Cough in idiopathic pulmonary fibrosis

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ABSTRACT   Many patients with idiopathic pulmonary fibrosis (IPF) complain of chronic refractory cough. Chronic cough is a distressing and disabling symptom with a major impact on quality of life. During recent years, progress has been made in gaining insight into the pathogenesis of cough in IPF, which is most probably "multifactorial" and influenced by mechanical, biochemical and neurosensory changes, with an important role for comorbidities as well. Clinical trials of cough treatment in IPF are emerging, and cough is increasingly included as a secondary end-point in trials assessing new compounds for IPF. It is important that such studies include adequate end-points to assess cough both objectively and subjectively. This article summarises the latest insights into chronic cough in IPF. It describes the different theories regarding the pathophysiology of cough, reviews the different methods to assess cough and deals with recent and future developments in the treatment of cough in IPF.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease of unknown cause with a median survival of 3–5 years after diagnosis [1]. Treatment of IPF aims at slowing or stopping the disease progression, increasing survival, reducing symptoms and improving quality of life (QoL) [2]. Currently, two anti-fibrotic drugs are available that slow down disease progression [3, 4]. In a small minority of patients lung transplantation is an option that can increase survival and improve QoL. Alleviating symptoms and improving QoL in IPF is often a major challenge to treating clinicians. Patients report that the symptoms that have the greatest impact on daily life are cough, shortness of breath and fatigue or malaise [2]. Chronic cough in IPF is not only often refractory, but is also an independent predictor of disease progression [5]. Better understanding of the underlying mechanism(s) causing cough in IPF and better treatments are clearly needed. This review summarises the latest insights on chronic cough in IPF.

Characteristics and demographics of chronic cough

Chronic cough is defined as a cough lasting for at least 8 weeks. In the general population it has a prevalence of 9% to 33% in the USA and Europe [6]. It is a frequent reason for seeking medical advice, with a high number of medical consultations [7]. The most important risk factor for chronic cough is cigarette smoking. Prevalence of chronic cough is three times higher in chronic smokers as in never- or ex-smokers [6].

No reliable data on the prevalence of cough in IPF exist. Some studies report that up to 80% of patients experience chronic cough [5, 8]; however, lower numbers are also reported [4]. This may be attributed to method of reporting and the definition of cough used (any cough *versus* disabling cough). When cough is present in IPF, it is severe and difficult to treat [8]. The cough is mostly nonproductive and dry, although some patients experience nonpurulent sputum production, possibly related to traction bronchiectasis in advanced IPF or concomitant chronic obstructive pulmonary disease (COPD). The urge to cough cannot be relieved by coughing [9].

Cough frequency is high in patients with IPF, with median (range) 24-h cough counts varying from 226 (36–946) to 520 (117–1493) depending on the population studied [10, 11]. The cough frequency in IPF is similar to patients with chronic cough presenting to a cough specialist clinic, and higher than in patients with asthma or COPD (asthma median (range) 24-h cough rate 62.4 (0–341), COPD ex-smokers 117.6 (range 14.4–648)) [10, 12]. Strikingly, IPF patients experience more cough symptoms during daytime (median hourly cough rate 14.6 during the day *versus* 1.9 during the night), analogous with COPD and asthma patients [10, 12]. Chronic cough in IPF is not related to age or gender, and is more common in "advanced" disease and in never-smokers [5, 10], the latter is in contrast to chronic cough in the general population [6]. There is no clear explanation why IPF patients without a history of smoking cough more, but this may be related to the phenotype of IPF [13].

Effect on the patient

In general, chronic cough can impact severely on different aspects of life [14]. Problems with sleeping, raucous vocal sounds and musculoskeletal pain of the chest can occur [9]. Chronic cough can cause relationship difficulties, avoidance of public areas, decreased social interaction and work-related problems affecting physical, mental and social health [14, 15]. In IPF, the limited studies about cough and QoL also show that cough is a very disabling and distressing symptom impacting QoL [9, 10]. Some patients also experience cough-related urinary incontinence with a dramatic impact on QoL [16]. Moreover, the social impact of chronic cough in IPF further compounds limited exercise ability, reduced walking distance and the need to use supplemental oxygen.

