The Role of Gefapixant in the Management of Chronic Cough

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Chronic cough affects about 10% of the population, and there is a paucity of scientifically approved therapeutic choices. The global burden of chronic cough is underestimated because a significant number of patients do not seek help, yet it has an impact on health-related quality of life and healthcare resource use. In this review, we have defined chronic cough, described the pathophysiology of cough, and critically analysed various therapeutic options, with a particular focus on the first-in-class P2X3 antagonist, gefapixant. The efficacy of gefatpixant is proven in various stages of development, as shown in major trials such as the COUGH-1 (NCT03449134) and COUGH-2 (NCT03449147) studies. The recommended dose for chronic cough is 45 mg twice daily; higher doses have shown side effects, including taste disturbance. Prospects in the management of chronic cough promise various therapeutic options, including newer P2X3 antagonists and other specific agents modulating aspects of the cough reflex pathway.

Keywords

P2X3 receptor antagonists, chronic cough, gefapixant, quality of life, drug treatment, clinical trial

Acknowledgements: Thank you to the University Hospitals Birmingham library services, in particular Phil O'Reilly, for conducting literature searches informing this article. Evidence search: Chronic Cough: Pathology, mechanism and treatment options. Phil O'Reilly. (13th August 2021). Birmingham, UK: University Hospitals Birmingham (UHB) Library and Knowledge Service.

Disclosures: Alice M Turner has a grant undergoing contracting via her institution with MSD. Rajarajan Anandavelu has no financial or non-financial relationships or activities to declare in relation to this article.

Review process: Double-blind peer review.

Compliance with ethics: This study involves a review of the literature and did not involve any studies with human or animal subjects performed by either of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analysed during the writing of this article.

Authorship: The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Received: 1 November 2021

Accepted: 17 March 2022

Published online: 6 July 2022

Citation: *touchREVIEWS in Respiratory & Pulmonary Diseases.* 2022;7(1):15–20

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Support: No funding was received in the publication of this article.

With the advent of newer drugs targeting the biochemical pathways that lead to cough, it is increasingly important to understand the definition, pathogenesis and management of this symptom. Several specialist bodies also recognize the need for guidance in this area, and the American College of Chest Physicians (ACCP) and European Respiratory Society (ERS) have both published on the topic.[1,2] This article briefly reviews important concepts in cough, before discussing the role of newer agents in managing patients' symptoms, with a particular focus on gefapixant.

Cough is defined as an expulsive motor act characterized by three phases:

- an inspiratory effort (inspiratory phase)
- a forced expiratory effort against a closed glottis (compressive phase)
- an opening of the glottis and rapid expiratory airflow (expulsive phase).[3]

Chronic cough was previously referred to as cough lasting more than 3 months, based on the Medical Research Council definition of chronic bronchitis;[4] however, the new definition suggests that a cough lasting more than 8 weeks constitutes a chronic cough.[5] Chronic cough can be present even after extensive investigations and treatment. It is referred to as refractory chronic cough (RCC) when the cough persists after the trial of various treatments, or unexplained chronic cough (UCC) when no clear aetiology has been identified to explain the symptom.[6] The global prevalence of chronic cough is above 10% in Europe, America and Oceania (12.7%, 11.0% and 18.1%).[7] The most common age of presentation is in the sixth decade, and it is more common in women.[2]

