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# Chronic cough — treament in line with guidelines

## Abstract

Chronic cough is one of the most common symptoms in clinical practice that is associated numerous negative consequences. The pathophysiology of chronic cough is complex, and its most common causes include respiratory diseases, neurological disorders, exposure to tobacco smoke, and medications. Understanding the physiology of cough and the mechanisms of cough hypersensitivity can improve the outcome of the treatment. At the turn of 2019 and 2020, the European Respiratory Society (ERS) issued guidelines concerning diagnostic evaluation and therapeutic management (pharmacological and non-pharmacological treatment) of chronic cough that persists despite causal treatment as well as cough of unknown etiology.

The aim of the treatment, preceded by a thorough clinical evaluation, is to control the cough reflex while maintaing the protective function of cough. The following aspects should be taken into account in therapeutic management: antiasthmatic medications, medications reducing gastric acidity as well as prokinetic and neuromodulatory medications. Non-pharmacological methods include physiotherapy and speech therapy. To improve treatment results, it is necessary to seek new antitussive medications and physiotherapy methods, understand cough phenotypes and introduce more effective methods of cough measurement. Due to the limited efficacy of the currently used medications, researchers are currently conducting clinical trials involving new antitussive medications, with mechanisms of antitussive activity other than the ones which are currently applied.

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**Key words:** chronic cough, physiology of cough, cough treatment, cough hypersensitivity

## Abbreviations

ACE — angiotensin-converting-enzyme
ATP — adenosine triphosphate
CQLQ — cough-specific quality of life questionnaire
ERS — European Respiratory Society
GABA — γ-amino butyric acid binding
LABA — long-acting $\beta_2$-agonists
LCM — leicester cough monitor
LCQ — leicester cough questionnaire
NAEB — non-asthmatic eosinophilic bronchitis
NMDA — N-methyl-D-aspartate
COPD — chronic obstructive pulmonary disease
PPI — proton pump inhibitors
PSALTI — physiotherapy and speech and language therapy intervention
RCC — refractory chronic cough
TMCC — the therapy program for management of chronic cough
TRPV1 — transient receptor potential vanilloid 1
VAS — visual analogue scale

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## Introduction

Chronic cough is usually defined as a symptom than persists for a period longer than 8 weeks [1]. Due to the deterioration of the quality of life, occupational, social and family isolation, as well as other undesirable consequences of cough, there is a need to seek more effective methods of its diagnostic evaluation and treatment; chronic cough is one of the most common symptoms, with a prevalence estimated at 10% of the world population [2]. Frequency of cough increases with age, which especially concerns women aged 40 and above [3]. Studies conducted in Great Britain indicate that patients who suffer from chronic cough feel lost in the health care system. They usually attend numerous doctor's appointments, receiving various diagnoses. Only 30% of patients felt that they ultimately received the help that they needed. Twelve to twenty-two percent of patients without radiological changes are diagnosed with idiopathic cough, which means that there is no causal treatment to be administred. At the turn of 2019 and 2020, the European Respiratory Society (ERS) [5] published guidelines concerning the diagnosis and treatment of chronic cough that persists despite causal treatment as well as refractory chronic cough (RCC).

## Causes and clinical evaluation of chronic cough

A study conducted by the European Lung Foundation revealed that median duration of chronic cough in a group of almost 4,000 patients was 2–5 years, and in 20% of patients cough persisted for more than 10 years [4]. Chronic cough occurs in many pulmonary diseases, including such common diseases as asthma, chronic obstructive pulmonary disease (COPD), lung cancer and interstitial lung diseases with fibrosis, including idiopathic pulmonary fibrosis (IPF). The ERS guidelines indicate multiple phenotypes of cough (Fig. 1), with a particular focus on cough hypersensitivity syndrome, which is more common in women over 40 years of age [6]. However, increased sensitivity to tussive stimuli also occurs in many other diseases.

