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Recommendations

Guidelines for the management of chronic cough in adults. Endorsed by the French speaking society of respiratory diseases (*Société de Pneumologie de Langue Française*, SPLF), the *Société Française d'Oto-Rhino-Laryngologie et de Chirurgie de la Face et du Cou* (SFORL), the *Société Française de Phoniatrie et de Laryngologie* (SFPL), the *Société Nationale Française de Gastro-entérologie* (SNFGE)

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ABSTRACT

Patients with chronic cough experience a high alteration of quality of life. Moreover, chronic cough is a complex entity with numerous etiologies and treatments. In order to help clinicians involved in the management of patients with chronic cough, guidelines on chronic cough have been established by a group of French experts. These guidelines address the definitions of chronic cough and the initial management of patients with chronic cough. We present herein second-line tests that might be considered in patients with cough persistence despite initial management. Experts also propose a definition of unexplained or refractory chronic cough (URCC) in order to better identify patients whose cough persists despite optimal management. Finally, these guidelines address the pharmacological and non-pharmacological interventions useful in URCC. Thus, amitryptilline, pregabalin, gabapentin or morphine combined with speech and/or physical therapy are a mainstay of treatment strategies in URCC. Other treatment options, such as P2 × 3 antagonists, are being developed.

Abbreviations: ATP, Adenosine triphosphate; CQLQ, Cough quality-of-life questionnaire; ICS, Inhaled corticosteroids; DLCO, Diffusing capacity for carbon monoxide; TPE, Therapeutic patient education; VAS, Visual analog scale; HAS, Haute autorité de santé (French Health Authority); ACEI, Angiotensin-converting enzyme inhibitor; PFT, pulmonary function test; FeNO, Fractional exhaled nitric oxide; PPI, Proton pump inhibitors; LCQ, Leicester Cough Questionnaire; CPAP, Continuous positive airway pressure; GERD, Gastroesophageal reflux disease; CRS, Chronic rhinosinusitis; OSAS, Obstructive sleep apnea syndrome; SCS, Somatic cough syndrome; UACS, Upper airway cough syndrome; TBM, Tracheobronchomalacia; URCC, Unexplained or refractory chronic cough; TRP, Transient receptor potential; UA, Upper airways

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Introduction

Cough is triggered by the activation of a reflex arc aiming at protecting the airways from the intrusion of a foreign body. This is a defense mechanism very useful to the body to preserve the functioning of the respiratory tract [1]. When cough exceeds its protective function, it is perceived as a noisy and disturbing symptom leading to disability for patients. Cough is such a common symptom in the general population and is one of the most common reasons for consultation in general medicine [2]. Acute cough following viral infection accounts for a large part of these consultations [3]. This type of cough is most often transient and require no assessment. However, some patients experience chronic cough with no spontaneous resolution for which a specific management is required. In order to define the most appropriate management of chronic cough, guidelines for clinical practice have been developed by the French speaking societies.

Method

The working group conducted a systematic review of the literature for each question in order to identify and summarize current evidence regarding the management of chronic cough. Pubmed MEDLINE and Embase databases, and Cochrane Central Register of Controlled Trials were consulted using the keywords "cough" or "chronic cough" in order to retrieve relevant articles published between January 1985 and December 2021. Only publications written either in French or English were selected. The proposed guidelines were classified as grade A, B, or C according to a decreasing level of scientific evidence, in accordance with the guide conceive to analyze literature and grading guidelines published by ANAES (January 2000) (Table 1). All other proposals should be considered as narrative statements based on a professional agreement. For the latter, the formulation used was transcribed as follows: "The experts suggest that clinicians. . .". After the formulation of these guidelines, an independent board reviewed and corrected them.

What is the definition of chronic cough and refractory chronic cough and their epidemiology?

Definition and epidemiology of chronic cough

Cough is defined as a sudden and noisy expulsion of air from the lungs, caused by airway irritation. Chronic cough is mainly mentioned based on patients' anamnesis. Patients sometimes present cough at the time of the consultation and it contributes to establish the diagnosis of chronic cough. However, the absence of cough during the consultation should not rule out chronic cough diagnosis, as this disorder fluctuates over time [4]. During the anamnesis, it is important to differentiate chronic cough from hemming (throat clearing) being often called "cough" by patients.

The definition of chronic cough is unanimous in the recent medical literature. Indeed, according European [5] and American [6] guidelines, chronic cough is defined as cough lasting 8 weeks or longer. This duration has been chosen arbitrarily, but it leads to differentiate acute from chronic cough. Indeed, acute cough is mostly due to viral infection and is characterized by a less-than 3-weeks duration. This distinction in clinical practice is important because the management of chronic cough differs from that of acute cough. For these reasons, the expert group believes that French practices need to be harmonized with international practices (Table 2).

Although chronic cough is not included in the International Classification of Diseases 10th Revision (ICD-10), many experts consider that this disorder should be identified as a disease itself with its own phenotypes, causes and management [5]. If the perception of the disease is altered, we assume that it might contribute to improve the management of patients with chronic cough patients (Table 2).

A 2015 meta-analysis of 90 studies has shown an overall prevalence of chronic cough of 9.6% worldwide [7]. Three studies have used the 8-week consensus definition and found a prevalence of 12% in the UK, 2.2% in Japan and 1.1% in Nigeria, respectively [8–10]. There is a clear geographical disparity worldwide with a higher prevalence in Europe and the United States compared to Asia and Africa.

Table 1
Correspondence between the literature assessment and guidelines grade(grid adapted from the Sackett score).

Strength of guidelines	Level of scientific evidence provided by the literature
Grade A	High-powered randomized comparative trials
	Meta-analysis of randomized comparative trials
	Decision analysis based on well-conducted studies
Grade B	Low-powered randomized comparative trials
	Well-conducted non-randomized comparative studies
	Cohort studies
Grade C	Case-control studies
	Comparative trials with historical series
	Comparative studies with significant biases
	Retrospective studies
	Case series
	Descriptive epidemiological studies (cross-sectional, longitudinal)
Professional agreement	Any other publication (case report, expert opinion)
	Lack of publication

Table 2
Summary of guidelines for the definition of chronic cough.

	Guidelines	Grade
Guideline 1	The experts suggest that chronic cough is defined as a cough lasting 8 weeks or longer	Professional agreement
Guideline 2	The experts suggest that clinicians do not rule out the diagnosis of chronic cough if the patient does not cough at the time of consultation	Professional agreement
Guideline 3	The experts suggest that clinicians identify chronic cough as a disease and not as a symptom and to present it as such to patients	Professional agreement
Guideline 4	The experts suggest that clinicians use the terminology "refractory or unexplained chronic cough (URCC)" for chronic cough that does not improve despite adequate management	Professional agreement
Guideline 5	The experts suggest that URCC should be defined as chronic cough that has been adequately monitored for at least 6 months and it meets one of the following criteria: - No identified cause despite an extensive clinically-oriented investigation, including at least exhaustive anamnesis, ENT nasofibroscopy, chest X-ray and spirometry. - Or absence of cough improvement despite the management of clinically obvious causes of chronic cough.	Professional agreement
Guideline 6	The experts suggest that clinicians should investigate, during anamnesis of a patient with chronic cough, the features of cough hypersensitivity syndrome, in particular triggering factors for cough suggestive of hypertussia or allotussia	Professional agreement

In France, few data are available. A recent study conducted in 15,152 subjects has shown a 4.8% prevalence of self-report chronic cough in the past 12 months [11]. Among these patients, 41% reported being diagnosed with chronic cough by a health care provider and 28% of diagnosed patients underwent any cough treatment.