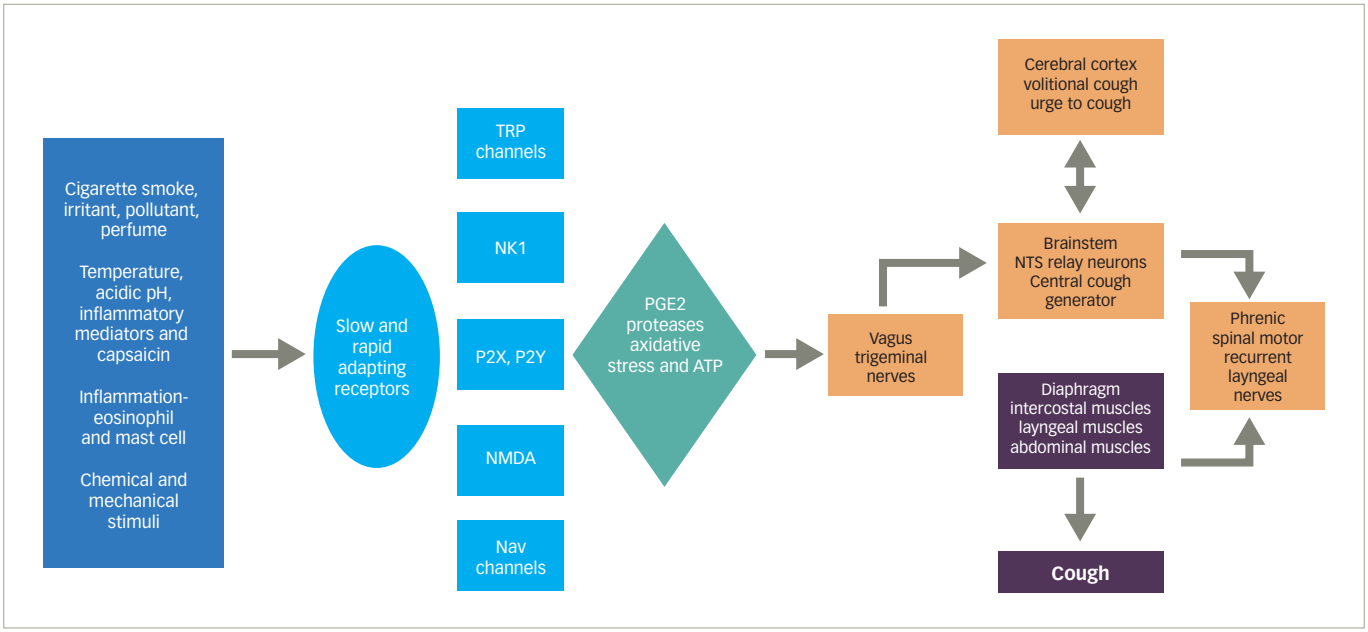
Cough affects several health-related quality-of-life (HRQoL) symptoms, such as stress urinary incontinence (particularly, but not exclusively, in women), interference with speech, cough syncope and mental health issues.[8] Along with the cough itself, these symptoms seem to be important reasons for patient attendance to hospital, often at specialist outpatient clinics.[2] Therefore, patients should be asked about all of the symptoms mentioned above during a consultation. The HRQoL can be formally assessed and quantified with tools such as the Leicester Cough Questionnaire (LCQ) or the Cough-specific Quality of Life Questionnaire;[9,10] however, these tools are rarely used outside tertiary services for RCC and research.

Pathogenesis of cough

The trigger for the cough reflex includes inflammatory or mechanical changes due to inhalational, mechanical and chemical irritants. The changes activate various receptors, such as rapidly adapting receptors (RARs), slowly adapting receptors (SARs) and C fibres, which are located in the larynx, the carina and the proximal airways.[11]

The key receptor is the mechanically gated sodium ion channel, which can sense acid stimulation. The next is the transient receptor potential vanilloid-1 (TRPV-1) channel, which senses capsaicin. These are the channels for both RARs and C fibres. Activating stimuli for these channels include heat,

Figure 1: Neural pathway for cough reflex



Nav = voltage-gated sodium channels; NK = neurokinin; NMDA = N-methyl-d-aspartate; NTS = Nucleus tractus solitarius; PGE2 = prostaglandin E2; TRP = transient receptor potential.

acid, bradykinin, arachidonic acid derivatives and adenosine triphosphate. Prostaglandin E2 and F2 alpha and bradykinin exert a stimulating effect on the channels, thus leading to cough. In addition, SARs found in the airway smooth muscle are stimulated by histamine and leukotriene D4, which are released from the mast cells and the eosinophils; furthermore, they relay the afferent signals responsible for cough and, over time, become sensitive at low-level stimuli and contribute to the hypersensitivity of the reflex. The afferent fibre signals from the airways are relayed through the vagus nerve to the cough centre in the nucleus tractus solitarius, and from there to the cerebral cortex. The efferent fibre signal goes through the spinal motor nerves and the phrenic and recurrent laryngeal nerves to the diaphragm, intercostal, laryngeal, and abdominal muscles, causing the patient to cough. It is also interesting to note the connection to the cerebral cortex, as that aids the voluntary control of cough reflex.[11] This process is summarized in *Figure 1*.

Common causes of chronic cough

Patients with chronic cough often have various underlying causes for their symptoms. There can be a combination of aetiologies for the same symptom. Therefore, addressing them accordingly can help resolve the cough and avoid unnecessary treatment.

