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Review Article

# Chronic cough and cough hypersensitivity syndrome

*Tosse crônica e síndrome de hipersensibilidade à tosse*

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**ABSTRACT**

Chronic cough is a prevalent condition worldwide, affecting individuals across all age groups. It is a complex and difficult-to-treat disorder, as multiple pulmonary and extrapulmonary conditions can present with chronic cough, which in turn may occur without an identifiable cause or be resistant to therapies targeting the various associated conditions. Most patients with chronic cough exhibit cough reflex hypersensitivity – that is, they cough in response to relatively innocuous stimuli –, causing significant impairment in quality of life and psychological burden. In recent years, there has been a paradigm shift in the diagnosis of refractory chronic cough, recognizing it as a distinct condition resulting from cough reflex hypersensitivity rather than merely a symptom of underlying conditions. In this review, we provide an update on chronic cough, highlighting cough reflex hypersensitivity.

**Keywords:** Chronic cough, hypersensitivity, neurotransmitter receptors, reflex.

**RESUMO**

A tosse crônica é uma condição prevalente no mundo, em todas as faixas etárias. Trata-se de um distúrbio complexo e de difícil tratamento, pois diversas condições pulmonares e extrapulmonares podem se manifestar com tosse crônica, que, por sua vez, pode ocorrer sem uma causa identificável ou ser resistente a terapias destinadas a tratar as diversas condições associadas à tosse crônica. A maioria dos pacientes com tosse crônica apresenta hipersensibilidade ao reflexo da tosse, ou seja, apresenta tosse em resposta a estímulos relativamente inócuos, o que causa considerável comprometimento de qualidade de vida e impacto psicológico. Nos últimos anos, houve uma mudança de paradigma no diagnóstico de tosse crônica refratária, reconhecendo-a como uma condição distinta, resultado da hipersensibilidade ao reflexo da tosse ao invés de ser apenas um sintoma decorrente de condições subjacentes. Nesta revisão, temos uma atualização sobre tosse crônica, realçando a hipersensibilidade ao reflexo à tosse.

**Descritores:** Tosse crônica, hipersensibilidade, receptores de neurotransmissores, reflexo.

## Introduction

The cough reflex is a vital physiological mechanism for protecting the airways from chemical and mechanical irritants and preventing aspiration. Coughing preserves gas exchange function in the lungs by helping eliminate aspirated particulate matter and irritants that are inhaled or formed at mucosal inflammation sites.[1,2] The cough reflex is regulated by coordinated interaction between peripheral sensory nerves, which are distributed throughout the respiratory tract, and the cough center, which is located in the nucleus of the solitary tract in the brainstem.[1]

Coughing can also be a warning sign of pathological conditions, such as vomiting, rib fractures, urinary incontinence, syncope, muscle pain, fatigue, and depression. Quality of life is significantly impaired in patients with refractory or unexplained chronic cough,

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including negative effects to physical and psychological health. Recent studies have focused on discovering the mechanisms that regulate the peripheral and central processes involved in the cough reflex.[3-5]

This reflex mechanism is divided into 3 phases: (1) an inspiratory phase; (2) forced expiratory effort against a closed glottis; (3) and opening the glottis with rapid expiration, which generates a characteristic cough sound.[3]

The cough reflex involves afferent vagal nerve pathways, which are abundant throughout the upper and lower respiratory tract, including the larynx, trachea, carina, intrapulmonary bronchi, and lung parenchyma.[6] Afferent branches of the vagus nerve are also present in the esophagus, tympanic membrane, diaphragm, and pericardium.[7,8]

Inflammatory, mechanical, or chemical stimuli activate peripheral receptors in the sensory nerves of the airways: Aδ fibers (mechanoreceptors) and C fibers (chemoreceptors), which originate from the jugular or nodular ganglia. These stimuli are then transmitted through the vagus nerve to the paratrigeminal nucleus and the nucleus of the solitary tract in the medulla oblongata.[9] Central cough receptors send signals via efferent pathways in the vagus, phrenic, and spinal motor nerves to activate the diaphragm and expiratory muscles involved in coughing.[8]