Chronic cough is caused by complex pathophysiological phenomena and in many patients, it is caused by more than just one factor. In physiological conditions, cough prevents unwanted particles or substances from entering the airways and, at the same time, when a foreign body is present in the airways or production of bronchial secretion increases, it enables their removal. It occurs through various mechanisms, so we cannot speak of one, universal cough reflex since the pathway of transmission is both afferent and

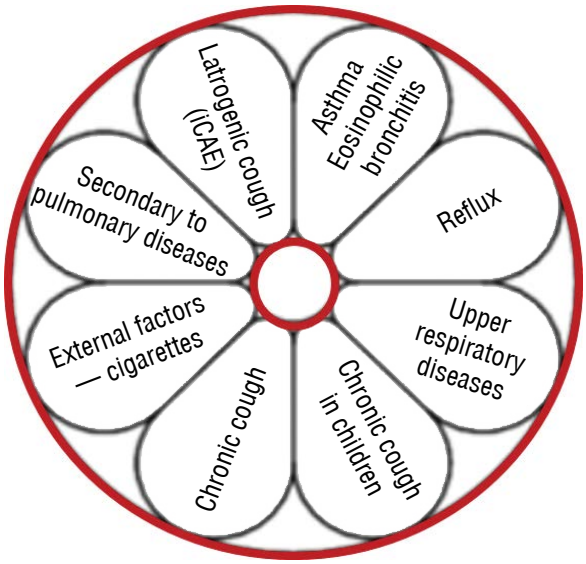


**Figure 1**. Causes of chronic cough according to [5]

efferent, depending on the type of stimulation. The afferent pathway involves mainly fibers of the vagus nerve: myelin Aδ fibers and non-myelin C fibers. The first ones react mainly to touch, and sudden acidity increase in the airways. Probably, mainly Aδ fibers are involved in the cough reflex that prevents foreign bodies from entering the airways and helps expectorate large amonuts of sputum. The reflex leads to an immediate tightening of the upper airways, which in practice is manifested by chocking, for example after aspirating a food particle. The C fibers mainly transmit signals in response to chemical irritation, including: capsaicin, bardykinin, ATP, adenosine and nicotine. This group of fibers may be responsible for cough in the course of receptor irritation resulting from inhaling chemical substances, such as tobacco smoke, or bronchial mucositis, including neurogenic inflammation [7].

Nerve fibers Aδ and C are activated through stimulation of receptors located at their endings. These include mainly transient potential receptors, but also receptors P2X3, which have the structure of ion channels that open upon the attachment of specific ligands, such as capsaicin or ATP. Signals transmitted through the vagus nerve activate the nerve cells of the solitary nucleus and the nucleus of the spinal trigeminal nerve, in which, in the dorsolateral medulla oblongata, there is an area (paratrigeminal nucleus) that receives signals from the vagus, trigeminal and lingual-pharyngeal nerve [8]. This area, which is still poorly understood, is most likely responsible for the transmission of signals to the thalamus and cerebral cortex that result in the "urge to cough" as well as habitual cough [8]. In the central nervous system, si-