Asthmatic cough and eosinophilic bronchitis

Bronchial asthma can present as chronic cough.[2] Diagnosis of cough-variant asthma requires the demonstration of a variable airflow obstruction or a positive test for bronchial hyperresponsiveness, such as methacholine challenge, as with any form of asthma.[2] Adults presenting with chronic cough should be assessed for eosinophilic inflammation, which can usually be done by induced sputum or fractional excretion of nitric oxide (FeNO).[2] Chronic cough is rarely assessed by bronchoscopy. It remains to be elucidated whether blood eosinophil count can be used as a surrogate marker in non-asthmatic bronchitis.[2] Patients with eosinophilic bronchitis can be distinguished from patients with asthma as they do not have bronchoconstriction or hyperresponsiveness.[12] Hence, tests for sputum eosinophilia are an important adjunct to classical asthma tests. Management focuses on strategies that treat asthma and eosinophilic bronchitis, such as inhaled corticosteroids, antileukotrienes and bronchodilators.

Reflux cough

Oesophagopharyngeal or gastro-oesophageal reflux has been attributed to causing chronic cough. The review by Kahrilas et al. found only a modest therapeutic benefit for acid-suppressive therapy, even in patients with acid reflux.[13] Patients with chronic cough have also been found to have oesophageal dysmotility, which may contribute to the symptom.[14] The dysmotility can be formally assessed by formal oesophageal manometry studies and is more sensitive than barium swallow. As per the ACCP guidelines, antireflux surgery should be considered in patients with acid exposure detected by pH manometry and refractory to medical therapy.[1]

Postnasal drip/upper airways cough syndrome

Postnasal drip, rhinitis and rhinosinusitis are collectively grouped under the term upper airway cough syndrome as per ACCP guidelines.[1] Upper airway cough syndrome includes symptoms secondary to these conditions, alongside laryngeal symptoms. Chronic cough occurs as a result of the sensory neural pathways described previously in this anatomical region. There is a role for first-generation antihistamines as a therapeutic option for chronic cough secondary to rhinitis, although there is no randomized trial supporting this.[15]

Iatrogenic cough

Medication side effects also account for chronic cough, especially drugs such as angiotensin-converting enzyme (ACE) inhibitors, bisphosphonates, calcium channel blockers and prostanoid eye drops.[2] Cough secondary to ACE inhibitors are noted in about 15% of patients taking them.[16] Stopping any such medications is therefore important in the initial phase of assessing and managing RCC.

Chronic cough assessment in clinic

As per the ERS guidelines, the initial assessment consists of patient history, clinical examination, and blood and radiological investigations.[2]

Table 1: Plausible options for chronic cough

Drug classification	Drug	Supporting guidance/evidence reference
Non-prescription products	Dextromethorphan, guaifenesin	1,2
Antihistamines	Diphenhydramine	2
Macrolides	Azithromycin	2
Opiates	Codeine and morphine	1, 2, 17
Neuromodulator agents	Gabapentin, pregabalin, tricyclic antidepressants	NCT04256733 (18), NCT02482818 (19) (2,20)
Novel agents		
• TRPV1 antagonists	XEN-D0501	21
• P2X3 antagonists	Gefapixant	22–26
	BLU-5937	NCT04678206 (27)
	Sivopixant	NCT04110054 (28)
	Eliapixant	NCT03310645 (29)
• NK1 receptor antagonist	Orvepitant	VOLCANO 1 & VOLCANO 2 (30)

NK = neurokinin; TRPV1 = transient receptor potential vanilloid.

The patient history should focus on the duration, trigger factors, risk factors and family history. Underlying causes such as malignancy, foreign body inhalation, and drugs such as ACE inhibitors should be excluded. Cough severity, cough frequency, and the patient's perception of cough and its impact on patient quality of life should also be included in the assessment.[2]

Examination should include the throat, ears and cardiorespiratory system. Chest X-ray is the first line of investigation; if normal, additional investigations should be considered to evaluate other common causes. Additional investigations include: lung function test, including reversibility and FeNO, to assess for airway inflammation and bronchitis; induced sputum analysis for eosinophil count; sputum culture and acid-fast bacillus tests to identify infections; methacholine challenge to test lung reactivity; chest computed tomography (CT) if there is any abnormality on chest X-ray, and bronchoscopy depending on CT findings; laryngoscopy to rule out inducible laryngeal obstruction; rhinoscopy to check for nasal polyps and clearing of mucus from the sinus; and sinus CT, which would help diagnose sinusitis. Oesophageal pH monitoring and manometry are indicated in patients with history of peptic symptoms. If the chest X-ray is abnormal, investigations should be based on the abnormality detected.[2]