## Epidemiology and classification of cough

Coughing is one of the most common symptoms in individuals who seek medical attention. Coughs are classified according to duration. *Acute cough* persists < 3 weeks, *subacute cough* persists 3-8 weeks, and *chronic cough* persists > 8 weeks.[10]

Although acute cough is usually the result of a viral infection of the upper respiratory tract, it can also have other etiologies, such as pneumonia or foreign body aspiration. Symptomatic upper respiratory tract infection occurs 2 to 5 times a year in adults and 7 to 10 times a year in school-aged children. However, only 40% to 50% of patients present with a cough. In the absence of an underlying comorbidity, acute cough is usually benign and self-limiting. Acute cough can also manifest exacerbation of a chronic disease, such as asthma or chronic obstructive pulmonary disease.[10]

Cough lasting between 3 and 8 weeks is called subacute cough. The most likely diagnoses are post-infectious cough or an exacerbation of asthma or chronic obstructive pulmonary disease. For subacute cough induced by viral infection, the proposed mechanism includes increased cough reflex sensitivity due to the infection.[11]

Chronic cough, defined as lasting > 8 weeks in adults, has a global prevalence of 4% to 10% and is frequently associated with pain, dizziness, urinary incontinence, and even loss of consciousness. As a result, chronic cough is associated with considerable psychological stress, social stigma, lower quality of life, and impaired activities of daily living and work productivity. Furthermore, due in part to the inefficacy of current antitussive treatment, people with coughs frequently undergo repeated medical consultations, involving expensive and extensive diagnostic tests, as well as unsuccessful therapeutic trials.[12,13]

### *Chronic cough*

Chronic cough affects approximately 40% of the world's population at some point in their lives.[14] At the end of the 20th century, an "anatomical diagnostic protocol" was proposed for investigating isolated persistent cough in the absence of an identified underlying pathology. Chronic cough has been considered merely a symptom of an underlying condition, such as asthma, gastroesophageal reflux disease (GERD), or rhinosinusitis, and treatment could be used empirically even without typical features of these diseases.[15]

Main causes of chronic cough are[16]:

- Upper airway cough syndrome
- GERD
- Medications: ACE inhibitors
- Asthma
- Cough variant asthma
- Non-asthmatic eosinophilic bronchitis
- Chronic bronchitis
- Bronchiectasis
- Tuberculosis
- Occupational exposure
- Interstitial lung diseases
- Bronchoaspiration/foreign body
- Smoking
- Cardiac causes
- Tumors
- Psychogenic disorders

### *Upper airway cough syndrome*[17]

Chronic rhinitis or rhinosinusitis has been shown to be an independent risk factor for chronic cough. However, the exact mechanisms of chronic cough in patients with rhinosinusitis are not fully understood. Initially, the pathogenesis of upper airway cough syndrome (UACS) was considered a consequence of post-nasal drip. However, studies have shown that only a small proportion of patients with post-nasal drip complained of chronic cough, and conversely, some patients with UACS did not present with post-nasal drip. Chronic cough related to UACS includes allergic rhinitis, non-allergic rhinitis, and chronic rhinosinusitis.[18]

In the general population, UACS is reported as the cause of chronic cough in 9% to 82% of cases. This wide variation is mainly due to the slow adaptation of the term to clinical practice and the difference in treatment patterns between different countries. There is relative agreement that, in non-smokers, UACS is considered the first or second most common cause of chronic cough worldwide. UACS is also frequently associated with other conditions that can cause chronic cough.[17]

It is postulated that the pathogenesis of UACS is secondary to factors such as post-nasal drip, chronic upper airway inflammation, and sensory nerve hypersensitivity. Upper airway secretions would signal a chemical, thermal, or mechanical response that could provoke the cough observed in UACS. Nerve signaling is predominantly mediated by unmyelinated C fibers. These C fibers are sensitive to a large number of chemical and inhaled mediators, including capsaicin. Capsaicin receptors are found in transient receptor potential vanilloid 1 (TRPV1), which are highly expressed in sensory afferent nerve fibers in the airways.[17]

### *Gastroesophageal reflux disease*[19,20]

GERD is a clinical condition caused by the chronic retrograde reflux of acidic stomach contents into the esophagus, resulting in uncomfortable symptoms, complications, or both. GERD is diagnosed based on clinical symptoms (heartburn, regurgitation, and non-cardiac chest pain) and empirical response to proton pump inhibitors.

