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Review Article

Management of chronic refractory cough in adults

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ABSTRACT

Cough is a common respiratory symptom that is considered to be chronic when it lasts more than eight weeks. When severe, chronic cough may significantly impact an individual's quality of life, and such patients are frequently referred for specialist evaluation. Current international guidelines provide algorithms for the management of chronic cough: in most cases, treatment of the underlying disease is sufficient to improve or resolve cough symptoms. Severe chronic cough may significantly affect patients' quality of life and necessitate frequent referral for specialist evaluations. In this narrative review, we summarize non-pharmacologic and pharmacologic management of adult patients with chronic cough of known cause that persists after proper treatment (chronic refractory cough, CRC) or chronic cough of unknown cause in adult patients. If chronic cough persists even after treatment of the underlying disease, or if the chronic cough is not attributable to any cause, then a symptomatic approach with neuromodulators may be considered, with gabapentin as the first choice, and opioids or macrolides as alternatives. Speech pathology treatment and/or neuromodulators should be discussed with patients and alternative options carefully considered, taking into account risk/benefit. Novel promising drugs are under investigation (e.g. P2×3 inhibitors), but additional studies are needed in this field. Speech pathology can be combined with a neuromodulator to give an enhanced treatment response of longer duration suggesting that non-pharmacologic treatment may play a key role in the management of CRC.

1. Introduction

Cough is a physiological response to mechanical and chemical stimuli due to irritation of cough receptors located mainly in the epithelium of the upper and lower respiratory tracts, pericardium, esophagus, diaphragm, and stomach. A complex reflex arc through the vagus, phrenic, and spinal motor nerves to the expiratory musculature generates an inspiratory and forced expiratory effort to clear the airways [1]. Under pathological conditions of known and unknown etiologies, chronic refractory cough (CRC) may become a major medical problem because patients may need to undergo repeated examinations before reaching a diagnosis, and/or try several treatments with sometimes poor symptom control, worsening their quality of life and increasing economic burden.

Cough is one of the most common respiratory symptoms to result in outpatient clinical referral. The initial assessment aims to classify duration and severity of the clinical presentation with guidelines from the American College of Chest Physicians (ACCP) listing three categories based upon duration: acute cough, lasting less than three weeks; subacute cough, lasting between three and eight weeks; and chronic cough, lasting more than eight weeks [2–4]. In the acute phase, when life-threating features are present, such as acute worsening of dyspnea, increased sputum production, hemoptysis, fever, and weight loss, management of underlying etiologies is an urgent priority. Subacute or chronic cough may become a bothersome symptom that significantly impairs quality of life, sometimes persisting for months or years after treatment.

In order to optimize and select a treatment for chronic cough, and particularly CRC, current guidelines suggest applying a diagnostic algorithm to identify possible underlying diseases [2–4]. In the majority of cases, a number of associated conditions are identified [5], most commonly upper airway cough syndrome (formerly named postnasal drip), asthma, gastroesophageal reflux, eosinophilic bronchitis, and intolerance to drugs such as angiotensin converting enzyme inhibitors. Other well known triggers and diseases associated with cough include cigarette smoking, occupational irritants, foreign bodies, chronic

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obstructive pulmonary disease (COPD), chest neoplasms, bronchiectasis, cystic fibrosis, and interstitial lung diseases. After excluding these causes, triggers and diseases, some patients may experience chronic cough of unclear etiology, which is called 'chronic idiopathic cough' or 'unexplained chronic cough'. The term CRC has also been introduced, which includes cough that persists despite optimal treatment of the underlying disease(s) [2–4]. In this review we focus on the management of CRC of known or unknown cause in adults.

Over the past decade, international guidelines have been developed to help physicians in clinical practice to diagnose, assess the severity of, and manage cough – particularly chronic cough [3,6]. These guidelines recommend identifying the potential causes of chronic cough and then suggest specific treatments for any underlying disease. Moreover, they address the treatment of cough in patients whose underlying disease remains unknown.