The ACCP guidance, which is similar to the ERS guidelines, also suggests checking for red flag signs such as haemoptysis, a change in cough in patients over the age of 45 years, prominent dyspnoea at rest or night, hoarseness, systemic symptoms (e.g. fever, weight loss, peripheral oedema with weight gain, trouble swallowing when eating or drinking, vomiting, recurrent pneumonia), and abnormal respiratory examination or abnormal chest radiograph coinciding with duration of cough.[1]

Therapeutic choices for chronic cough

There are various options for the treatment of chronic cough, all of which require regular reviews to assess the treatment response. The treatment should target the likely cause of the chronic cough. For example, the patient group with symptoms of acid reflux disease would benefit modestly from protein pump inhibitors, as supported by evidence from a systematic review.[13] Similarly, empirical treatment in the form of inhalers for cough-variant asthma or first-generation antihistamine along with a decongestant for patients with upper airway cough syndrome would be useful methods for treating the underlying aetiologies. This would also be diagnostic as per the ACCP criteria. In addition, the empirical treatment is likely to resolve cough in a significant percentage of patients.[1]

Cough is not usually refractory or unexplained after a thorough diagnostic evaluation with carefully assessed empirical trials. However, when no cause is found or the symptom is not responsive to therapy targeting the likely underlying cause, plausible options trialled are summarized in *Table 1*.[1,2,17–30]

Non-pharmacological interventions

Cough suppression techniques and breathing exercises can increase abdominal excursion, relax the neck, throat and shoulders, and decrease laryngeal muscle tone. Vocal hygiene and hydration advice can also have an impact on chronic cough. Breathing training, in particular, has been used as an effective intervention to support patients with chronic cough.[31] A systematic review by Chamberlain et al. has shown that non-pharmacological interventions can improve the impact of cough-related quality of life and reduce cough frequency, but there are limited comparative studies to suggest the ideal effective components or the most effective interventional techniques for reducing chronic cough.[32] It is recommended to refer patients to a speech and language therapist, who can ensure patients are taught non-pharmacological intervention techniques.[2]

Non-prescription products

Although non-prescription products (e.g. dextromethorphan and guaifenesin) are available, none are effective, as noted in randomized controlled trials.[33]

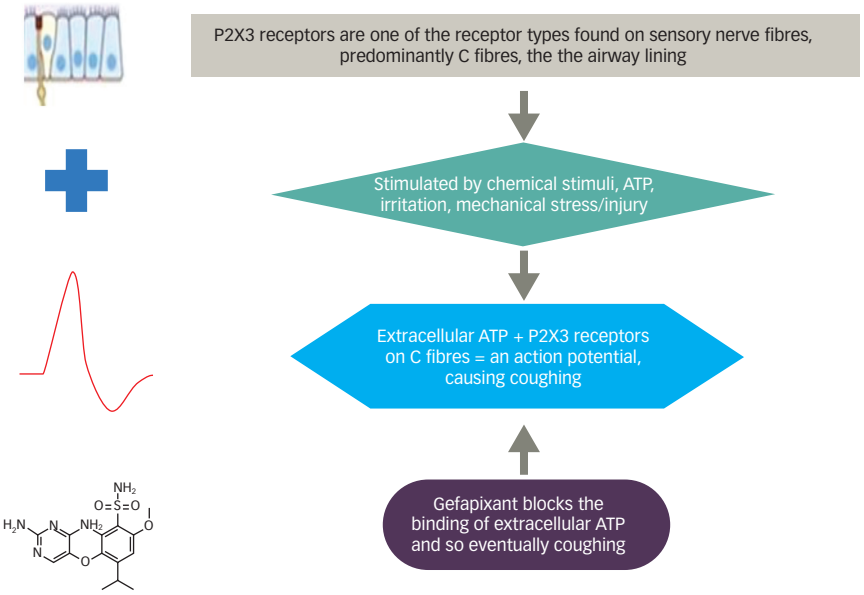
Antihistamines

ERS guidelines for chronic cough recommend first-generation antihistamines to treat chronic cough without any salient supporting evidence from randomized controlled trials, especially in the treatment of upper airway cough syndrome. The mechanism of action is proposed to be an anticholinergic effect on the central nervous system.[2]