Because studies have shown the limitations of non-objective diagnosis, diagnostic evaluation, such as upper gastrointestinal endoscopy, is recommended based on the clinical scenario, especially in patients with warning signs such as dysphagia.[21]

Chronic cough can be an extraesophageal manifestation of GERD.[19] The pathophysiology of GERD is multifactorial, and proposed mechanisms include hypotonia of the lower esophageal sphincter, hiatal hernia, and elevated intra-abdominal pressure. Three possible pathophysiological mechanisms contribute to the development of GERD-related chronic cough. The first is called "reflux theory," which includes acid reflux, microaspiration, and bronchial reflux. The second mechanism, "reflex theory," includes the esophagogastroduodenoscopy reflex, which is associated with increased sensitivity to the cough reflex and the development of neurogenic inflammation. The third proposed mechanism is esophageal dysmotility. The "reflex theory" proposes that stimulation of subesophageal mucosal receptors by reflux substances activates the cough center through the esophagus and causes the cough reflex.[22]

### *Medications: angiotensin-converting enzyme inhibitors*

Common side effects of ACE inhibitors include dry cough, hypotension, hyperkalemia, headache, dizziness, and renal failure. Their mechanism of action is based on the ACE blockade, which is responsible for converting angiotensin-I to angiotensin-II, as well as for the degradation of several hemodynamically active peptides, including bradykinin. Persistent dry cough is the most common adverse effect of ACE inhibitors, an effect probably related to increased bradykinin production. The prevalence of dry cough in patients using ACE inhibitors ranges from 10% to 35%. It can develop in the first week, the first month, or after several years after beginning the medication; it is dose-independent and is more frequent in women.[23-25]

### *Cough variant asthma and non-asthmatic eosinophilic bronchitis*

Both are considered bronchial inflammatory conditions that frequently manifest as chronic cough, with different diagnostic criteria and different responses to asthma therapy commonly used for diagnosis.[26]

### *Cough variant asthma*

Sometimes coughing can be the only symptom of asthma. Transient ischemic attack refers to asthma when coughing is the only or the predominant

symptom, without complaints such as wheezing or chest tightness. This diagnosis was first described in the late 1970s, when patients with bronchial hyperresponsiveness to methacholine experienced cough improvement after treatment with a short-acting β2-agonist, which was associated with 12% reversibility, indicating a direct relationship between airway caliber and cough. However, these criteria may no longer be valid, given that a study found that up to one-third of patients with cough variant asthma (CVA) have normal spirometry and no bronchodilator response. In such situations, the diagnosis can be established by demonstrating bronchial hyperresponsiveness to methacholine or mannitol.[26]

### *Non-asthmatic eosinophilic bronchitis*

First described in 1989, non-asthmatic eosinophilic bronchitis is characterized by chronic cough and airway eosinophilia without objective evidence of asthma, i.e., without reversibility and/or bronchial hyperresponsiveness. Bronchial eosinophilia should be investigated through induced sputum collection, bronchoalveolar lavage, and/or bronchial biopsy. The eosinophil count in patients with non-asthmatic eosinophilic bronchitis is > 2.5%. Another non-invasive test that could be performed would be the measurement of the fraction of exhaled nitric oxide (FeNO), but they are not routinely recommended. Non-asthmatic eosinophilic bronchitis does not respond to bronchodilators, and symptoms are typically responsive to inhaled corticosteroids.[26]

In most immunocompetent, non-smoking adults with normal chest X-ray results who do not have tuberculosis and are not using ACE inhibitors, the underlying cause of chronic cough is due to one or more of the following: (1) lower airway cough syndrome (asthma, cough-variant asthma, or non-asthmatic eosinophilic bronchitis); (2) upper airway cough syndrome; or (3) GERD.[27]