The prevalence of chronic cough has been estimated as up to 13% of the general population, and may be associated with significant impairment of quality of life, together with anxiety and depression [7–9]. This is especially common in patients who undergo numerous consultations and/or unsuccessful therapeutic trials before getting the diagnosis unexplained chronic cough or CRC. Therefore, there is increasing interest in understanding possible mechanisms for these clinical conditions.

In a previous perspective, we reviewed the definitions, mechanisms, and diagnosis of chronic cough in adults [10]. In this perspective we review the pharmacologic and non-pharmacologic management of chronic cough of known or unknown cause in adult patients.

2. Cough hypersensitivity syndrome

The European Respiratory Society (ERS) Task Force introduced the term 'cough hypersensitivity syndrome' in 2014, and defined it as a 'clinical syndrome characterized by troublesome coughing triggered by low levels of thermal, mechanical or chemical exposure' [11]. In pathological conditions, inflammation of central and/or peripheral components of the cough reflex may be triggered by innocuous stimuli resulting in excessive coughing due to neuroinflammation defined as 'cough reflex hypersensitivity'. Assuming cough hypersensitivity syndrome represents a common mechanism responsible for troublesome persistent cough of known or unknown causes, peripheral and central neural pathways for cough signal and receptors become new target for treatment and may help to understand clinical aspects of 'difficult to treat cough'.

The concept of cough hypersensitivity syndrome includes both chronic troublesome cough of known cause that remains troublesome even after treatment of the underlying cause (CRC), and chronic idiopathic cough with no identifiable cause.

3. Which patients should be considered for speech pathology therapy and/or neuromodulatory therapy?

Most chronic respiratory diseases can manifest with chronic cough as one of the symptoms, although chronic cough is rarely the dominant symptom and it usually responds to treatment of the underlying disease. Unfortunately, with the exception of asthma, in which respiratory symptoms including cough are largely reversible upon treatment, chronic cough due to other chronic respiratory diseases, such as COPD or bronchiectasis, only partially responds to specific treatment. However, unless the cough remains hacking and troublesome, this partial response is usually sufficient, and does not require additional speech pathology and/or neuro-modulatory treatment. In fact, in most cases (including chronic respiratory infections, pneumonia, bronchiectasis, interstitial lung diseases, cystic fibrosis or productive cough in COPD) cough should be reduced but not abolished as it is an important defense mechanism. In contrast, such additional treatment should be considered for patients with one or more of these diseases when chronic cough remains hacking and troublesome even after adequate treatment of the underlying disease, and in those with chronic hacking and troublesome cough of unknown origin [2–4]. This additional approach to treatment may be non-pharmacologic and/or pharmacologic.

4. International guidelines for the treatment of chronic refractory cough

The two most influential guidelines for the management of cough, and particularly CRC, are: 1) those developed [4] and updated [2] by the ACCP, and 2) those developed by the ERS [3]. The definitions, classification, diagnosis and differential diagnosis, assessment of severity, and management (non-pharmacologic and pharmacologic) are similar in these guidelines, and we refer the reader to the original documents for a detailed description. In this review we focus on the management of CRC of known and unknown origin, describing all available approaches, but highlighting whether or not they are recommended by guidelines.

5. Non-pharmacologic treatment

As mentioned above, coughing is the sudden expulsion of air from the lungs through the upper airways when the vocal cords are open [1,6,12]. The increased tension in the larynx is involved in phonation, respiratory function as part of the conducting airways, and swallowing, with laryngeal motor dysfunction at any point potentially leading to dysphonia and triggering chronic cough [12,13]. Voice problems and vocal cord dysmotility have been estimated in up to 40% of adults with chronic cough [14]. Singing, talking and shouting are the activities most frequently associated with increased tension of the larynx and may be identified as a trigger of chronic cough. Phonation may be associated with a decreased lower esophageal sphincter tone, which in turn can promote acid reflux from the stomach and stimulate pressure receptors in the larynx, resulting in chronic cough [15], which, together with stimulation of pressure receptors in the larynx, may lead to chronic cough.