Unexplained or refractory chronic cough (URCC)

Definition. The main problem in the management of chronic cough is the difficulty to identify the etiology of the disorder. Indeed, depending on the study, the rate of patients with chronic cough with no obvious cause despite investigations varies from 1 to 46% [12–25]. This variability is due to the fact that the definition of unexplained cough differs from one study to another. In addition, despite the identification of the most common cough causes, its treatment is not always associated to cough improvement. In the English literature, the term "Refractory or Unexplained Chronic Cough" is used to describe chronic cough for which either no cause is identified or causes treatment fail to improve cough [5,6,26,27]. There is currently no international consensual definition of refractory or unexplained chronic cough, even though it is a major concern in clinical practice. The identification of this entity is a crucial step both for patients to identify their disorder and for physicians to initiate a specific management.

The expert group proposes the following definition (Table 2):

Refractory or unexplained chronic cough is a chronic cough that has been adequately monitored for at least 6 months and it meets one of the following criteria:

- No cause identified despite an extensive clinically-oriented investigation, including **at least** exhaustive anamnesis, ENT nasofibroscopy, chest X-ray and spirometry.
- Or absence of cough improvement despite optimal management of clinically common causes of chronic cough.

Cough hypersensitivity syndrome. The concept of cough hypersensitivity syndrome has been recently introduced to explain the failure to identify etiologies despite investigations in a number of patients or the persistence of chronic cough despite optimal management of the suspected etiologies [28]. Cough hypersensitivity syndrome is therefore an entity allowing explaining the mechanisms of some URCC. In cough hypersensitivity syndrome, there is an increased sensitivity to low-level tussigenic stimuli (hypertussia) or cough-triggering by non-tussigenic stimuli (allotussia) (Table 3). For this reason, cough is often absent at night because the receptors are not stimulated during sleep. The clinical features of cough hypersensitivity are detailed in Table 3 [29]. The mechanisms are unclear, but might involve a hypersensitivity of cough receptors [28]. Women aged 50–60 years seem to be predominantly affected by this entity [30].

Table 3
Features of chronic cough hypersensitivity. Currently, there is no tool to confirm the diagnosis of cough hypersensitivity. The symptoms listed in this table have been described as being associated with cough hypersensitivity but are not specific to this diagnosis. According to Chung et al. [29].

Features of chronic cough hypersensitivity
1 Upper airway irritation (larynx, pharynx), upper airway paresthesias
1 Cough triggered by non-tussigenic stimuli (allotussia): talking, laughing
1 Increased sensitivity of cough to inhaled stimuli (hypertussia)
1 Difficult-to-control paroxysmal cough
1 Triggering factors:
- Singing, talking, laughing, deep breathing: mechanical activation
- Temperature change, cold air: thermoactivation
- Aerosols, perfumes, fragrances: chemoactivation
- Supine position
- Meals
- Exercise

What is the initial management of chronic cough?

The initial management of chronic cough is to assess the impact of cough on patients' quality of life, to identify serious causes of chronic cough, and to manage its common causes (Fig. 1).

Assessment of chronic cough

Chronic cough has a major impact on patients' quality of life (Table 4). Patients express the severity of their cough according to 3 criteria: cough frequency, cough intensity and its impact on their daily life (poor sleep quality, inability to perform some activities) [31]. In most cases, physical complications are secondary due to an increase in intrathoracic and intra-abdominal pressure [32]. Sleep disorders in case of nocturnal cough, fatigue, headache, vomiting and sometimes even rib fractures are typical complications. Urinary incontinence, which may affect up to 50% of chronic cough patients, has a significant impact on the daily life [33]. Women with chronic cough are particularly affected, with 63.3% of cases reporting episodes of bladder weakness when coughing [34]. Moreover, social disability is the most common source of disability in patients with chronic cough [35] and the consultation is often prompted by a complaint about recurrent cough from relatives [36]. Thus, social disability seems to affect about 80% of patients and a third of the chronic coughers aged under 65 years had to sleep in a separate room because of their cough [36]. Due to this noisy and potentially disturbing symptom in everyday life (places of worship, library, theater, family meals), patients prefer to avoid some activities which have a major impact on their quality of life. Psychological complications are also very common and, depending on the study, depression criteria are observed in 15.8–53% of chronic cough patients [37,38].

In practice, cough assessment seems to be essential to determine its impact, discuss treatment initiation and assess treatment efficacy. An objective assessment based on cough recording may be useful. However, the devices that measure cough frequency are not widely used in clinical practice, although they are very efficient [39,40]. This is the gold standard for assessing treatment response [41] (Table 4).

The subjective assessment is based on the use of a visual analog scale (VAS), as this tool is easy to use in clinical practice (Table 4). The cough VAS appears to correlate moderately with objective measurements [42], but it is an interesting tool for the assessment of a treatment response [43–46]. A decrease by 17 mm is considered the minimum clinically relevant value for assessing treatment response in acute cough, but no data are available for chronic cough [47]. The Leicester Cough Questionnaire (LCQ) is a 19-item questionnaire using a 7-point Likert scale [48]. Overall, the LCQ correlates moderately with other objective or subjective measurements, but is a reliable tool for assessing the impact of cough and treatment response [46]. A score increased by 1.3–2 is considered the minimum clinically relevant value to assess treatment response (the maximum score is 7) [49,50]. Although LCQ has not been widely validated in French, a French version can be used in some cases to assess cough [51]. Regarding the Cough Quality-of-Life Questionnaire (CQLQ) and the Adverse Cough Outcome Survey (ACOS), both are too complex to be used in routine clinical practice.