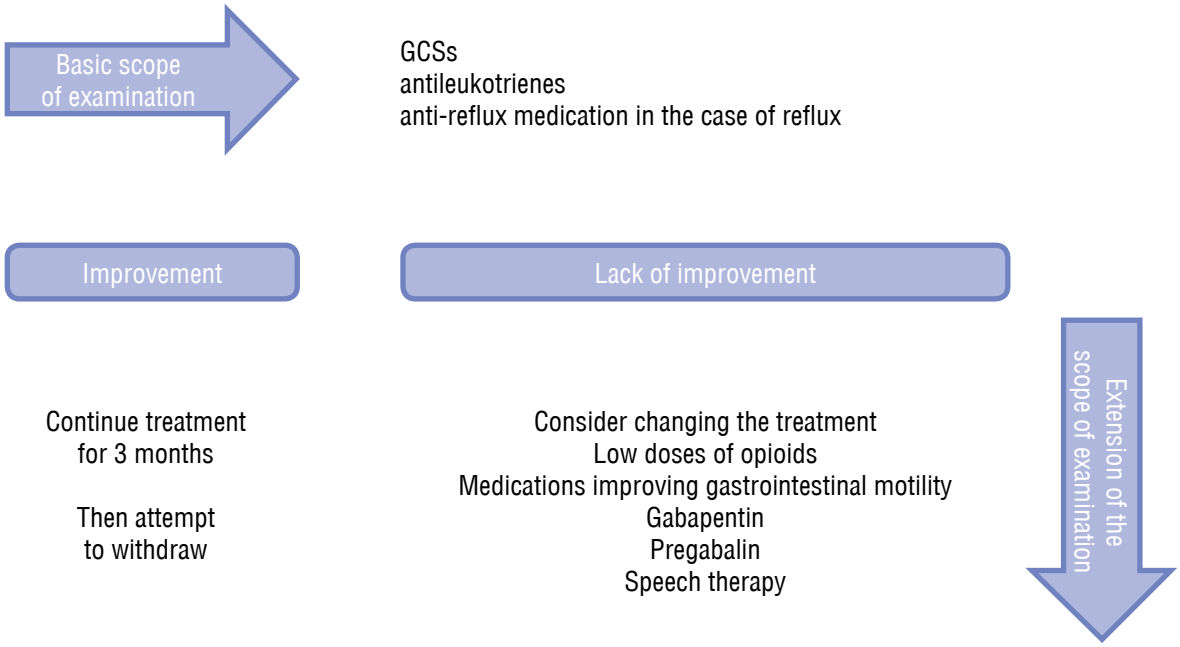


**Figure 2**. ERS-recommended regimen for the management of chronic cough

gnals are received mainly through the N-methyl-aspartate (NMDA), but also through γ-amino butyric acid binding (GABA) receptors. It is believed that a more thorough understanding of the central mechanisms may contribute to synthesizing new antitussive medications. In this context, understanding the physiology of cough becomes particularly important. At the same time, it seems that understanding the mechanisms of cough hypersensitivity, i.e. lowering the cough threshold in response to various factors, may also improve treatment results.

One of the mechanisms of cough hypersensitivity involves increased stimulation and excitation of the vagus nerve endings. Local, increased stimulation of C fibers by locally secreted cytokines whose receptors are also located at the endings of the vagus nerve (auto-excitation) has been suggested [9]. Pre-clinical trials indicate that the use of transient receptor potential vanilloid 1 (TRPV1) antagonist effectively inhibits the activation of the vagus nerve and stimulation of cough by capsaicin, prostaglandin E2 and bradykinin. At the same time, clinical trials involving TRPV1 antagonists did not confirm the expected effectiveness, which may suggest that an action involving only this mechanism may not be sufficient [7]. Receptor P2X is another potentially interesting therapeutic target. Clinical trials involving gefapixant — a P2X antagonist — are currently underway [10]. Other studies concern cough reflex transmission [7].

In the past, it was believed that in patients suffering from chronic cough without lesions in the region of the thorax the causes for the symptom should be sought in accordance with the 3R principle: reactivity of the bronchial tree (asthma, cough asthma, eosinophilic bronchitis), reflux, rhinitis. In a study conducted in the Netherlands, which involved an evaluation of nearly 10,000 individuals aged over 45 from a register kept in Rotterdam, chronic cough was diagnosed in 11% of patients. The risk of the occurrence of cough was significantly higher in patients diagnosed with asthma, COPD, chronic sinusits or reflux disease as well as active smokers [11]. Another factor that should be taken into account are the medications used by patients as ACE inhibitors and ACE receptor blockers increase sensitivity to stimuli that cause cough. It should be remembered that some patients (approx. 30% of women) diagnosed with chronic cough also suffer from cough hypersensitivity syndrome [6]. Cough hypersensitivity syndrome is defined as a condition in which cough constitutes the most important clinical component and is usually triggered by minimal levels of exposure [3]. Dysregulation both at the level of signal transmission and at the central level, including the cerebral cortex, is considered to be the leading mechanism [8].

Medications that are currently available are targeted at the above-mentioned mechanisms only to a small extent. In many cases, their effectiveness is not satisfactory and requires regular evaluation (Fig. 2). The optimal goal of antitussive treatment is to control hypersensitivity in the cough reflex while maintaining the protective role of cough. Understanding various phenotypes of refractory cough (RCC) and developing complex cough measurement methods are equally important to synthesizing new antitussive drugs.

It has been shown that patients do not always fully objectively assess the frequency and intensity of cough (especially in the case of cough occurring at night). American experts have recently published guidelines in which they recommended evaluating the impact of cough on patients' quality of life [12]. The evaluation is conducted with the use of questionnaires, such as: leicester cough questionnaire (LCQ) and cough-specific quality of life questionnaire (CQLQ) that are available in Polish [13]. Electronic cough monitors, most commonly the Leicester cough monitor (LCM), are recommended to evaluate cough frequency, while the capsaicin provocation test is recommended to assess the threshold of sensitivity to cough stimuli. In everyday practice, cough should be evaluated using at least visual-numeric scales.