The most common laryngeal motor dysfunction is vocal cord dysfunction (VCD), which consists of an involuntary vocal fold adduction during inspiration [14]. The link between voice problems and chronic cough is the rationale for the speech pathology approach in refractory cough [16]. Indeed, speech therapy, breathing exercises, cough suppression techniques, and patient counseling have been tried in the management of chronic cough. A systematic review reporting five studies of such interventions showed improved cough severity and frequency, although few studies used validated cough measurement tools [17]. The identification of specific components of this non-pharmacologic approach and its effectiveness on chronic cough was described by Vertigan et al. in a single-blind, randomized placebo-controlled trial [18]. Ninety-seven patients with refractory chronic cough were randomly assigned to the speech pathology intervention or placebo. Intervention consisted of four sessions over a two-month period by a qualified speech pathologist. The components of speech pathology treatment were education, vocal hygiene, cough suppressant strategies, and psychoeducational counseling. Chamberlain et al. conducted a multicenter randomized controlled trial in 75 patients with CRC, and observed an improvement in cough-specific quality of life (Leicester Cough Questionnaire) and cough frequency (Leicester Cough Monitor) as a consequence of implementing a combined physiotherapy and speech and language therapy intervention [19].

The educational component should determine the reasons for coughing and outline the possible negative consequences of ongoing chronic cough. Patients should understand the goals of therapy, which are to suppress cough despite the triggering sensation, and enhance patients' ability to voluntarily control the cough. Patients are taught to substitute a competing response, such as a distraction technique, cough suppression swallow, or relaxed throat breathing in order to reduce laryngeal constriction. Psychoeducational counseling should support

patients and their control over their cough, emphasizing that cough is a response to irritating stimuli rather than a phenomenon outside of their control. Vocal hygiene education aims to reduce or prevent laryngeal irritation by avoiding passive smoking, avoiding mouth breathing, and behavioral management of gastroesophageal reflux. Broaddus-Lawrence et al. documented that strategies to reduce coughing and throat clearing in individuals with voice disorders improved voice quality [20]. In addition, Solomon et al. found a beneficial effect on the larynx of adequate hydration, including attenuating or delaying elevation of phonatory threshold pressure [21]. Further, Vertigan et al. found that speech pathology management was effective in terms of the global clinical assessment, symptom response and analysis of voice parameters [18].

In a non-comparative study, Ryan et al. evaluated the presence of VCD in their participants and investigated the efficacy of speech pathology management for CRC in those with VCD. Subjects with VCD received speech pathology therapy from a speech pathologist in sessions every four weeks, which included education, vocal hygiene, cough suppression strategies, relaxed throat breathing techniques, and psychoeducational counseling [22].

The terminology of breathing exercises varies among studies, but breathing control/diaphragmatic breathing and relaxed breathing control techniques have all been described as aiming to relax the throat, neck, and shoulder muscles whilst increasing abdominal excursion and reducing upper chest movement. A non-comparative retrospective study by Murry et al. was the only one to include breathing exercises as a sole intervention rather than a composite package of care [23]. Sixteen adults with chronic cough underwent 2–13 sessions of respiratory retraining exercises over a 4–23-week period. Patients with (VCD) and chronic cough reported an aberrant laryngeal sensation which tended to normalize following a limited course of respiratory retraining, with improvement in patients' symptoms.

Ryan et al. documented a reduction in cough frequency following intervention using a validated objective outcome measure, the Leicester Cough Monitor [24,25]. Seventeen adults with chronic cough were assessed before, during, and after speech language pathology intervention by a qualified speech language pathologist over a period of 14–18 weeks.. This intervention also reduced laryngeal irritation, with subsequent lower cough sensitivity and lower urge to cough, whereas the cough threshold increased.

Patel et al. evaluated the effectiveness of outpatient-based cough physiotherapy in a pilot prospective observational study [26]. This study reported a significant reduction in cough frequency and an improvement in cough-related quality of life from the intervention, which consisted of education, counseling, cough control, breathing retraining, and vocal hygiene.

According to current ERS guidelines, multi-component physiotherapy/speech and language therapy interventions should be considered for CRC patients who wish an alternative to drug treatment [3]. The ACCP guidelines recommend identifying patients with oral-pharyngeal dysphagia, or the presence of conditions associated with high risk of aspiration, as they are potential candidates for speech pathology treatment [4].