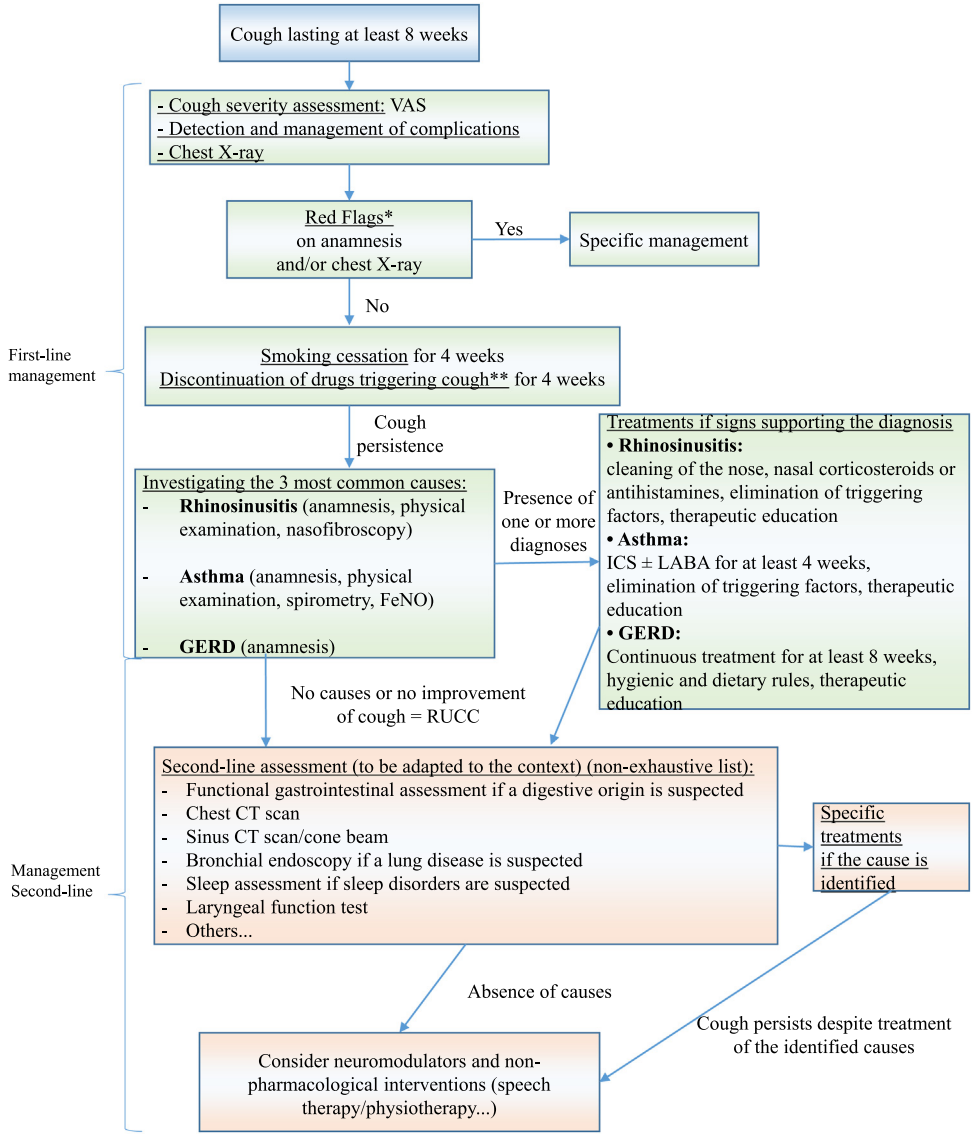

Fig. 1. First line management algorithm of chronic cough. *see Table 1, **after consulting the prescriber. ICS: inhaled corticosteroids, LABA: long-acting beta agonists, FeNO: fractional exhaled nitric oxide, GERD: gastroesophageal reflux disease, URCC: unexplained or refractory chronic cough.

Identification of severe etiologies of chronic cough

Cough is a symptom that may reveal a neoplastic disease, a severe chronic lung disease or a cardiac disease. For example, cough is observed in 23–37% of patients with all-site cancers and 47–86% of patients with lung cancer [52]. There is no existing robust data in the literature on features that should be used to detect severe disease. However, red flags have been published in the 2006 French consensus conference [53] and are summarized in Table 5.

Management of triggering factors

Some drugs, such as angiotensin-converting enzyme inhibitors (ACEIs), may trigger cough even after several years of use (Table 4). In fact, the involvement of ACEIs in the onset of cough has been well documented in large studies [54]. Moreover, angiotensin II receptor blockers are less involved in chronic cough than ACEIs [55]. It is well established that cough mostly occurs within the first 6 months. However, it may appear later [56,57]. When the drug is discontinued, cough often resolves within 4 weeks [58,59]. Regarding gliptins, they have been suspected as potential cause of cough, but scientific evidence is still lacking [60].

An exposure to tobacco smoke increases the risk of developing chronic cough (Table 4). In a Swiss study, the prevalence of chronic cough was 3.3% in non-smokers, 3.0% in former smokers and 9.2% in active smokers, respectively [61]. Passive smoking is also associated with cough [62]. In addition, smoking cessation has been shown to be an effective intervention for improving cough [63]. About 50% of cases improve within 4 weeks and a clear reduction or disappearance is observed in 94–100% of patients [64]. In a large Danish study (2408 smokers), smoking cessation or reduction significantly improved cough [65]. It should be noted that increased cough may be observed during smoking cessation [66,67]. The temporary use of the e-cigarette to avoid smoking resumption should be discussed on a case-by-case basis whether cough appears to be very disturbing/annoying [68]. Furthermore, using an e-cigarette may also lead to cough.

In adults, the mean duration of cough in case of pertussis is 42 days (range: 27–66 days) [69]. Therefore, pertussis is not a typical cause of chronic cough (Table 4).

Table 4
Summary of guidelines for the first-line management of chronic cough.

	Guidelines	Grade
Guideline 7	It is recommended to question patients with chronic cough about physical, social and psychological complications	Grade B
Guideline 8	It is recommended, when possible, to use an objective measurement of cough in patients with chronic cough	Grade B
Guideline 9	The experts suggest that clinicians should use a subjective assessment of cough at the onset and during the follow-up of all patients with chronic cough (VAS, LCQ…)	Professional agreement
Guideline 10	The experts suggest that clinicians should seek for the presence of red flags suggestive of a severe disorder in case of chronic cough. A diagnostic and therapeutic management is then chosen depending on the disorder.	Professional agreement
Guideline 11	It is recommended to determine if cough-inducing drugs could be triggering factors and to reassess cough 4 weeks after their discontinuation.	Grade A
Guideline 12	It is recommended to offer smoking cessation assistance to smoker patients with chronic cough. At least 4 weeks are needed to see the benefits of smoking cessation on chronic cough. In the absence of smoking cessation, reducing tobacco consumption is also a useful intervention to reduce cough	Grade A Grade A
Guideline 13	It is not recommended to perform pertussis PCR or serology in case of chronic cough	Grade B
Guideline 14	The experts suggest that clinicians perform chest X-ray as a first line of patients with chronic cough	Professional agreement
Guideline 15	It is recommended to investigate the presence of respiratory symptoms that may lead to the diagnosis of asthma in case of chronic cough	Grade A
Guideline 16	It is recommended to perform spirometry with a bronchodilator reversibility test in case of chronic cough with or without symptoms suggestive of asthma	Grade A
Guideline 17	The experts suggest that clinicians measure the fractional exhaled nitric oxide (FeNO) in case of chronic cough, if the equipment is available, to determine whether inhaled corticosteroids should be initiated.	Professional agreement
Guideline 18	It is recommended to initiate trial treatment with inhaled corticosteroids for at least 4 weeks in all chronic cough patients in the absence of any obvious etiology	Grade A
Guideline 19	It is recommended to initiate background treatment according to the current guidelines in case of asthma-like cough (asthma characterized by isolated cough).	Grade B
Guideline 20	In patients with chronic cough, the use of inhaled β2-mimetics, inhaled anticholinergics or anti-leukotrienes combined with inhaled corticosteroids is possible with a small effect on cough	Grade B
Guideline 21	In the context of chronic cough, anti-reflux treatment is only justified if clinical symptoms of reflux (heartburn, regurgitation) are present. If an anti-reflux medication is initiated, hygienic and dietary interventions may be combined	Grade A Grade C
Guideline 22	In the presence of symptoms suggestive of upper airway cough syndrome (UACS), it is recommended to initiate trial treatment combining the cleaning of the nasal cavities with physiological serum and nasal corticosteroids	Grade B
Guideline 23	Apart from allergic rhinitis, it is not recommended to use an antihistamine to treat upper airway cough syndrome (UACS)	Grade B
Guideline 24	Given their safety profile, it is recommended not to use decongestants to treat upper airway cough syndrome (UACS)	Grade C
Guideline 25	The experts suggest the clinicians refer the patient to an ENT specialist in case of refractory or unexplained chronic cough	Professional agreement
Guideline 26	The experts suggest that clinicians perform a morphological and functional examination of the pharyngolarynx during an initial ENT consultation for chronic cough assessment	Professional agreement
Guideline 27	The association of cough with food intake and/or symptoms suggestive of swallowing disorders and/or a pathological disorder likely to impair the pharyngolaryngeal function should prompt a specialized swallowing examination	Grade C