Macrolides

According to ERS guidelines, macrolides can be trialled for 1 month in patients with cough who have tried other treatments for chronic bronchitis; however, there is limited evidence to support use in RCC or UCC.[2]

Figure 2: Mechanism of action of gefapixant



Opiates

Opiates are rarely justified in the treatment of chronic cough; however, they can be a useful treatment option in palliative care where the underlying condition has limited therapeutic options and the cough is truly refractory to treatment (e.g. untreatable lung cancer). Drug options include codeine or low-dose slow-release morphine. As noted by Smith et al., even codeine doses as high as 60 mg are not effective in reducing objective or subjective cough frequency in patients with chronic obstructive pulmonary disease (COPD).[17] As morphine is several times stronger than codeine, the side-effect profile must be considered, in particular, respiratory depression, drowsiness, addiction and accidental overdose.[2] A pragmatic approach may be to trial codeine first; if there is no response, then trial low-dose slow-release morphine, provided there are no contraindications or cautions for the patient.[2]

Corticosteroids

The Cochrane systematic review of inhaled corticosteroids in subacute and chronic cough, noted that the study results were inconsistent due to marked heterogeneity in terms of assessment of cough severity and pulmonary function.[34] The review mentions that a trial of inhaled corticosteroids should only be considered after investigations such as chest X-ray and other investigations including spirometry to exclude conditions that do not require steroids and enable the assessment of baseline lung function test before a treatment trial.[34]

Neuromodulator agents

In the neuromodulator drug class, gabapentin and pregabalin have been evaluated individually by randomized controlled trials and proven to be effective in reducing LCQ scores.[20] The side-effect profile such as drowsiness, confusion, fatigue and blurred vision should be discussed with the patient prior to starting the drug regimen.[20]

Novel agents

This group of drugs has emerged from research into the neural pathways that lead to the cough reflex. While initial research on drugs has been unsuccessful, this does not preclude the development of other drugs in the class that may be more effective.

Transient receptor potential vanilloid-1 antagonists

TRPV1 antagonists were one of the first medications considered (see *Table 1*), but subsequent studies did not support them as they did not reduce the cough frequency.[21]

Transient receptor potential ankyrin-1 antagonists

Transient ion channel ankyrin 1 (TRPA1), along with TRPV1, has a role in chemosensation, reflex control linked to temperature, osmolarity and oxidative stress. The channels are also activated by reactive oxygen species induced by air pollutants, which is the cause for air pollutant-related cough. A double-blind, placebo-controlled study of a TRPA1 antagonist did not reduce the 24-hour cough frequency, Visual Analogue Scale scores or citric acid challenge.[35]

P2X3 antagonists

The adenosine-gated P2X3 receptor was the third receptor of interest, as it has effects on sensory neurons of cough pathway. Previously, the therapy options for patients experiencing RCC or UCC were limited; however, the void is now being filled by the P2X3 antagonists. Gefapixant is the forerunner in its class of non-narcotic, selective P2X3 antagonists. After the initial phase I and phase II trials, it is now at the advanced stage of development (*Figure 2*).[22–25,38]

Two randomized, double-blind, placebo-controlled, crossover, dose-escalation studies demonstrated dose efficacy over 30 mg in controlling the cough frequency in comparison to placebo.[22] In both studies, cough frequency was measured by 24-hour ambulatory acoustic cough monitoring. This has advantages over the approach in phase I studies, because patients were allocated to both arms of randomization after a 2-week washout period, after which the endpoints were noted. The authors did, however, note taste disturbance affecting patients at doses greater than 150 mg.[22] Another phase IIb, randomized, double-blind, placebo-controlled study in patients with RCC or UCC showed a positive outcome in terms of its primary endpoint of reducing awake cough frequency, as measured by 24-hour ambulatory cough recorder. They also demonstrated efficacy at a dose of 30–50 mg gefapixant to control the cough frequency compared with the original dose of

600 mg, and that higher dosage was associated with an increased number of side effects, including dysgeusia.[23]

During the phase II trial of gefapixant, it was noted that many patients with chronic cough had comorbidities known to cause cough, including gastroesophageal reflux disease (GERD; 56%), allergic rhinitis (47%) and asthma (30%); 12% of patients had been diagnosed with all three conditions.[24] Further studies are required to demonstrate which subgroup of patients who would benefit from gefapixant.