Despite the efficacy and advantages of speech pathology intervention, there is limited guidance in the literature as to when patients should be referred for treatment. Patients suitable for speech pathology intervention are those whose cough has persisted despite medical management. Speech pathology intervention may be particularly beneficial for patients with coexisting laryngeal disorders such as muscle tension dysphonia or inducible laryngeal obstruction [27].

6. Pharmacologic treatment

6.1. Neuromodulatory treatments

Pathological mechanisms may affect central and peripheral neuromodulators or cause a hypersensitivity of the cough reflex. Most studies

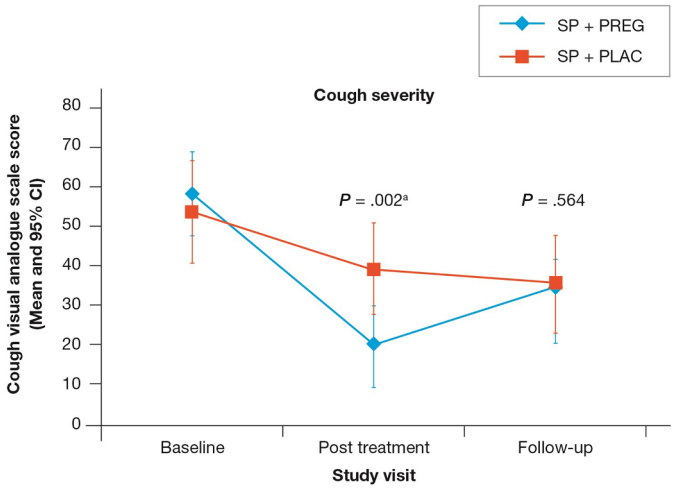

Fig. 1. Mean (95% CI) cough severity visual analog scale by visit and treatment group. Reproduced and modified with permission from Vertigan et al., Chest 2016 [28].

in CRC have focused on pharmacologic treatment or speech pathology treatment individually; few studies have evaluated the effectiveness of combined treatment. A randomized, double blind placebo-controlled trial by Vertigan et al. showed that combined treatment with pregabalin and speech pathology was more effective than speech pathology alone in terms of cough frequency, cough severity and cough-related quality of life [28]. In addition, the effect of the combined approach was still beneficial for the four weeks after cessation of pharmacological treatment (Fig. 1) [28].

A number of agents, both opioid and non-opioid, are thought to suppress cough via activity on the central cough center [2,3,11,12]. They modulate the enhanced neural sensitization, which is the key component of CRC. Codeine is the opiate traditionally used for cough, but despite widespread use data are limited (and conflicting) regarding efficacy in chronic cough, and a range of side effects have been reported. In a double-blind, placebo-controlled crossover study by *Smith* et al., 21 patients with COPD were randomly assigned to codeine 60 mg twice a day or placebo for one day [29]. No significant difference was noted between the groups in cough counts or subjective cough scores, although the study size was small and the dose of codeine low [29]. While codeine is not effective in chronic refractory cough, and not recommended by ERS guidelines (Table 1) [3], it may be useful in prolonged cough persisting after acute respiratory infections, including COVID-19 [30].

Morphine is effective in some but not all patients, and limited data are available from prospective studies. In a double-blind crossover trial by Morice et al., 27 patients who had a persistent cough of greater than three months duration and who had failed specific treatment were randomly assigned to receive slow-release morphine (5 mg twice daily) or placebo for four weeks. Morphine improved daily cough severity scores, although the cough reflex was unaltered [31]. Somnolence and constipation are common side effects, yet despite this morphine is recommended by guidelines (Table 1) [3,12].

Tramadol is an opioid similar to codeine and morphine. A pilot prospective study by Dion et al. on 16 patients with neurogenic cough highlighted the antitussive properties of tramadol [32]. However, tramadol is neither recommended nor discouraged by guidelines (Table 1) [2,3,12].