## Treatment

### Anti-asthmatic medications — inhaled corticosteroids, antileukotrienes, LABAs

In some patients, chronic cough occurs as a consequence of an acute respiratory infection (post-inflammatory hyperreactivity), eosinophilic bronchitis, or is a symptom that accompanies asthma (also cough-variant asthma) or COPD. In such cases, it is suggested to implement a short (2–4 weeks) trial of inhaled corticosteroids (ICS), antileukotrienes or a combination of ICS and long-acting bronchodilators. It is a weak recommendation based on evidence with little scientific value [1]. The authors of the guidelines emphasize that such a trial provides the greatest benefits to patients with asthma. Trials investigating the use of ICS in patients with chronic cough are also associated with a significant response rate, also in the group of patients receiving placebo [14]. In the case of COPD, the authors of guidelines relied on one randomized trial that showed improvement in patients with cough after the administration of a combination of 500 $\mu$ of fluticasone and 50 $\mu$g of salmeterol.

## Guidelines of the European Respiratory Society

The ERS guidelines provide answers to 8 questions: the first two concerned diagnostic evaluation and the other 6 — treatment of chronic cough. The following are the answers to questions 3–7. Question 8 concerns the use of antibiotics in chronic productive cough in children.

Question 3

Should anti-asthmatic drugs be used in patients with chronic cough?

- It is suggested to implement a short-term (2–4 weeks) treatment with inhaled corticosteroids (ICS) — conditional recommendation, low quality of evidence. The available evidence suggests that a large dose of ICS can be more effective than small or medium doses.
- It is suggested to implement short (2–4 weeks) treatment with antileukotrienes, especially in "asthmatic" patients (conditional recommendation, low quality of evidence).
- Brief (2–4 weeks) therapy with a combination of inhaled GCSs and LABAs in patients with established obstruction is suggested (conditional recommendation, moderate strength of evidence).

The recommendations are largely consistent with the opinion of US pulmonologists regarding chronic cough in patients with asthma and non-asthmatic eosinophilic bronchitis (NAEB) [16]. For example, in the case of the cough-variant asthma, specialists recommend inhaled GCSs; if the patient responds partially or does not respond to the treatment at all, it is recommended to increase the dose of steroids, use antileukotrienes and combine inhaled GCSs and LABAs. The authors emphasize that other diagnoses should be considered very carefully in each case. The level of evidence for these recommendations is 1B. Similarly, in the case of NAEB, it is recommended to administered inhaled GCSs and increase the dose or introduce antileukotrienes in the case of an insufficient response, as well as consider an alternative diagnosis. The level of evidence for this recommendation is 2C.

Question 4

Should acid suppressants (proton pump inhibitors) and H2-receptor antagonists be used to treat patients with chronic cough?

- It is suggested that acid-reducing treatment (PPI and anti-H2) should not be used in chronic cough treatment in patients who were not diagnosed with reflux disease (conditional recommendation, low quality of evidence).

Oesophageal reflux is among the common causes of chronic cough, but in the absence of diagnosis and presence of dyspepsia symptoms, the use of acid-reducing medications does not result in resolution of chronic cough. Therefore, the authors of the ERS guidelines suggest that anti-reflux medications should not be administered routinely. They also indicate that proton pump inhibitors cause significant adverse reactions. Due to the lack of evidence, prokinetic drugs are not recommended.

Question 5

Should prokinetic medications (macrolides, other prokinetics) be administered?

- Insufficient evidence to make recommendations (conditional recommendation, low quality of evidence).

Currently, there is insufficient evidence to recommend routine administration of macrolide treatment in patients with chronic cough. In the case of chronic bronchitis that is resistant to other treatments, we can consider a month-long treatment with macrolides, taking into consideration local guidelines concerning antimicrobial drug management. No randomized trials involving medications stimulating gastrointestinal motility, such as baclofen, metoclopramide or domperidone, have been conducted in patients with chronic cough.

Question 6

Which neuromodulatory medications should be administered?

- The authors recommend low doses of opioids: 5–10 mg twice a day (strong recommendation, moderate quality of evidence).
- It is suggested to try gabapentin or pregabalin (conditional recommendation, low quality of evidence).

### Neuromodulatory medications

The authors of the guidelines ask which neuromodulatory medications (i.e., opioids, pregabalin, gabapentin and tricyclic antidepressants) should be used in the treatment of chronic cough. For many physicians who do not work in the field of palliative medicine, a strong recommendation to use orally administered controlled-release opioids is significant in their everyday practice. A number of studies, including studies conducted in Poland, indicate that pulmonologists have concerns about prescribing opioids [17]. However, it is worth emphasizing that this recommendation is based on scientific evidence of moderate quality. Experts recommend administering a daily dose of morphine (5–10 mg up to twice a day) in slow-release products. Treatment should begin with the lowest dose available, and a daily dose of 30 mg should not be exceeded. Opioid treatment should be discontinued if no improvement is observed after 7–10 days. Clinical trials have shown that response to treatment is observed in about 50% of patients. Long-term administration of codeine is not recommended due to individual, genetically determined variants of CYP2D6 metabolism and adverse effects of the treatment [1].