Table 5
Red flags for which a severe disease should be considered in a patient with chronic cough. Adapted from the 2006 guidelines [53].

Red flags for which a serious disease should be investigated
- Impaired general condition,
- Recurrent infectious syndrome,
- Exertional dyspnea,
- Hemoptysis,
- Cough appearance or change in cough in a smoker,
- Dysphonia, dysphagia, swallowing the wrong way,
- Suspected cervical adenopathy,
- Abnormal cardiopulmonary clinical examination,
- Abnormal ENT clinical examination,
- Abnormal chest x-ray.

Chest X-ray

Chest X-ray is internationally considered as an essential first-line test for chronic cough [5,6]. The level of evidence regarding its usefulness in chronic cough is low [19,70]. To date, no study has investigated the impact of chest x-ray on the management of chronic cough yet. Given its ease of access and the possibility of detecting certain lung diseases, it is potentially interesting and it consists in a simple examination for the first-line management of chronic cough (Table 4). In case of abnormal lung auscultation or red flags as described above, a chest CT scan should be performed as part of first-line examination (see guideline 28).

Management of common causes of chronic cough

Asthma. Cough is included in the definition of asthma [71] and should therefore be considered along with the other respiratory symptoms characteristic of the disease (dyspnea, wheezing, chest tightness) if changes over time and in intensity, their worsening at night, on exertion, after an occupational exposure or an exposure to allergens or cold, in case of viral infection are suggested on patients' anamnesis (Table 4). In case of chronic cough, the diagnosis of asthma is frequent with a prevalence of 20–30% in non-smokers [72]. Its clinical likelihood should be assessed (see SPLF guidelines for asthma) [73], considering that, in adults, the presence of isolated cough is atypical in asthma.

Even when symptoms suggestive of asthma are present, spirometry performed before and after inhalation of a short-acting β2-mimetic by the patient is needed to ascertain the diagnosis [74] (Table 4). These measurements allow identifying an airway obstruction and determining its severity and reversibility. A significant reversibility is defined as an increase in FEV1 >200 mL or in FVC ≥12% from baseline after inhalation of a short-acting bronchodilator [74]. The absence of reversibility during a PFT does not rule out the diagnosis of asthma and its presence only confirms it if the symptoms are compatible and the reversibility is complete. A methacholine challenge test may then be discussed (see below).

Measuring the fractional exhaled nitric oxide (FeNO) to detect type 2 airway inflammation may allow predicting a favorable response to inhaled corticosteroids (ICS) and guiding both second-

line investigations and treatment in patients with chronic respiratory symptoms [75–79] (Table 4). It may be useful in the initial management of patients with chronic cough, as shown in a French study, where 86% of patients with FeNO ≥25 ppm responded to ICS [78]. Other studies have obtained similar results regarding FeNO thresholds ranging between 30 and 50 ppm [80–82], suggesting the need to conduct controlled trials to assess optimal FeNO thresholds in patients with chronic cough.

The effect of ICSs has been shown on chronic cough in patients with asthma [83]. In an unselected population of patients with chronic cough, the effects appear heterogeneous across studies [45,84-86]. In a meta-analysis of 9 studies, ICSs had a significant but modest effect on the reduction of cough severity reduction in patients with chronic cough [87]. Daily background treatment with ICSs for at least 4 weeks seems necessary.

A modest effect on cough has been found with other therapies such as long-acting β2-mimetics [88], anticholinergics [89] or anti-leukotrienes [90,91] (Table 4).

Gastroesophageal reflux disease (GERD). Cough is one of the extraesophageal symptoms of GERD, especially according to Montreal classification [92]. The association is potentially bidirectional, as reflux may be at the origin of cough (cough reflex sensitization and/or microaspiration), and cough may itself induce the occurrence of reflux episodes. While pathophysiological mechanisms are documented, the strategy for determining the possible involvement of GERD in a patient followed for chronic cough remains difficult. Recently, several guidelines have been proposed by international respiratory societies. The following proposals have been performed based on the literature, guidelines and collaborative work over the past 5 years [6,93-98].

In the context of chronic cough, the presence of clinical symptoms of reflux (Heartburn, regurgitation) suggests the need for appropriate anti-reflux treatment. Therefore, the indication for an endoscopic examination should follow the specific guidelines for reflux. Both disorders may coexist independently. However, in the context of chronic cough with symptoms of GERD, GERD treatment duration should be increased to 8 weeks, as controlling cough requires more time than for other symptoms related to GERD [99].

Apart from clinical symptoms of reflux, GERD should not be considered as a common cause of chronic cough. This position is in line with Cochrane reviews, which found no sufficiently robust association to justify the use of PPIs in chronic cough in the absence of clinical signs of reflux [100,101] (Table 4). This position, strengthened by the overprescription of PPIs and the potential risks of their long-term use, has been adopted by most international guidelines on cough.

Drug treatment for GERD may be combined with overweight control and hygienic and dietary rules in GERD (including elevating the head from bed and respecting a long interval (>3 h) between meals and the supine position) [102] (Table 4).

Chronic rhinosinusitis. Chronic rhinosinusitis (CRS) with or without polyps is defined by the presence of at least two symptoms: nasal obstruction or anterior or posterior rhinorrhea associated or not with facial heaviness and/or partial or total reduction in smell for more than 12 weeks [101]. There is no clear definition of posterior nasal discharge and its physiology and pathophysiology remain unclear: it could be defined as a feeling of discharge behind the nasal cavities in the pharynx. It may be objective as in chronic sphenoid rhinosinusitis [103] or subjective and non-specific outside of any pathological context. It leads to hemming, a throat clearing effort as if to clear the voice and the larynx, a very different behavior from a coughing effort, but sometimes assimilated by patients. This semiology is very common in the general population and cannot be interpreted without performing fibroscopy of the upper airways from the nasal cavities to the larynx. It is poorly specific and in most cases, it reflects a subjective posterior nasal discharge, i.e., not related to a pathophysiological explanation. In this case, the CT scan has a low yield, because any naso-sinusal opacities can only be meaningful if it is placed in their clinical and endoscopic context. They may be incidentalomas (non-pathogenic endosinusal mucosal opacity found in 50% of asymptomatic subjects in the general population) [104] or a pathological inflammatory context while the images alone are not discriminating.