Gabapentin and pregabalin are gamma aminobutyric acid (GABA) analogs that bind to the voltage-gated calcium channels and inhibit centrally neurotransmitter release. They are neuromodulators commonly used to control pain and epilepsy. Lee et al. reported data from 28 patients with chronic cough on the effectiveness of gabapentin: 68% had a clinically positive response, especially when laryngeal

Table 1
Summary of guideline recommended options for the pharmacologic treatment of chronic refractory cough [2,3,12].

Drugs	Smith and Woodcock 2016	CHEST Guidelines 2018	ERS guidelines 2020
Morphine	Recommended	Discouraged	Recommended
Gabapentin	Recommended	Recommended	Recommended
Pregabalin	Recommended	Recommended	Recommended
Tramadol	Neither recommended nor discouraged	Neither recommended nor discouraged	Neither recommended nor discouraged
Codeine	Neither recommended nor discouraged	Neither recommended nor discouraged	Not recommended
Dextromethorphan	Neither recommended nor discouraged	Neither recommended nor discouraged	Neither recommended nor discouraged
Amitriptyline	To be considered	Neither recommended nor discouraged	Neither recommended nor discouraged

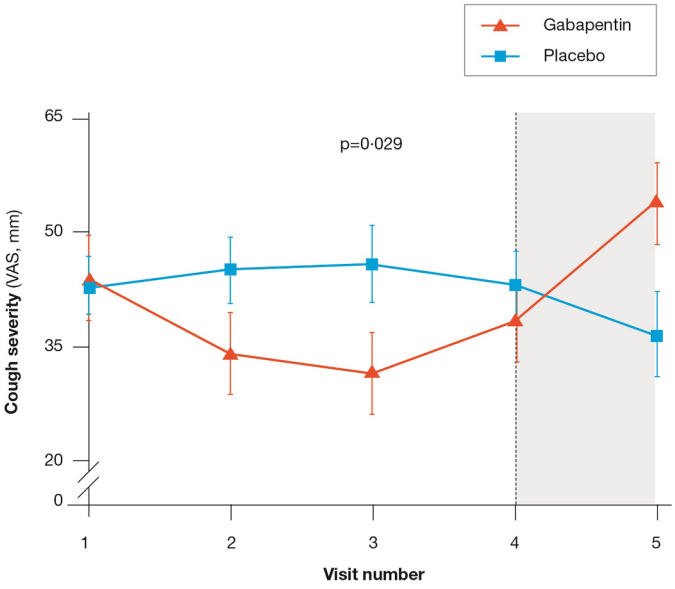

Fig. 2. Mean efficacy variable score for gabapentin versus placebo, during and after treatment in terms of cough severity. The dose was escalated from Days 1–6, and reduced from Days 78–83. Treatment was stopped completely by Visit 4 (Week 12; dotted line). Reproduced and modified with permission from Ryan et al. Lancet 2012 [35].

neuropathy was present; however, 17.8% complained of dizziness or somnolence [33]. In addition, Mintz et al. described six cases in which gabapentin was administered for intractable cough; complete resolution or a significant improvement in cough was observed in five of these cases [34]. Fatigue and drowsiness were reported as side effects [34]. Further, in a randomized trial by Ryan et al. in 62 patients who had experienced CRC for more than eight weeks, treatment with gabapentin for 10 weeks significantly improved cough-specific quality of life (Leicester Cough Questionnaire score), cough severity (visual analogue scale) and cough reflex sensitivity (defined by quantity of capsaicin needed to induce five coughs) with limited side effects, most commonly nausea, confusion, dizziness, dry mouth and fatigue (Fig. 2) [35]. After withdrawal of gabapentin, there was reduced effectiveness, in terms of Leicester Cough Questionnaire and mean cough severity, further supporting its antitussive effect.

In a recent randomized clinical trial by Dong et al. gabapentin was compared to baclofen in the treatment of suspected refractory gastroesophageal reflux-induced chronic cough [36]. Two hundred and thirty-four patients who failed an eight-week course of omeprazole and domperidone were recruited and randomly assigned to receive either gabapentin or baclofen for eight weeks. The authors concluded that the two drugs had similar therapeutic efficacy, but that gabapentin was preferable because of fewer side effects. These findings suggest that gabapentin does not act by reducing peripheral sensitization, but additional placebo-controlled randomized controlled trials are needed to explore how long a patient with CRC should remain on gabapentin to achieve resolution of symptoms. Gabapentin is recommended by current guidelines as a potential pharmacologic treatment for CRC (Table 1) [2,3,12].