The phase III trials COUGH-1 (NCT03449134) and COUGH-2 (NCT03449147) were international, randomized, parallel assignment, double-blind, placebo-controlled studies that assessed the efficacy and safety of gefapixant in reducing 24-hour cough frequency (per hour) at week 12 (COUGH-1) and at week 24 (COUGH-2).[25]

There were 730 adult patients in the COUGH-1 trial and 1,314 adult patients in COUGH-2 trial, all reporting either RCC or UCC for a period of 1 year. There were 548 females and 188 males in the COUGH-1 study and 984 females and 339 males enrolled in the COUGH-2 study. The mean age was 58 and 59 in COUGH-1 and COUGH-2 studies, respectively, thus reflecting the population who typically experience RCC. In COUGH-1 and COUGH-2 studies, approximately 61.1% and 67% of the patients were younger than 65 years old, respectively. The representative populations were predominantly from Europe (50%/54.3%) followed by North America (22.9%/22.4%), Asia–Pacific region (14.1%/6.2%) and others (13.0%/17%) in the COUGH-1 and COUGH-2 trials, respectively.[25] This is reasonably reflective of the population in whom the product might be used.

The primary outcome of the study was to measure the 24-hour cough frequency as assessed by an ambulatory digital audio recording device at weeks 12 and 24. Secondary outcomes included awake cough frequency at weeks 12 and 24, cough severity Visual Analogue Scale scores and LCQ scores. Use of both objective (audio recorded) and subjective measures (e.g. LCQ and other HRQoL measures) ensured that the studies were robust, in that cough was objectively measured and patient centred. Patients were randomized to having gefapixant 45 mg twice daily, gefapixant 15 mg twice daily or placebo, allowing a study of the dose response. The primary outcome measures determined that the gefapixant 45 mg twice daily group of patients had a statistically significant decrease in 24-hour cough per hour at 12 weeks (COUGH-1) and at 24 weeks (COUGH-2). However, the gefapixant 15 mg twice daily group of patients did not achieve the primary endpoint, suggesting that the higher dose is required for a clinically relevant effect. Efficacy in predefined subgroups of patients based on age, sex, region, age, duration of cough, baseline cough frequency, baseline cough severity, or primary diagnosis were also demonstrated.[26]

In both COUGH-1 and COUGH-2 trials, there was no association with serious adverse events noted in a dose-dependent manner. More patients in the COUGH-1 trial discontinued due to adverse effects in the 45 mg dose group (15% of patients) compared with the 15 mg dose group (3% of patients). Similarly, discontinuation was 20% in patients receiving the 45 mg dose and 8% in patients receiving the 15 mg dose in the COUGH-2 trial. It was noted that most of the taste-related adverse effects were mild to moderate and the incidence was similar in higher dose group: about 58% in COUGH-1 trial and 68.6% in COUGH 2 trial in patients in the 45 mg dose group, and 10.7% in COUGH-1 and 19.5% in COUGH-2 in patients in the 15 mg dose group.[25]

In the same class of P2X3 antagonists, a medication called BLU-5937 is currently under phase II study (NCT04678206) to evaluate the efficacy and safety in adults with refractory cough.[27] Similarly, sivopixant and eliapixant are also under evaluation for patients with RCC, and to date, two phase II studies (NCT04110054/NCT03310645) have been completed.[28,29] In terms of the newer selective P2X3 antagonists, sivopixant and eliapixant have completed phase IIa double blinded, crossover studies where they have both shown efficacy in reducing the cough frequency, and both appear to have fewer taste-related side effects compared with gefapixant.[36,37]

Future work on this class of medication might assess whether biomarkers can predict the responders to these medications. Similarly, dose range or escalation of dosage required when symptoms worsen while undergoing treatment requires additional research. Moreover, we also need to evaluate the applications in primary care in addition to secondary care, along with the cost effectiveness of treatment.

Conclusion

Chronic cough is often resolved by treating the underlying disease (e.g. asthma, eosinophilic bronchitis, upper airway cough syndrome or GERD), but for the minority of patients with a diagnosis of RCC, the newer pharmacological approaches could be considered. It is possible that RCC and UCC terminology could be combined in the future, as refractory or unexplained chronic cough. In addition, an increase in the knowledge of the pathophysiology of the cough reflex has led to the development of novel agents, including gefapixant. Future work may focus on developing predictors of response to specific treatment by further research into cough phenotypes and endotypes.[38] Similarly, combined non-pharmacological and pharmacological measures can be considered, given the complex mechanism of chronic cough.[39] ❑

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