In the nosological context of CRS, concomitant cough is most often part of an impaired nose-bronchi relationship (polyposis and asthma, sarcoidosis, granulomatosis with polyangiitis [eosinophilic or non-eosinophilic]. . .) because the pathophysiology is expressed throughout the respiratory tree. In this context of active naso-sinus inflammation with purulent posterior discharge, 89% of patients complain of posterior nasal discharge while it is objective. Only 9% of patients experience purulent posterior nasal discharge associated with cough in the absence of concomitant bronchial etiologies [105].

The term “upper airway cough syndrome” (UACS) is used to describe rhinosinus disorders leading to chronic cough [106]. The use of physiological serum for nose cleaning has shown its efficacy in reducing chronic cough in UACS according to data from small studies [107] (Table 4). Nasal corticosteroids have also appeared to be effective in reducing chronic cough in UACS according to data from small studies [108,109]. Apart from allergic rhinitis, the efficacy of antihistamines has not been proven in UACS [110] (Table 4).

Since cough is an airway protection reflex involving the pharyngolaryngeal area, a thorough anatomical and functional examination of this area should be performed. The structural examination of the pharynx and larynx should rule out an organic cause of cough (tumor, infection). The functional examination, and in particular the laryngeal and phoniatric one, is intended to rule out a motor and/or sensitive [111] or functional cause [112]. This implies an assessment of the pharyngo-larynx by nasofibroscopy with instructions related to the main functions involved: breathing, swallowing, speech, effort with closed glottis, voluntary coughing.

It will be guided by the anamnesis. Thus, the relationship between swallowing disorders and cough being well established [113], any complaint or associated disease suggestive of a possible swallowing disorder will justify a swallowing test under nasofibroscopy [114]. In case of doubt, a specialized phoniatric and/or neurological assessment should be requested.

The areas innervated by the vagus nerve should be carefully assessed to identify a trigger zone (e.g., pharyngolaryngeal papilloma, auricular foreign body, etc.), that when detected (although rare), allows an easy management [115] (Table 4).

What are the second-line tests in chronic cough?

The list of tests presented below is neither systematic nor exhaustive. These tests should be performed according to the context. These tests are presented independently of each other with no hierarchical order of prescription.

Chest CT scan

The impact of chest CT scan on the management of chronic cough has been sparsely investigated in the literature. A retrospective study conducted in 59 chronic cough patients has shown the presence of relevant abnormalities to explain chronic cough on chest CT scans in 36% of patients [116]. In another study, 59% of chronic cough patients showed abnormalities on chest CT scans [117]. In a recent retrospective study in 595 chronic cough patients with normal physical examination and chest X-ray, only 30 (5.0%) patients underwent examinations or were treated based on CT-scan findings [118]. In addition, chest CT had an impact on cough management and cough improvement in only 3.0% and 1.5% of patients, respectively (Table 6). It is therefore not possible to formulate guidelines on the value of chest CT regarding the management of chronic cough. It seems to be mandatory in case of suspected lung diseases (respiratory symptoms

Table 6
Summary of guidelines for the second-line assessment of chronic cough.

	Guidelines	Grade
Guideline 28	The experts suggest that clinicians perform a chest CT scan in patients with chronic cough associated with abnormal lung auscultation or red flags suggestive of neoplasia. In other cases, its usefulness should be assessed on a case-by-case basis. In a context of refractory chronic cough, if a CT scan is performed, the experts propose to perform it during inspiration and expiration	Professional agreement Professional agreement Professional agreement
Guideline 29	Plethysmography should be performed and/or DLCO should be measured in case of underlying lung disease or suspected underlying lung disease.	Professional agreement
Guideline 30	The experts suggest that clinicians do not to systematically perform a methacholine challenge test in case of chronic cough, even if it is refractory. This test should be performed on a case-by-case basis according to the clinical context and in the absence of airflow limitation	Professional agreement
Guideline 31	When possible, the experts suggest that clinicians perform a cough challenge test for the follow-up of patients with URCC	Professional agreement
Guideline 32	The experts suggest that clinicians perform a bronchoscopy in case of URCC when a bronchopulmonary disease is strongly suspected, especially when the chest CT scan is abnormal or when endoscopy is needed for the management of a lung disease. In case of URCC with a normal chest CT scan and in the absence of associated respiratory symptoms, the experts suggest not to perform bronchial endoscopy	Professional agreement Professional agreement
Guideline 33	When bronchoscopy is performed in the context of URCC, the experts suggest that clinicans perform microbiological, cytological (bronchial aspiration or broncho-alveolar lavage) and histological (staged bronchial spur biopsies) analyses The experts suggest that clinicians do not to perform distal transbronchial biopsies	Professional agreement
Guideline 34	In case of refractory or unexplained chronic cough in the absence of digestive symptoms, systematic gastrointestinal endoscopy is not justified	Grade C
Guideline 35	In case of refractory or unexplained chronic cough, a functional gastrointestinal assessment (esophageal pH-impedance monitoring and/or manometry) without treatment should be discussed, especially in patients with digestive symptoms and ineffective anti-reflux treatment	Grade C
Guideline 36	Sinus X-ray is not recommended in case of chronic cough	Grade A
Guideline 37	The experts suggest that clinicians do not to perform a sinus CT scan in case of chronic cough in the absence of a prior ENT clinical examination including nasofibroscopy	Professional agreement
Guideline 38	It is recommended to perform a phoniatric functional assessment of the larynx, which can provide diagnostic (in particular neurological) or therapeutic (rehabilitative or interventional) guiding findings	Grade C
Guideline 39	The experts suggest that clinicians perform nocturnal polygraphy or polysomnography to detect OSAS in case of URCC with excessive daytime sleepiness and/or when snoring and/or obesity are associated	Professional agreement

associated with cough, abnormal lung auscultation, warning signs suggestive of a neoplastic disease). It is less relevant in other cases.

Methacholine challenge test, plethysmography, DLCO measurement, and cough challenge test

In case of chronic cough, plethysmography may be performed to complete spirometry to measure non-mobilizable lung volumes and thus assess thoracic distension in the context of an obstructive ventilatory disorder and to confirm the presence of a restrictive ventilatory disorder [119] (Table 6). Measuring the DLCO and highlighting altered gas exchange are useful for diagnosing lung diseases such as interstitial lung diseases [74] (Table 6). A bronchial methacholine challenge test may also be proposed to help in the diagnosis of asthma or asthma-like cough (normal spirometry and intermediate probability) in case of airway hyperreactivity, but also to suggest other lung diseases (non-asthmatic eosinophilic bronchitis or chronic obstructive pulmonary disease [COPD]) [120] (Table 6). Its role in the management is difficult to assess, as the studies are dated [121]. These pulmonary function tests are therefore useful as second line to help in the management of lung diseases for which cough may be one of the symptoms.

The cough challenge test is a specific method for objectively assessing cough (Table 6). This test consists in stimulating the afferent nerve fibers innervating the larynx, trachea and bronchi through inhalation of increasing concentrations of a tussigenic agent. The test allows observing a response that consists in triggering 2 or 5 coughs and inducing a feeling of need to cough [122,123].