Although chronic cough can affect up to 10% of the general population, approximately 5% of these patients present with unexplained or refractory chronic cough despite extensive investigation and treatment of a diagnosed underlying disease.[28]

Individuals with chronic cough often report a persistent urge to cough and increased sensitivity to stimuli, such as ambient temperature changes and exposure to aerosols and perfumes. In some situations, the simple act of talking or singing can trigger coughing fits.[13]

Chronic cough is now considered indicative of nervous system dysregulation. Both central and peripheral nerve pathways regulate coughing and, although the mechanisms that drive the development of cough hypersensitivity are not fully understood, sensitization of these nerve pathways contributes to cough reflex hypersensitivity.[12,13]

## Transient receptor potential and purinergic receptors

The cough reflex can be triggered by various inflammatory or mechanical changes in the airways or other locations, such as the lower third of the esophagus. The sensory nerve receptors that respond to these stimuli are defined by their conductive properties (rapidly adapting receptors, slowly adapting receptors, or C-fiber receptors). Rapidly adapting receptors are stimulated by cigarette smoke, acidic and alkaline solutions, hypotonic and hypertonic saline solutions, mechanical stimulation, pulmonary congestion, atelectasis, bronchoconstriction, and reduced pulmonary compliance — all of which can cause coughing. C-fiber receptors, a type of nociceptor, are highly sensitive to chemicals such as bradykinin, capsaicin (a vanilloid extract from peppers), and hydrogen ions (acidic pH).[29]

Chemoreceptor neurons (or nociceptors) send signals from the periphery, through afferent fibers, to the cough center in the central nervous system, mediating transmission between the central and peripheral nervous systems. These neurons express a wide variety of receptors and ion channels that are distributed along the peripheral fibers. The most important family of ion channels that detects and transmits noxious stimuli is the transient receptor potential (TRP) family. This family consists of proteins that are conserved, non-selective, and permeable calcium channels. In general, TRP channels act as molecular sensors of multiple stimuli, ranging from changes in pH, chemical agents, temperature, and osmolarity.[30]

The TRP superfamily consists of 28 members, which are subdivided into 6 subfamilies according to their sequence homology: TRPC (canonical, 7 members), TRPV (vanilloid, 6 members), TRPM (melastatin, 8 members), TRPA (ankyrin, 1 member), TRPP (polycystin, 3 members), and TRPML (mucolipin, 3 members). TRP proteins share a common structure consisting of 6 transmembrane domains. TRP channels consist of 4 pore-forming

TRP protein subunits that can assemble as homo- or heterotetramers. TRP channels modulate cellular function by opening voltage-gated ion channels, which leads to intracellular events such as neuronal depolarization and smooth muscle contraction.[29]

TRPV1, the transient receptor pontential vanilloid 1, is present throughout the respiratory tract, from the nose to the bronchi and vascular wall. TRPV1 is activated by exogenous chemical irritants (e.g., ethanol), elevated temperatures (> 43 °C), low extracellular pH, and some endogenous mediators. The main exogenous ligand is capsaicin, the active ingredient in chili peppers. Pro-inflammatory agents or physical stimuli can reduce the activation threshold for TRPV1 agonists. Under normal conditions, only temperatures > 43 °C activate TRPV1, but this threshold can decrease to 35–37 °C after acidification of the medium. This phenomenon is very important in inflammation because it drastically reduces the pH (to 6.4) and rapidly activates TRPV1. TRPV1 sensitization facilitates channel activation by low-intensity stimuli, and the process occurs after inflammation or tissue damage, which is triggered by various pro-inflammatory substances such as substance P, bradykinin, and prostaglandins. TRPV1 mediates signaling initiated by GPCR receptors, including bradykinin and prostaglandin E2.[29,30]

TRP subfamily ankyrin member 1 (TRPA1), an ion channel that functions as a sensor of cold temperatures, can be activated by temperatures below 17 °C. Isothiocyanates, components found in natural products such as wasabi, mustard, and horseradish, can also activate TRPA1 channels.[30]

TRP subfamily melastatin member 8 (TRPM8) is expressed throughout lung tissue and bronchial epithelial cells in humans. TRPM8, primarily recognized as a thermoregulator, is activated by low temperatures (between 15 and 28 °C), but it can also be activated by exogenous chemicals that produce a cooling sensation, such as menthol and eucalyptol.[29] Table 1 provides a summary of the main TRPs.