Administration of pregabalin decreases levels of neurotransmitters such as glutamate, noradrenaline, and substance P [37]. In a case report by Li et al., pregabalin prescribed to alleviate postherpetic neuralgia also relieved the patient's chronic cough, with no serious adverse events reported after two years of follow-up [38]. Halum et al. documented its effectiveness on laryngeal sensory neuropathy through a retrospective study in 12 consecutive patients [37]. The risk/benefit of pregabalin versus gabapentin for the treatment of CRC needs to be carefully considered. The magnitude of change in the Leicester Cough Questionnaire and cough severity in this pregabalin study was greater than the gabapentin study [35,39], however, adverse effects were more common with pregabalin than with gabapentin. Some aspects of the study design may have amplified the differences between gabapentin and placebo. First, the known CNS effects of gabapentin might have impacted treatment masking, thus favoring gabapentin. Second, baseline cough frequency was higher in the gabapentin group, although not significantly, providing more ‘space’ for a positive effect. Third, the population examined was highly selected, possibly identifying the optimal target population, but limiting the use of gabapentin to very few patients in real life. In addition, pregabalin has a greater abuse potential than gabapentin, most likely due to its more rapid absorption and faster onset of action. Pregabalin is a treatment option recommended by current guidelines (Table 1) [2,3,12].

Dextromethorphan is probably the most commonly used non-opioid agent for cough; it is considered to have opiate properties [40]. However, few studies have evaluated the efficacy of dextromethorphan in chronic cough, and those available were conducted in adults and used small sample sizes (16–99 patients in each study), with conflicting results [41,42]. Due to the absence of appropriately designed and powered randomized clinical trials, dextromethorphan is neither recommended nor discouraged by guidelines [2,3,12].

Amitriptyline is a tricyclic antidepressant and inhibitor of serotonin reuptake that has been investigated by Jeyakumar et al. for the treatment of CRC due to post-viral vagal neuropathy [43]. In this prospective, randomized, controlled study in 28 patients, the majority of patients receiving amitriptyline achieved a complete response, whereas none of those receiving the combination of codeine and guaifenesin responded [43]. The authors do not report whether any patients experienced side effects during the study. Secondly, Bastian et al. conducted a prospective uncontrolled cohort study in 12 consecutive patients [44]. All patients were treated with a single dose of open label 10 mg of amitriptyline for 21 days. At least a 40% reduction in self-reported symptoms was recorded, suggesting that a trial of amitriptyline 10 mg (or of other antineuralgia type medications) may be helpful in chronic cough [44]. Finally, a retrospective case series by Norris et al. in 12 patients with recurrent laryngeal nerve sensory neuropathic symptoms documented improvement in neuropathic symptoms when treatment with amitriptyline over two months [45]. Four patients with no response or intolerable side effects were prescribed gabapentin [45]. Amitriptyline is neither recommended nor discouraged by guidelines (Table 1) [2,3,12].

Taking into account all the studies mentioned so far, several neuromodulators with at least one positive randomized controlled trial

were evaluated. These therapies seem promising for the treatment of chronic cough. The CHEST Expert Cough Panel recommends only gabapentin (Table 1) [2], the risk-benefit profile to be reassessed after six months before continuing the drug. ERS guidelines recommend a trial of low dose slow-release morphine (5–10 mg twice daily) in adults with CRC. They also suggest a trial of gabapentin or pregabalin in adults with CRC [3].

In conclusion, there are few effective treatments for cough with an acceptable therapeutic ratio; more selective agents with a more favorable side effect profile are needed.

A possible role of inhaled drugs in the management of CRC has been also investigated. Local anesthetics (e.g., lidocaine or bupivacaine) are currently used in the palliative management of cough associated with malignancies. In addition, an older study with ipratropium bromide reported a significant reduction in cough severity and a good safety profile in patients with chronic persistent cough, although the sample size was small ($N = 14$) and results have not been subsequently replicated [46]. Subsequent preclinical research suggests that tiotropium can directly modulate airway sensory nerve activity and thereby the cough reflex, through a mechanism unrelated to its anticholinergic activity [47].