Unfortunately, individual responses to tussigenic stimuli are not a marker of the cough hypersensitivity syndrome due to a significant inter-patient variability. However, as a group, individuals with this syndrome experience cough and a feeling of need to cough at significantly lower rates than healthy subjects [124,125]. An increased tussigenic sensitivity in these patients has been shown for a range of stimuli, including citric acid, capsaicin, adenosine triphosphate (ATP) and hyperosmotic solutions [126–130].

Given the large variability in responses to cough challenge testing using a given tussigenic agent, recent studies have suggested that multiple pathways might lead to cough hypersensitivity [124,125], and the use of a range of tussigenic agents, each of which being an agonist of a specific ion channel, might in the future be used to predict the response to specific treatment in patients with refractory chronic cough [131,132].

Bronchial endoscopy

Flexible bronchoscopy is not a first-line examination for assessing chronic cough, and its place is not clearly established, due to the lack of large prospective studies assessing its impact. In retrospective studies, the diagnostic yields of flexible bronchoscopy when performed as a second-line examination range from 11% to 41% (when combined with staged bronchial biopsies and bronchoalveolar lavage) [133–135] (Table 6). The diagnoses made based on endoscopy include: bacterial and fungal infections/colonizations, eosinophilic bronchitis, tracheobronchomalacia (TBM), osteochondroplastic tracheobronchopathy, bronchial tuberculosis, and tracheobronchial amylosis.

This examination should therefore be proposed in the presence of URCC with a strong suspicion of bronchopulmonary disease, after a chest CT scan (expiratory CT scan in case of suspected TBM) when the findings are abnormal or to confirm a suspected diagnosis (Table 6).

Gastric endoscopy, pHmetry, manometry

In case of URCC in the absence of digestive symptoms, endoscopy has a poor yield that does not support its use in this context [136,137] (Table 6). In a context of URCC with digestive symptoms, endoscopy is indicated based on the presence of digestive symptoms. Endoscopy allows: 1) ruling out morpho-parietal abnormalities of the upper gastrointestinal tract (esophagitis, in particular

diverticulum), and 2) determining the anatomical landmarks (esophageal junction) required to perform esophageal function testing. Upper gastrointestinal endoscopy is required to rule out morphological abnormalities before performing functional gastrointestinal testing.

In the absence of esophageal morphological abnormality, functional testing may help to identify a gastrointestinal involvement in URCC, especially in case of associated digestive symptoms [138]. High-resolution esophageal manometry may detect potential esophageal motility disorders [139] (Table 6). Esophageal pH-impedance testing, performed alone or under effective anti-reflux treatment, allows detecting acid, non-acid or low-acid, or even gaseous refluxes, and detecting statistically significant relationships between the occurrence of cough and refluxes (calculation of the symptom-association probability) [138,140] (Table 6). When an exploratory approach is chosen to detect GERD-related chronic cough, it should involve a gastroenterology center with expertise in esophageal testing.

Sinus imaging, nasofibroscopy

The 2008 HAS technological report did not find any indications for standard sinus radiography for the assessment of acute sinusitis in adults and children or for chronic headache [141]. These guidelines were in line with those of the French Language Society of Infectious Pathology on systemic antibiotic therapy in routine practice for upper respiratory infections in which imaging is not recommended to make the diagnosis [142]. In a recent international systematic review of the literature, standard X-rays are no longer indicated in acute or chronic rhinosinusitis [143].

Sinus CT scan (or currently cone beam) is the gold standard examination. However, the international community highlights that it is not necessary for the diagnosis of inflammatory and infectious diseases [143]. The diagnosis is based on clinical and endoscopic findings (Table 6). All CT images should be interpreted according to their clinical context. This is especially important since CT scan does not allow distinguishing between edema, retention, secretions, polypoid mucosal formations, true polyps or early tissue lesion. Moreover, the radiological normalization is delayed by 4–6 weeks after an acute episode. Finally, naso-sinusal opacities are present in 18–66% of healthy subjects in the absence of any particular pathological or symptomatic context [104] and are part of the "normal" images of the naso-sinusal cavities and should not be interpreted as pathological findings. A CT scan of the facial mass is indicated when a factor for recurrence of acute infectious episodes is investigated, when a tumor is suspected because of its unilateral nature, when an infectious or tumor complication is investigated, in the presence of acute episodes of sinusitis at risk of serious complications such as sphenoidal, frontal and ethmoidal locations, in case of diagnostic doubt, or when surgery is indicated.

In chronic naso-sinusal inflammatory disease, the Anglo-Saxons use the Lund-Mackay scanographic score. A score ≤ 2 has no pathological value, a score ≥ 5 would positively predict a definite pathological status [143]. However, while this score correlates well with endoscopic findings [144], it poorly correlates with clinical findings [145,146]. The CT scan may therefore be replaced by endoscopy in most clinical situations (Table 6).

Specialized phoniatric assessment

ENT examination should be completed by a specialized functional assessment of the larynx when the first etiological assessment is negative. It is intended to rule out rarer causes and to guide symptom management (Table 6).

It should include an analysis of all functions in which the laryngopharynx is involved. During nasofibroscopy, breathing (rapid +/- forced), saliva swallowing but also of an ideally liquid and pasty food with a color contrasting with the mucous membranes, and efforts with closed glottis (with for example a forced palm-to-palm contact) should be tested. The morphological examination will investigate the presence of lesions of the posterior commissure such as laryngitis, granuloma or even forms of Jackson's ulcer [147]. This analysis may be completed by laryngeal adductor reflex tests by inserting the end of the fiberscope in the endolarynx.

Observing a paradoxical vocal cord adduction during inspiration will support a respiratory laryngeal dysfunction commonly associated with cough due to laryngeal hyperexcitability. This finding will support the need for a rehabilitative speech therapy or even interventional treatment such as superior laryngeal nerve blocks [148], botulinum toxin injections, or intracordal filler injections [149].

Another type of abnormality that affect one or more functions (swallowing, breathing, speech, etc.) will lead to refer the patient to a neurologist in order to complete the etiological assessment. Indeed, several neurological disorders, including an extra pyramidal syndrome and/or a cerebellar syndrome and/or a dysautonomic syndrome may start with dysfunctions of the pharyngolaryngeal junction several years before the diagnosis [150–153].

Respiratory polygraphy

Studies including cohorts of patients with chronic cough and OSAS have shown a frequent co-prevalence of both entities with up to 60% of chronic cough patients with an apnea hypopnea index ≥ 5/hour and about one third of the OSAS patients with chronic cough symptoms [154–158]. A female predominance and a common association with GERD are observed [155]. The nocturnal predominance of cough is not systematic [159]. OSAS-induced upper airway inflammation and GERD may be the pathophysiological mechanisms interconnecting these 2 entities [160,161]. The efficacy of continuous positive airway pressure (CPAP) treatment for OSAS has been shown on GERD, cough sensitivity and cough intensity, including in a randomized placebo-controlled study assessing CPAP [155,159,162] (Table 6).

What is the treatment for URCC (pharmacological and non-pharmacological intervention)?