Purinergic receptors are another family of receptors involved in various cellular activities, such as coughing. They are activated by purine nucleotides, such as adenosine 5'-triphosphate (ATP) and adenosine (or adenine), as molecules that signal cellular stimulation. One such receptor is P2, a subtype of purine receptor. It includes ligand-gated ion channels, known as P2X, and G protein-coupled receptors, known as P2Y.[31,32]

P2X receptors are homotrimers or heterotrimers, and their activation induces the influx of extracellular cationic ions, such as sodium and calcium, into the cell, thereby depolarizing the cell membrane. P2X receptors are expressed throughout the body and are associated with a variety of physiological and pathological processes.[31]

There are 7 types of P2X receptor (P2X1-7), and the expression of P2X3 receptors in afferent neurons of the vagus nerve has become extremely important for understanding the mechanisms involved in chronic cough. Aberrant activation of these receptors leads to hypersensitivity of these nerve endings, which is one of the characteristics of "cough hypersensitivity syndrome" (which will be described below).[31]

ATP is the primary ligand of the P2X3 receptor. ATP, which is released from cells in response to damage by exogenous and endogenous factors, subsequently participates in airway extracellular fluid, acting as an alarmin, i.e., producing further inflammation. The underlying cause of ATP release is still a matter of debate; it is likely due to inflammatory stimuli, air pollution, tobacco smoke, or gastroesophageal reflux.[32]

## Cough hypersensitivity syndrome

At the end of the 20th century, an “anatomical diagnostic protocol” was proposed to investigate the causes of isolated persistent cough in the absence of an easily identifiable pulmonary pathology, in which symptoms were categorized to guide diagnostic investigation and direct targeted therapy. The etiology of chronic cough has changed significantly in recent years; previously it was considered merely a symptom of underlying conditions such as asthma, gastroesophageal reflux, or rhinosinusitis, often treated empirically in the absence of typical characteristics of these diseases. Currently, refractory chronic cough (persistent cough despite optimal treatment of conditions associated with chronic cough) or cough with an unidentified underlying cause is considered a unique entity and is essentially a disease in itself (Figure 1).[9,15,33]

Refractory chronic cough could be the diagnosis in about 40% of patients with chronic cough who are referred to specialists. Diseases previously supposed to be the main causes of chronic cough, such as asthma, are now considered treatable factors, so their causative contribution is overestimated in many patients.[15]

**Table 1**
Key transient receptor potentials TRPs involved in chronic cough

| Receptor | | Subfamily | Temperature activation | Stimuli |
|---|---|---|---|---|
| Transient potential receptor (TRP) family | TRPV1 | Vanilloid | > 43 °C | Capsaicin and pH reduction |
| | TRPV4 | Vanilloid | > 25 °C | Pro-inflammatory substances such as PGE2, histamine, and serotonin |
| | TRPM8 | Melastatin | < 25 °C | Menthol, eucalyptol, and cold temperature |
| | TRPA1 | Ankyrin | < 17 °C | Garlic, menthol, acrolein, isothiocyanates (mustard, wasabi, and horseradish) |

The 2021 European Respiratory Society guidelines on chronic cough adopted a different paradigm. Most patients with chronic cough present with cough reflex hypersensitivity, which is characterized by laryngeal paresthesia and an increased response to tussigenic stimuli or innocuous stimuli that would not trigger a cough in a healthy individual. Hence, chronic cough was considered "the disease." This hypothesis arose from the observation that most patients reported cough triggered by low levels of thermal, chemical, or mechanical exposure, including cold air, perfumes, odors, and aerosols. These external stimuli suggest hypersensitivity to other innocuous stimuli. Cough reflex hypersensitivity was considered the underlying pathophysiological mechanism of chronic cough, which has been called cough hypersensitivity syndrome.[33]