6.2. Experimental pharmacologic neuromodulatory treatments

The recognition that chronic cough is characterized by hypersensitivity of the peripheral and central neural pathways involved in cough has expanded the range of potential therapeutic targets currently under evaluation. A novel approach is to focus on molecular pathways rather than neural mechanisms [48].

The primary vagal fibers mediating cough are A-fibers and C-fibers, which are responsive to mechanical and chemical stimuli, respectively [49]. P2×3 receptors are expressed by airway vagal afferent nerves and contribute to the hypersensitization of sensory neurons [50]. Based on laboratory studies, increased sensitivity of P2×3 receptors on the airway sensory nerve fibers (e.g., vagal afferent C fibers) could mediate sensitization of the cough reflex and could therefore be a potential cause of refractory cough [51]. Adenosine triphosphate (ATP) plays a significant role in the activation of sensory C fibers, and this activation is inhibited by blockade of P2×3 and P2×2/3 receptors. In a randomized, cross-over trial of 24 patients with refractory cough, an investigational P2×3 antagonist, gefapixant, previously known as AF-219, decreased cough counts during the two-week study blocks by 75% compared with placebo [51]. However, taste disturbance was noted in all patients taking gefapixant and caused six patients to withdraw from the study; nausea was also common (38%). In a Phase 2, double-blind, two-period study by Morice et al. there was a reduction in the cough reflex in patients treated with gefapixant 100 mg [52]. Two randomized, double-blind, placebo-controlled, two period crossover, dose-escalation studies by Smith et al. of gefapixant at lower doses has reported efficacy with fewer side effects [53]. Finally, in a multicenter randomized placebo-controlled parallel trial Smith et al. investigated the effect of gefapixant on chronic cough [54]. Data are available only as an abstract, in which the authors describe a significant improvement in the cough frequency when compared to placebo [54]. These results support a promising therapeutic target in development for P2×3 receptor hypersensitivity in refractory cough, but further study is needed to determine safety and efficacy in a larger number of patients.

Transient receptor potential (TRP) channels are present in abundance in the airways and are expressed in many cell types of the airway including primary sensory afferent nerves, epithelial cells and smooth muscle cells [48]. Several agents for pain are in development that target these receptors. However, since TRP channels are directly activated by changes in temperature, chemicals, mechanical stimulation, pH and osmolality, and may evoke cough, they been proposed also as treatments for chronic cough. Of particular interest in relation to cough are members of the vanilloid (TRPV1, TRPV4), anykrin (TRPA1) and melastatin (TRPM8) families. To date, pharmacologic modulation of TRP channels for the treatment of cough has been disappointing and remains to be investigated as a potential target for chronic cough. TRPV1 was the first channel to be considered as a key regulator of cough, but two Phase 2, double-blind crossover studies by Belvisi et al. and Khalid et al. on TRPV1 failed to show improvements in spontaneous cough frequency [55,56]. The TRPA1 channel is activated by a range of physical and chemical factors including cold temperatures, mechanical stimulation, inflammatory mediators and acrolein (a component of cigarette smoke). Although animal studies demonstrated effectiveness of TRPA1 antagonists in reducing cough in response to tussive challenges, in a double-blind placebo-controlled study in patients there was no reduction in cough frequency over 24 h, or no reduction in citric acid-induced cough [48]. TRPV4 is recognized as an osmosensor and responds to diverse stimuli including non-noxious temperatures, shear stress and mechanical stimulation. A clinical trial with the TRPV4 antagonist, GSK2798745, was terminated early, presumably due to lack of efficacy [48]. Finally, TRPM8 is activated by cooling compounds such as menthol, icilin and eucalyptol [48].

Voltage-gated sodium channels (NaV) mediate the initiation and propagation of action potentials in afferent sensory nerves and represent a potential therapeutic target for cough. Lidocaine, a non-selective NaV channel blocker, has been used clinically to alleviate cough and has been reported to be safe [57]. However, a Phase 2 double-blind crossover study using a novel blocker targeting a subtype selective inhibition of the NaV1.7 (GSK2339345) failed to illustrate an antitussive response [58].