There is currently no approved medication for chronic cough. Smoking cessation remains crucial in the management of chronic cough. Any intervention allowing achieving smoking cessation is recommended. However, due to the disability associated with chronic cough, some treatments with a proven efficacy in this indication should be discussed. A 2018 meta-analysis has confirmed the efficacy of neuromodulators in chronic cough [163] (Table 7). If a neuromodulator is considered, the treatment should be discussed in a multidisciplinary meeting. The combination of several neuromodulators or the comparison of different neuromodulators has never been investigated. It is therefore not possible to present a prioritization of these treatments.

Neuromodulators

Amitriptyline. Amitriptyline is a non-selective monoamine reuptake inhibitor belonging to the class of antidepressants. Two randomized studies assessing the effect of amitriptyline on chronic cough have been published. In a study conducted in 28 patients, the dose of 10 mg of amitriptyline given at bedtime has been compared to the codeine/guaifenesin combination. Compared to the control arm, amitriptyline was significantly associated with a response greater than 50% [164] (Table 7). In another randomized placebo-controlled study in 18 patients with chronic pharyngolaryngeal neuropathy, a subjective improvement was observed in 67% of patients treated with amitriptyline compared to 44% of patients treated with placebo. The difference was not significant due to a lack of power.

Pregabalin/gabapentin. Pregabalin and gabapentin are gamma-aminobutyric acid analogs and are classified as antiepileptics. Two

Table 7
Summary of guidelines for refractory or unexplained chronic cough treatment.

	Guidelines	Grade
Guideline 40	In case of refractory or unexplained chronic cough, the use of a neuromodulatory treatment is recommended. The prescription of such a long-term treatment should be discussed after assessing the benefit/risk ratio.	Grade B Professional agreement
Guideline 41	The experts suggest that clinicians use the lowest effective dose of neuromodulator in case of refractory or unexplained chronic cough.	Professional agreement
Guideline 42	In case of unexplained or refractory chronic cough, the use of amitriptyline is recommended. The prescription of such a long-term treatment should be discussed after assessing the benefit/risk ratio.	Grade C Professional agreement
Guideline 43	In case of unexplained or refractory chronic cough, the use of pregabalin or gabapentin is recommended. The prescription of such a long-term treatment should be discussed after assessing the benefit/risk ratio.	Grade B Professional agreement
Guideline 44	In case of unexplained or refractory chronic cough, the use of low-dose morphine (5−10 mg/day of morphine sulfate twice daily) is recommended. The prescription of such a long-term treatment should be discussed after assessing the benefit/risk ratio.	Grade B Professional agreement
Guideline 45	In case of unexplained or refractory chronic cough, the use of azithromycin is not recommended.	Grade B
Guideline 46	The experts suggest that clinicians use menthol compounds in chronic cough patients to occasionally control cough.	Professional agreement
Guideline 47	In chronic cough patients, the experts suggest that clinicians do not use codeine or antitussives that are usually prescribed for acute cough.	Professional agreement
Guideline 48	Specialized functional speech therapy is recommended in case of URCC	Grade B
Guideline 49	The experts suggest that clinicians follow patients over time, given the risk of recurrence due to the difficulty in maintaining the adaptations and techniques needed for the functional management.	Professional agreement
Guideline 50	A physiotherapy program including ventilatory re-education is recommended in patients with refractory chronic cough with 4 sessions over one or two months.	Grade B
Guideline 51	A comprehensive speech therapy and/or physiotherapy program is recommended in patients with refractory or unexplained chronic cough.	Grade B
Guideline 52	A clearance physiotherapy is recommended in case of productive chronic cough in patients with bronchiectasis.	Grade A
Guideline 53	Mindfulness meditation is a technique that may be proposed in chronic cough patients.	Grade B
Guideline 54	The experts suggest that clinicians use the term "somatic cough syndrome" instead of the term "psychogenic cough".	Professional agreement
Guideline 55	It is not recommended to make a diagnosis of somatic cough syndrome based solely on the fact that the patient does not cough at night	Grade C
Guideline 56	It is recommended (as soon as these treatments will be available) to use P2 × 3 receptor antagonists to treat refractory or unexplained chronic cough.	Grade A

randomized studies have assessed these drugs in chronic cough. In a study conducted in 62 refractory chronic cough patients, gabapentin escalated to a dose of 1800 mg/day significantly improved the LCQ score and cough frequency compared to palcebo [165] (Table 7). Interestingly, there was no effect on cough receptor sensitivity, suggesting a central effect. In another study, speech rehabilitation alone has been compared to pregabalin combined with speech rehabilitation in 40 refractory chronic cough patients [166] (Table 7). Cough severity, cough frequency and cough-related quality of life improved in both groups. The improvement in LCQ score and cough VAS was greater with the combined treatment than with speech rehabilitation alone. There was no significant difference in cough frequency improvement between both groups.

Morphine. Only one randomized controlled trial has assessed the effect of low-dose morphine in 27 patients with chronic cough [167]. Compared to placebo, a dose of 10 mg of sustained-release morphine sulfate twice daily significantly improved the LCQ score (Table 7). The study duration was 4 weeks. The long-term effects of morphine therapy expose patients to dependence and side effects for which no data are available in chronic cough.

Antibiotics

Azithromycin. The long-term effect of azithromycin on chronic cough has been assessed in a randomized controlled trial [168]. A clinically relevant improvement in LCQ score was observed with azithromycin (mean change: 2.4; 95% CI: 0.5; 4.2) but not with placebo (mean change: 0.7; 95% CI: −0.6; 1.9), but the difference between both groups was not statistically significant (Table 7). A meta-analysis has found no improvement in cough with azithromycin, but various diseases such as asthma, COPD or chronic cough were included in this meta-analysis [169].

Others

Menthol has been shown to increase the cough reflex threshold and could reduce cough [170] through its action on the TRPM8 receptors [171] (Table 7).

Studies that assess codeine are dated and contradictory [172]. The data in the literature do not allow recommending its use in chronic cough. The level of evidence for other antitussives is also too low to recommend their use in cough [173] (Table 7).

Speech therapy

In case of URCC, functional approaches may also be proposed [174,175].

This type of management, mainly provided by speech therapists, has been described in four steps by Australian teams [176], with the objective of suppressing cough, reducing sensitivity to triggering factors and increasing the laryngeal sensitivity threshold (SPEICH—C program). This management is based on cognitive concepts of motor learning and behavioral plasticity on the one hand, and allows the patient to learn metacognitive strategies on the other hand.

The initial assessment should be based on an evaluation of morphological and analytical oropharyngeal deficiencies, pharyngolaryngeal functional dynamics, but above all on patient anamnesis in order to target the context of cough onset, their perception in terms of functional limitations, and their feelings and perceived psychosocial limitations, which will allow targeting the whole management (Supplementary data)

This management is considered effective when it is adequately targeted, i.e., in the absence of a non-functional disorder at the origin of URCC, with an efficacy of 88% compared to 14% in a control group [175] (Table 7). Different specific approaches to functional rehabilitation may be proposed as a complement. Therapeutic patient education (TPE) is a rapidly developing field and preliminary studies have shown its efficiency in reducing chronic cough intensity and frequency. Laryngeal maneuvers may also be proposed by trained professionals in order to reduce pharyngolaryngeal tensions and

optimize the proprioceptive capacities of the patients allowing them to better appropriate the techniques.