The proposed mechanisms for cough reflex hypersensitivity include airway hyperinnervation, increased central cough activation, and reduced central cough suppression. Investigations into cough reflex hypersensitivity should exclude treatable traits, i.e., secondary factors that worsen chronic cough. If possible, a cough provocation test should be performed, for example, with capsaicin or ATP. Non-pharmacological interventions for cough reflex hypersensitivity include avoiding triggers and managing treatable factors. Speech therapy and physical therapy have also proven effective. Drug treatment targets abnormal pathways of the cough reflex, both peripheral and central. The neuromodulators amitriptyline, gabapentin, and pregabalin have been tested with moderate success, although side effects are common.[15]

New antitussives that target peripheral receptors, such as P2X3, effectively reduce cough frequency and appear to be safe. Gefapixant was the first P2X3 receptor antagonist to successfully complete phase 3 trials and, in late 2023, was approved for use in the European Union, Switzerland, and Japan. Drug efficacy is consistent across all ages, sexes, and cough frequency and severity. Although antagonism of heterotrimeric P2X2/3 receptors also results in dysgeusia, the side effects of gefapixant are mostly mild, reversible upon discontinuation, and generally tolerable, resulting in 22.1% treatment discontinuation vs 5.7% with placebo at 52 weeks in clinical trials. Other antagonists, currently in phase 3 trials, are more selective for the P2X3 receptor and are associated with less dysgeusia.[15] Eliapixant, filapixant, and camlipixant are currently being tested as more selective P2X3 receptor antagonists.[28]