The recommendation is based on a small number of trials involving pregabalin and gabapentin. The authors of the ERS guidelines suggest that the above-listed medications should not be used for more than 10 days if there is no improvement. Gabapentin doses should not exceed 1,800 mg per day and pregabalin doses should not exceed 300 mg per day [1]. The treatment should always begin with gradually increased doses (e.g., the minimum time to reach the dose of 1,800 mg of gabapentin should not be less than 7 days), should be conducted by a person with experience in this type of treatment and should be compliant with SmPC. Both medications can cause the following adverse effects: dizziness, drowsiness, ataxia, seizures, hyperkinesia, dysarthria, amnesia, tremor, insomnia, headache, sensory and coordination disturbances, nystagmus, exaggeration, diminishment, or loss of reflexes, and viral infections.

Question 7

Should non-pharmacological therapy (speech therapy, physiotherapy) be used to treat patients with chronic cough?

- The guidelines suggest a trial of non-pharmacological methods in patients with chronic cough (conditional recommendation, moderate quality of evidence).

## Physiotherapy, speech therapy — teaching patients to control cough

For over a decade, physiotherapy and speech therapy have been drawing interest as methods that can be used in patients with chronic cough that persists despite causal treatment or occurs due to an unknown cause. The European guidelines suggest a trial of such a therapy, although this recommendation is conditional, mainly due to the lack of scientific evidence [5]. One meta-analysis contains only two trials that involved a total of 162 patients. The authors emphasize the beneficial effect of the intervention (PSALTI, physiotherapy and speech and language therapy intervention) on quality of life and reduction in the number of coughing incidents per day, however, the effect was not long-lasting and persisted for approximately 4 weeks after the completion of the trial [18]. The lack of structured programs and the limited availability of the method in many countries constitute additional complications.

Analysing the available programs, authors from Portugal proposed a structured, four-week therapy program for the management of chronic cough (TMCC) with 30–45-minute sessions. The program is composed of three elements: the first one is counselling on cough and proper laryngeal function, the second — cough suppression, control and reduction techniques, and the third comprises pulmonary and laryngeal methods of controlling breath, cough and phonation [19]. Preliminary results of a program that includes speech physiotherapy components similar to those proposed by experts from Portugal were published by authors from Warsaw [20]. In a group of 15 patients, the authors obtained a significant re-

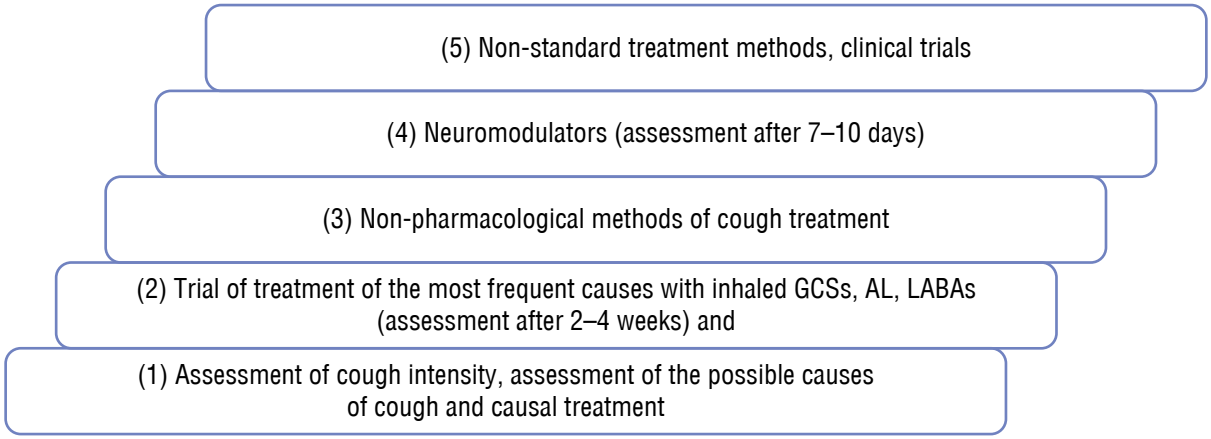


**Figure 3**. Treatment ladder for patients with chronic cough

duction in the frequency of cough measured by the visual analogue scale (VAS), improved quality of life and, importantly, a significantly increased threshold of sensitivity to cough stimuli, measured by the capsaicin provocation test.