Pathophysiology of chronic cough

A detailed overview of the pathophysiology of cough is beyond the scope of this review; however, a summary of the mechanisms that may play a role in cough in IPF [17] is shown in figure 1. Imbalance between stimuli and responses results in increased coughing. Minor stimuli such as laughing, talking, smoke, perfume and temperature changes already induce a cough reflex [6, 18]. This is also known as cough hypersensitivity syndrome and can occur in patients with and without pulmonary disease [19].
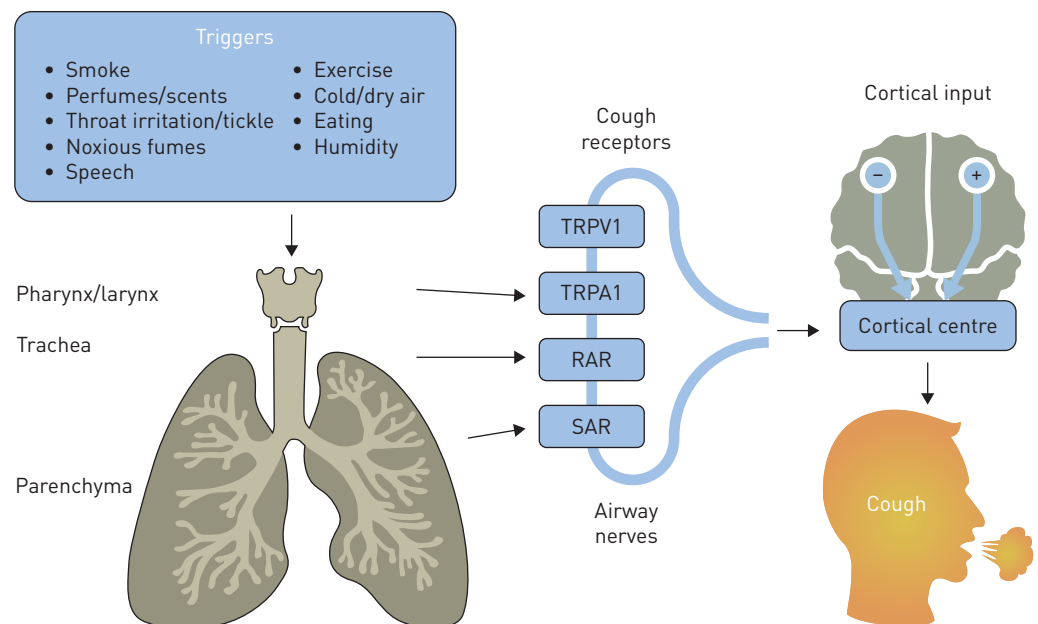

FIGURE 1 Pathophysiology of cough. TRPV1: transient receptor potential vanilloid 1; TRPA1: transient receptor potential ankyrin 1; RAR: rapidly adapting receptor; SAR: slowly adapting receptor. Reproduced from [17] with permission from the publisher.

The cough reflex has an afferent pathway, with sensory nerve fibres of the vagus nerve located in the ciliated epithelium of the upper airways and cardiac and oesophageal branches from the diaphragm [20]. These afferent impulses go to the brain stem and cortical centre, which are important in regulating the cough response. In response this activates the efferent motor pathway of the cough reflex, by sending impulses *via* the vagus, phrenic and spinal motor nerves to the diaphragm, abdominal wall and muscles, resulting in cough [17, 18, 20].

The afferent part of the cough reflex involves at least three broad classes of nerves: C-fibres, rapidly adapting receptors (RARs) and slowly adapting receptors (SARs) [20]. 1) C-fibres are sensitive to thermal and chemical stimulation, such as capsaicin, citric acid and hypertonic saline. TRPV1 and TRPA1 are C-fibre receptors that are very responsive to chemicals [20, 21]. 2) RARs are rapidly responsive to mechanical stimulation, such as changes in, for example, diameter, length and compliance of the airways. RARs are also sensitive to changes in PH and osmolality but relatively insensitive to other chemical stimulation [22, 23]. 3) SARs are highly sensitive to mechanical forces and are thought to be the afferent fibres involved in the Hering–Breuer reflex, which terminates inspiration and initiates expiration when the lungs are adequately inflated [20].