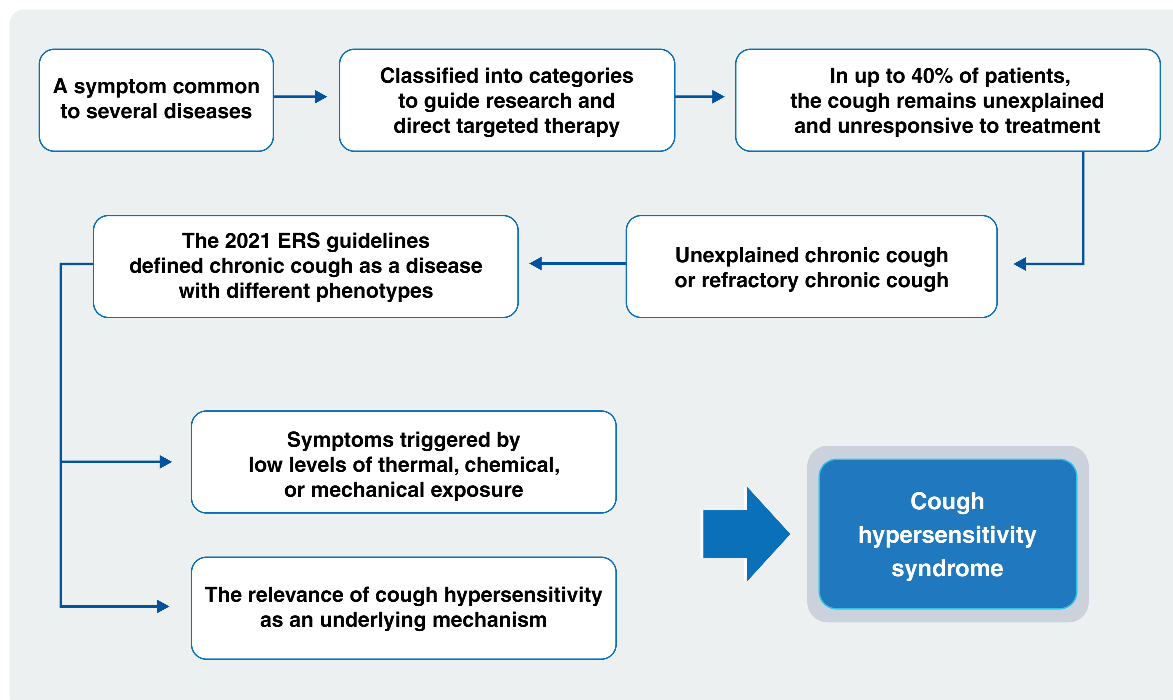


**Figure 1**
Paradigm shift in chronic cough[9,33]
ERS: European Respiratory Society.

## Neuromodulators

Although most patients with refractory chronic cough benefit from neuromodulators, tachyphylaxis and dependence can occur, and patients should be monitored for these complications.[34]

### *Low-dose morphine sulfate*

Studies using 5 mg and 10 mg of slow-release morphine sulfate have found that approximately 60% of patients with refractory chronic cough achieved good clinical response. However, side effects were frequent, with 40% experiencing constipation. Morphine is primarily an opioid receptor agonist and acts on central inhibitory cough pathways. The main concern regarding the use of low-dose morphine has been the potential for dependence and abuse. Some countries do not recommend it for chronic cough.[34]

### *Amitriptyline*

Amitriptyline is a tricyclic antidepressant and serotonin reuptake inhibitor that can be an effective and well-tolerated as short- and long-term treatment for refractory chronic cough in adults. Amitriptyline reduces the frequency and severity of cough and improves quality of life in patients with refractory chronic cough. Dose reduction and restarting are often necessary. Larger studies and randomized clinical trials are needed to better understand the outcomes of amitriptyline for idiopathic cough.[35,36]

### *Gabapentin*

A lipophilic structural analog of the neurotransmitter gamma-aminobutyric acid, gabapentin is a calcium channel modulator that acts on both central and peripheral cough reflex nerve pathways. It can also

modulate TRP channels, NMDA receptors, protein kinase C, and inflammatory cytokines, in addition to reducing TNF-α and IL-6 levels in the spinal cord of rats. It also has a dose-dependent effect. Gabapentin can reduce the peripheral sensitivity of the cough reflex by modulating peripheral TRP channels and inflammatory factors at cough-related sites.[28,37]

Gabapentin efficacy for refractory chronic cough has been investigated in randomized controlled trials. Quality of life improved in patients who received gabapentin, although its action on central receptors is associated with side effects, including sedation and unsteadiness. Serious adverse events described in the literature include rhabdomyolysis and acute renal failure in patients with diabetes. It also presents the potential for dependence.[28,35]

### *Pregabalin*

Pregabalin and gabapentin have similar structures. Pregabalin acts on calcium channels in the central nervous system, reducing the release of neurotransmitters such as glutamate, norepinephrine, and substance P. Although studies have found improved laryngeal hypersensitivity scores, the side effects are frequent and include blurred vision, cognitive changes, dizziness, and weight gain.[28,35]

### *Baclofen*

A gamma-aminobutyric acid receptor agonist, baclofen inhibits the release of substance P and interacts with serotonin, dopamine, and other neurotransmitters. Baclofen inhibits capsaicin-induced cough, and research suggests it is quite beneficial for refractory GERD and GERD-associated chronic cough. The vasovagal reflex relaxes the lower esophageal sphincter and predisposes individuals to acid reflux. In some clinical trials, baclofen had a significant effect on transient lower esophageal sphincter relaxation. Central nervous system side effects can include dizziness, drowsiness, asthenia, and nausea. These effects are dose-dependent and are related to its binding to presynaptic gamma-aminobutyric acid receptors in the brainstem and other parts of the central nervous system while simultaneously reducing the release of excitatory neurotransmitters.[38,39]

## Conclusions

Chronic cough is rapidly becoming recognized as a unique entity that may or may not be associated with other comorbidities such as asthma, rhinosinusitis, and/or GERD. Greater understanding of cough receptors and the cough reflex has led to a new paradigm for the diagnosis, investigation, and treatment of chronic cough. Safe and effective therapies are being developed, primarily targeting peripheral cough receptors, where hypersensitivity to the cough reflex likely originates.

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