The tachykinins, substance P, neurokinin A and neurokinin B are released both from the peripheral endings of afferent nerves (predominately C-fibers) and from central neural structures. The tachykinin receptor, neurokinin 1 receptor, has gained attention as a target for chronic cough treatment. In a Phase 2, double-blind study (VOLCANO-1) by Smith et al. on 244 patients, significant improvements in objective cough frequency and sustained reductions in daytime cough frequency were documented [59].

Nicotinic acetylcholine receptors, or nAChRs, respond to the neurotransmitter acetylcholine and to nicotine and are found in the central and peripheral nervous system. Dicpinigaitis et al. studied the alpha7 (α7) subtype of the nAChRs, which is responsible for the antitussive effect of nicotine through the activation of GABAergic interneurons in the brainstem [60].

Azithromycin belongs to the class of macrolide antibiotics. It is commonly used in the treatment of a variety of infections, including community-acquired respiratory tract infections and mycobacterial infections, and macrolide antibiotics also have anti-inflammatory actions. Hodgson et al. investigated the potential effects of azithromycin on chronic cough in a randomized, double-blind, placebo-controlled study [61]. Treatment with azithromycin for eight weeks failed to improve health status in patients with chronic cough when compared with placebo.

Erythromycin was studied by Yousaf et al. in a randomized, double-blind, placebo-controlled parallel trial; the authors documented no difference in the change in cough frequency between the erythromycin and placebo group, although there was a significant difference in the change in sputum neutrophils over a 12 week period (a reduction with erythromycin and an increase with placebo) [62].

PA-101 is a novel formulation of cromolyn sodium and thought to act as a mast cell stabilizer. In a randomized placebo-controlled trial by Birring et al. PA-101 was delivered via a high efficiency eFlow nebulizer to 52 patients with idiopathic pulmonary fibrosis and chronic cough [63]. No treatment benefit was observed for PA101 [63].

In conclusion, there have been important developments in elucidating pathophysiological mechanisms underlying chronic cough. Additional information regarding neurobiology has introduced a number of novel pharmacological treatment options, including drugs targeting the P2×3 receptor, which seems to be the most promising.

7. Conclusions

Cough is one of the most common respiratory symptoms, and is defined as chronic when it lasts for more than eight weeks. In the majority of cases, it represents the most troublesome symptom of common respiratory and non-respiratory diseases. If chronic cough persists even after treatment of the underlying disease, or if the chronic cough is not attributable to any cause, then a symptomatic approach with neuromodulators may be considered, with gabapentin as the first choice [2,3,12], and opioids or macrolides as alternatives. Speech pathology treatment and/or neuromodulators should be discussed with patients and alternative options carefully considered, taking into account risk/benefit.

Novel promising drugs are under investigation (e.g. P2×3 inhibitors), but additional studies are needed in this field. Speech pathology can be combined with a neuromodulator to give an enhanced treatment response of longer duration suggesting that non-pharmacologic treatment may play a key role in the management of CRC. International guidelines, based on consensus opinion and observational data, provide detailed investigation and treatment algorithms [2,3,12]. However, there are broad national and international differences in the delivery of health care resulting in differences in available diagnostic tests and management strategies, both in primary and specialist care. Quality of life is frequently impaired in patients with chronic cough, who often also have increased economic burden. Smith et al. provides a simplified approach through four steps: identification and treatment of obvious causes; focused testing for, and treatment, of asthma, gastro-esophageal reflux and rhinosinusitis; investigations to rule out rarer causes of cough; and management of idiopathic or refractory chronic cough [12]. The lack of knowledge or limited economical resources in several areas may be handled by identification of referral centers for multidisciplinary management (respiratory physician, ear, nose and throat specialist, gastroenterologist, psychologist, lung function and molecular biology lab, respiratory physiotherapist and speech therapist) of chronic refractory cough and the feasibility of clinical trials to implement this field.

Declaration of Competing Interest

None.

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