Finally, interventions targeting other functions of the pharyngolaryngeal junction are sometimes needed, such as speech or swallowing interventions.

In all cases, the difficulties in maintaining the necessary adaptations over time require regular follow-up of patients, even after management discontinuation [177] (Table 7). The follow-up is usually close and then increasingly spaced once the adaptations have become part of the patient's daily life.

Physiotherapy

In addition to drug treatments, non-pharmacological management, including physiotherapy, may be considered. The triggering factor for cough will guide the therapeutic choice as for pharmacological treatments. Physiotherapy will mainly promote cough cessation through physiological maneuvers (pursed lips) and techniques leading to secretion clearance. The effect could be due to a reduction in cough reflex sensitivity in addition to eliminating the triggering factor.

When associated with bronchial congestion, as in bronchiectasis and cystic fibrosis, cough and its impact on daily life are reduced when decongestion techniques are used.

Comprehensive techniques at the interface of physiotherapy and speech therapy have also been proposed. One of the scarce studies on the topic has shown that two sessions including physiotherapy and speech therapy significantly improved cough at 2 months in patients with refractory cough [178] (Table 7). LCQ score improved by more than 1.3 (improvement in all 3 domains) with a greater gain compared to pharmacological treatments. Sleep and cough frequency also improved [178]. These physiotherapy and speech therapy sessions consisted of voluntary cough suppression, cough distraction or substitution techniques, and respiratory retraining similar to what is done in ventilatory dysfunction. In addition, patients received advice on how to detect triggers such as cold, smoking, physical exercise, talking, laughing and smells.

The benefit of a similar program on cough frequency and impact on the quality of life has been confirmed in two randomized controlled trials [175,179]. After 4 sessions over one [179] and two months [175] respectively, a greater benefit was observed compared to the control group in terms of cough severity, frequency and impact (Table 7). This benefit on cough frequency persisted at 3 months, but not on cough impact [179].

Other non-pharmacological therapies

It seems difficult to list all non-pharmacological interventions. A controlled study has analyzed the effect of mindfulness meditation on cough [180]. Mindfulness meditation consists of voluntarily paying attention to the present moment without judging. Exercises focused on breathing or body position are performed as part of mindfulness meditation. This technique allows reducing the cough reflex in healthy volunteers and chronic cough patients [180] (Table 7).

Sophrology is also a technique used in cough centers, but scientific data remains limited.

Management of somatic cough syndrome (psychogenic cough)

To be consistent with the Somatic Symptom Disorder classification [181], the English literature has replaced the term "psychogenic cough" by "somatic cough syndrome" (SCS) [182]. We believe that this terminology should be adopted in France, as it better reflects the mechanism of psychogenic cough (Table 7).

Historically, SCS has been described as a barking or honking cough that does not occur at night or that disappears during activities requiring concentration [183]. The main difficulty is that these features are not specific to SCS. In a meta-analysis on SCS, barking or honking cough was reported in only 8 out of the 18 studies included in the analysis, and non-sleep coughing in only 3 out of the 18 studies [184]. In clinical practice, tracheobronchomalacia or bronchial dilations are associated with barking or honking coughs. In addition, cough hypersensitivity syndrome, as described in section 1c, is most often associated with cough that does not occur at night, because in this entity, dysfunctional cough receptors are not stimulated at night. A context of anxiety or depression also does not support a diagnosis of SCS. Indeed, refractory chronic cough is associated with a high prevalence of anxiety or depression [185].

The diagnosis of SCS is thus complex in clinical practice. The American College of Chest Physicians recommends using the DSM-5 criteria, but they are not specific and are difficult to use in practice. When cough is part of a more global somatic syndrome, SCS may be considered. Apart from this situation, a comprehensive management of chronic cough should be preferred, including both pharmacological and non-pharmacological interventions.

What is the perspective of the molecules being developed?

New pharmacological targets have been assessed in preclinical and clinical studies conducted over the past decade. While some have failed to prove their benefit (Transient Receptor Potential (TRP) A1 and V1 channels, $\alpha 7$ nicotinic receptors) [186], the studies focused on the P2 $\times$ 3 purinergic receptors have shown conclusive results. P2 $\times$ 3 receptors are ligand-dependent cation channels (Ca^{2+}, Na^{+}, Mg^{2+}, K^{+}...). the opening of which is triggered by ATP. Homotrimeric P2 $\times$ 3 receptors are expressed in the peripheral sensory nerves and nucleus tractus solitarius and might be involved in the pathophysiology of chronic cough. They share a strong structural homology with the heterotrimeric P2 $\times$ 2/3 receptors, also expressed in sensory neurons and playing a role in taste perception. Several P2 $\times$ 3 receptor antagonists are currently in clinical development. Their international non-proprietary name ends with the suffix -pixant and they include gefapixant, eliapixant, sivopixant as well as the BLU-5937 and BAY1902607 molecules. Two phase III studies in a total of 2044 patients have confirmed the efficacy of gefapixant at the highest of the two doses tested (45 mg x 2), with a reduction in cough frequency by 18.6% (95% CI [9.2−27.1]) compared to placebo at week 12 of treatment [187] (Table 7). This effect was associated with a clinically significant improvement in the quality-of-life score (improvement in LCQ score greater than 1.3 in more than 70% of patients) and in cough severity assessed using a VAS (improvement greater than 30 mm in 42.8% (week 12) and 50.6% (week 24) of patients) [188]. The molecules belonging to this pharmacological class are generally well tolerated. The main adverse effects were taste disorders (dysgeusia, hypogeusia, ageusia) due to the relative selectivity of the different molecules and their concomitant blockade of both P2 $\times$ 3 and P2 $\times$ 2/3 receptors.

Conclusion

The current guidelines propose to update the definitions of cough and to introduce the concept of refractory or unexplained chronic cough (URCC). This is a key concept for patients to obtain recognition of their disorder, both for themselves and in order to improve their management. The management of chronic cough is inherently multidisciplinary. Furthermore, non-pharmacological interventions are a major part of patient treatment and their use is essential. Chronic cough management is changing rapidly with the imminent launch of new treatments. Those new treatments should be used after rigorous management because a misuse will lead to detrimental effects on patients and society.

Declaration of Competing Interest

LG has been an investigator in clinical trials for Bayer, Merck, AstraZeneca, GSK and Novartis, and reports grants or consultation fees from Bayer, Merck, AstraZeneca, GlaxoSmithKline, Novartis, and Sanofi-Regeneron that are not related to the submitted work. SGDL declare grant from AstraZeneca and fees for consulting from MSD. SC declare fees for consulting from MSD and Olympus. WT declare fees for consulting from AstraZeneca and non-financial support from ASTEN. NG declare non-financial support from PulmonX, Roche, BMS, MSD, Astra Zeneca, Novartis, Pfizer, Novatech and fees for consulting from PulmonX, Roche, BMS, MSD, Astra Zeneca, Novartis. MP declare fees for consulting from Doctolib and AMGEN and non-financial support from AMGEN. All the other co-authors declare no disclosure of interests.

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Supplementary materials

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