## Antitussive medication administration regimen — treatment ladder

As in the treatment of pain and dyspnoea, the development of a therapeutic ladder can be considered in the case of chronic cough (Fig. 3). Currently available treatments make it possible to achieve a therapeutic effect in only a fraction of patients. Significant opportunities in improved treatment of chronic persistent cough, despite treatment for the underlying cause or of unknown cause, are seen in new groups of drugs such as transient receptor potential channel antagonists or P2X3 receptor antagonists. A second phase clinical trial with a selective TRPV4 antagonist (GSK2798745) was terminated early due to the lack of treatment efficacy [21]. A second phase clinical trial involving gefapixant — a P2X3 receptor blocker — revealed that it showed significant efficacy in cough suppression and a good safety profile. Trials involving voltage-gated sodium channel blockers, new neuromodulators and neurokinin-1 receptor antagonists are underway. Lignocaine (a non-selective blocker of voltage-gated sodium channel) administered by spray or nebulization has been effective in treating refractory chronic cough [22].

## Treatment of cough in patients receiving palliative care

Causes of cough in patients receiving palliative care are usually the same as in the general population. It is assumed that approximately 20–40% of patients staying at palliative medicine units are suffering from cough. In some patients, cough (especially with increased expectoration) may be a symptom of an exacerbation of a comorbid condition (COPD or bronchiectasis) or acute pneumonia that can be effectively treated. Cough can also be caused by other conditions that can be treated causally, such as gastroesophageal reflux disease or adverse effects of medications, for example angiotensin-converting-enzyme inhibitors. It can be caused by tumours of the lung, pleura, and mediastinum or metastases to the chest [24]. Cough occurs in 90% of patients with advanced lung, head and neck cancer [25]. In palliative care patients with cystic fibrosis or other lung diseases, chronic infections can contribute to the occurrence of cough, especially during exacerbations, in which case antibiotics are a useful treatment method.

In some conditions with concomitant cough (radiation pneumonitis, pulmonary lymphangiosis, lung parenchymal damage after chemotherapy or radiation therapy), systemic steroids constitute the first-line treatment. It also concerns patients suffering from cough in advanced diseases. Empirically, treatment with systemically administered steroids at a dose of 20–40 mg per day, equivalent to prednisone, is applied for a period of approx. 2 weeks. Dexamethasone at a daily dose of 8 mg is used in everyday clinical practice to reduce inflammation and swelling around tumours. So far, however, no clinical studies in this area have been conducted. If the treatment is ineffective, it should be discontinued after several days to avoid late adverse effects [23].

Specific causes of cough in patients receiving palliative care include ineffective swallowing. The cough reflex is triggered by attempts to remove the accumulated secretions due to muscle weakness and inability to coordinate effective swallowing. In the final hours and days of life, cough may occur in 80% of patients;

contributing factors include asthenia, muscle weakness as well as increased secretion in the airways. Apart from other symptomatic therapies, anticholinergic treatment can be administered to reduce the production of bronchial secretions, thereby reducing the intensity of coughing [24]. It should be emphasized that medications that are currently recommended by the ERS for the treatment of cough that persists despite standard treatment show limited efficacy.

Treatment of cough in patients receiving palliative care frequently involves off-label medications, the efficacy of which has not been clearly demonstrated in controlled clinical trials yet. A quick antitussive effect can be provided by paroxetine, usually administered at a dose of 10 mg [27], as well as furosemide [28] and lignocaine administered by nebulization [29].

## Summary

Treatment of chronic cough is a therapeutic challenge. In each case, it should be considered whether all potential causes of cough have been identified and appropriate therapy has been administered. The severity of symptoms should also be assessed. The decision on the appropriate symptomatic management to reduce cough intensity should always be made after detailed consideration of the clinical context (e.g., administration of inhaled steroids is not recommended in patients with airway colonisation with pathogenic bacteria and frequent pneumonia) and with full knowledge that the therapy is on a trial basis. If improvement is not achieved, the selected treatment should be abandoned. The potential side effects that may cause additional suffering and impair patients' quality of life, such as constipation while using morphine, should also be considered. It should also be noted that drugs recommended or suggested for the treatment of chronic cough are mostly not licensed for this indication.

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The authors declare that there is no conflict of interest.

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