Recently it has also been recognised that neuroplasticity, whereby nerves switch phenotype, can occur in different disease processes [24]. Voluntary cough and the sensation of an urge to cough have their origin in the cerebral cortex [18].

Pathophysiology of cough in IPF

The pathophysiology of chronic cough in IPF is still unknown and is complicated by the frequent confounding comorbidities in this population. Different concepts of the possible mechanisms of cough in IPF have been proposed [25].

There is some evidence that the cough reflex sensitivity in patients with IPF is increased [8, 26], suggesting an upregulation of sensory fibres in the lungs [8, 26]. However, the studies assessing cough sensitivity were performed before the publication of the current international guidelines for the diagnosis of IPF in 2011 [1]. Assuming that increased cough reflex sensitivity may play a role in at least part of the IPF population, the question remains what causes this enhanced sensitivity.

A possible explanation could be that mechanical distortion of the lung, caused by the fibrosis, directly influences nerve fibres. As RARs and SARs are sensitive to mechanical changes they could be influenced in sensitivity or quantity by the traction forces of the fibrosis [22, 25]. Nerves that inhibit cough might also be destroyed due to fibrosis [22]. This corresponds with the finding of increased cough reflex sensitivity to mechanical stimulation of the chest wall in IPF patients, compared with controls. An increased sensitivity was especially found following low frequency stimulation of the posterior basal lung base, the area where lung fibrosis in IPF is typically most extensive [22]. This mechanism may also explain the observation that cough seemed to be more frequent in advanced IPF, although in another study this correlation was not found [5, 10]. Moreover, this is in line with clinical findings that patients often report starting to cough when talking or not being able to stop coughing once they start. The transmission of vibration caused by talking or even coughing itself might lead to increased mechanical stimulation of the sensory receptors, perpetuating a cycle of more cough and more vibration [27].

Another explanation for enhanced cough sensitivity could be the higher levels of neurotrophins that have been found in the sputum of patients with IPF than in controls [8, 25]. Neurotrophins induce the survival and development of different subgroups of sensory neurones and can also cause increase capsaicin sensitivity, enhancing cough reflex [8, 25, 26]. Immunohistochemical studies have shown that non-neuronal cell types, such as bronchial and alveolar epithelial cells, mesenchymal cells, lymphocytes and macrophages, can express neurotrophins [28]. In patients with idiopathic interstitial pneumonias, an increased expression of neurotrophins in the lung was shown, suggesting that they may potentially modulate sensory nerve proliferation and neuroplasticity [29]. Immunoblots revealed more neurotrophin expression in IPF/usual interstitial pneumonia than in nonspecific interstitial pneumonia and respiratory bronchiolitis-associated interstitial lung disease [29]. The underlying drivers of increased neurotrophin expression in IPF are unknown, although in other diseases inflammation is related to increased neurotrophin expression [30].

Interestingly, cough is an independent predictor of disease progression and the amount of coughing is not clearly related to the pulmonary function measurements [10]. LESLIE [31] suggested that recurrent stretch injury caused by pressure changes during breathing may explain why fibrosis in IPF typically commences in the peripheral basal part of the lung. LESLIE [31] argues that in these areas the traction forces and alveolar collapse are greatest, leading to sheer stress, lung injury and activation of fibrotic cascades. By analogy, mechanical ventilation in IPF can be a risk factor for acute exacerbations of the pulmonary fibrosis [32]. If pressure differences play a role in the pathogenesis of IPF, it could be speculated that the

pressure differences caused by cough might influence disease behaviour itself. One could hypothesise that cough is not only a symptom, but may also contribute to enhance activation of profibrotic mechanisms and disease worsening in IPF.

Furthermore, cough could be evoked centrally through cortical influences. The urge to cough, induced by capsaicin inhalation, activates many areas of the cerebral cortex [33]. Administration of a placebo prior to capsaicin testing can decrease activity in several brain regions [34]. This suggests that expectations of treatment can influence central processing of peripheral sensory input [34]. Suppression of cough by cortical influences could also explain why IPF patients cough less during their sleep.

Comorbidities influencing cough

In patients with IPF, a number of potential causes of chronic cough must be excluded before chronic cough may be considered directly linked to the underlying disease. In at least half of patients comorbidities may play a role (table 1) [35].

