing to cough hypersensitivity and their role as treatment targets for refractory chronic cough?



Which research trend is most likely to improve management of refractory chronic cough (RCC)?

Thank You!

Questions/Comments

Complete the evaluation
By scanning the QR code