Gastro-oesophageal reflux disease (GORD) is highly prevalent in IPF, yet classical symptoms are often absent [37, 38]. GORD-associated microaspiration of acid and non-acid reflux in the airway is thought to induce epithelial damage and may cause fibrosis [45]. Traction caused by lung fibrosis also can result in a weakened lower oesophageal sphincter, leading to gastro-oesophageal reflux and microaspiration [38, 46]. Cough receptors could be directly stimulated through aspiration of gastric secretions in the larynx and the upper airways [6]. Moreover, the presence of acid in the distal oesophagus may induce cough, probably through an oesophageal–tracheobronchial reflex [47]. Disappointingly, a study by KILDUFF et al. [48] showed no improvement of cough by anti-acid treatments, but a paradoxical increase in non-acid reflux. It might well be that non-acid reflux is influencing cough more than acidic reflux [48]. Unfortunately, cough itself may also increase trans-diaphragmatic pressure and promote GORD [47].

Obstructive sleep apnoea (OSA) is common in IPF [39]. OSA itself, with intermittent hypoxaemia, may promote profibrotic mechanisms [49]. In the general population, chronic cough is more prevalent in OSA and can be improved by treatment with continuous positive airway pressure (CPAP) [50]. A complicating factor is that obstruction of the upper airway in OSA could increase the trans-diaphragmatic pressure difference promoting GORD [51, 52]. GORD, on the other hand, may promote OSA, through microaspiration of gastric substances, creating an inflammatory reaction blocking the airway [53]. GORD, chronic cough and, as recently shown, IPF can be improved by treatment of OSA [49, 51]. Figure 2 shows the interplay between IPF, GORD, OSA and cough. Further research is needed to disentangle these interactions.

Additional comorbidities not directly linked to IPF should also be evaluated, especially cardiovascular comorbidity and associated treatment. Left heart disease and the use of beta-blockers are possible causes of chronic cough. Angiotensin converting enzyme (ACE) inhibitors as a cause of chronic cough should always be checked. ACE inhibitors can cause enhanced cough receptor sensitivity leading to cough just after taking the drugs, but also even months later. Symptoms can improve days after drug removal, but can take longer to disappear completely [6]. In the work-up of cough in IPF, infections, chronic sinusitis, COPD-associated chronic bronchitis and pulmonary malignancies should also be excluded.

Assessment of cough in IPF

In recent years, many tools have been developed to assess different aspects of cough; subjectively using cough questionnaires or visual assessment scales, and objectively using cough recorders and cough challenge tests. All these instruments have been developed for chronic cough in a general population and are reviewed elsewhere [55]. Experience and validation of these tools in patients with IPF are limited (table 2 provides an overview).

TABLE 1 Comorbidities influencing cough in idiopathic pulmonary fibrosis (IPF)

Comorbidity	Frequency in IPF (%)	Reference(s)
GORD	21–94	[36–38]
OSA	59–88[#]	[38–40]
Emphysema	30–55	[41]
ACE inhibitor use	9–15	[5, 42]
Chronic sinusitis/UACS	17–34	[5, 42, 43]
Lung cancer	4.4–16	[41, 44]
Infection	11–20	[3]

GORD: gastro-oesophageal reflux disease; OSA: obstructive sleep apnoea; ACE: angiotensin converting enzyme; UACS: upper airway cough syndrome. [#]: with high mean body mass index of 28–32 kg·m^{-2}.
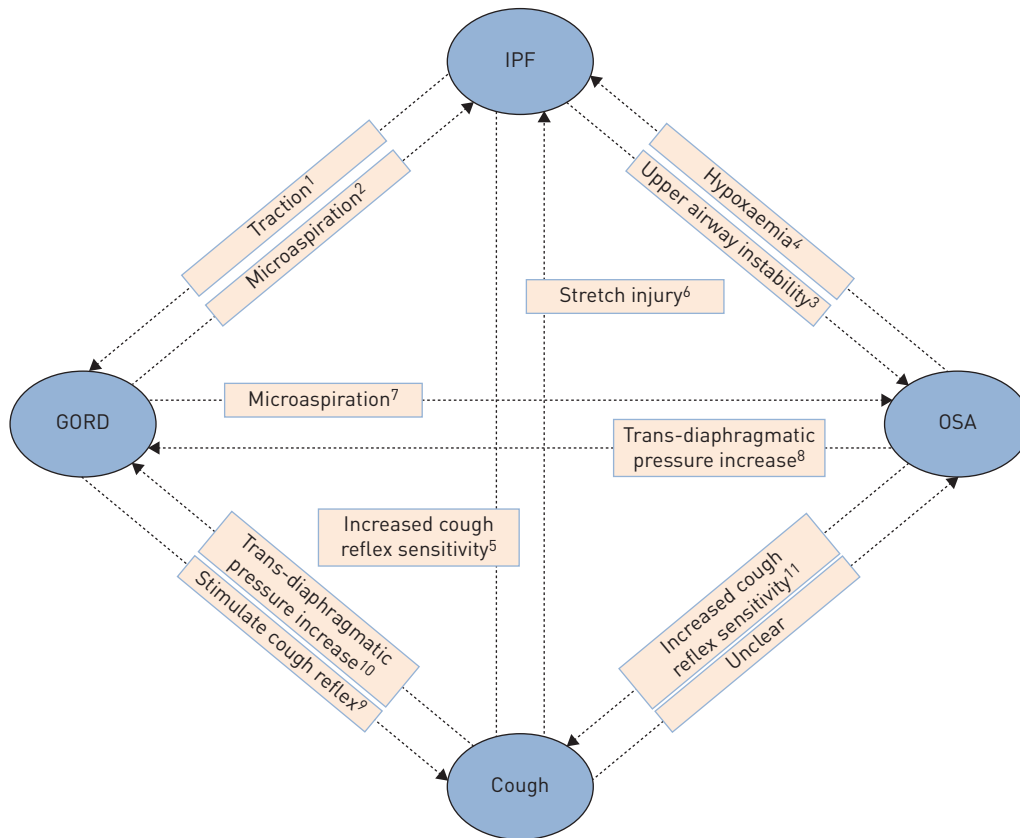
FIGURE 2 Interactions between idiopathic pulmonary fibrosis (IPF), gastro-oesophageal reflux disease (GORD), obstructive sleep apnoea (OSA) and cough. 1: traction leading to a weaker lower oesophageal sphincter tonus [45]; 2: microaspiration inducing epithelial damage [38, 46]; 3: restriction inducing instability of the upper airway [39]; 4: intermitted hypoxaemia promoting profibrotic mechanisms [49]; 5: increased cough reflex sensitivity [22–31]; 6: pressure causing stretch injury and activation of fibrotic mechanisms [31]; 7: microaspiration causing an inflammatory reaction blocking the airway [53]; 8: obstruction increasing trans-diaphragmatic pressure [51, 52]; 9: aspiration directly and acid reflux indirectly stimulate the cough reflex [6, 47]; 10: cough increasing trans-diaphragmatic pressure [47]; 11: less central inhibition and inflammation increasing cough reflex sensitivity [54].

By analogy with chronic cough, we would recommend the visual analogue scale to measure the severity of IPF related cough in a clinical setting, as it is fast and easy to use [60]. When designing a clinical trial, validated subjective as well as objective cough outcome measures should be incorporated.

Treatment of cough in IPF

In clinical practice, cough in IPF is a major challenge for the treating physician and patient, as it is often refractory. The first step in the management of chronic cough in IPF consists of addressing possible comorbidities as described in table 1.

Conventional anti-tussive therapy is often not beneficial [8]. Oral corticosteroids have been shown to improve cough symptoms in IPF patients in one small nonrandomised study [8], and low doses of prednisone are sometimes tried in daily practice to relieve cough, and later are slowly tapered if beneficial. However, no effect on QoL and survival was found and possible side-effects should be taken into consideration. Although opiates are recommended in the palliative setting, their effect has not been proven in IPF [1, 27]. Caution is warranted as opiates may influence the protective mechanism of cough, but might be a useful option for palliation of severe cough in patients with advanced IPF. With respect to GORD, no good evidence on the work-up and treatment of GORD-related cough in IPF exists, while the effect of proton pump inhibitors on cough is debated [48, 61].

A 24 week single centre double-blind cross-over study with thalidomide for treatment of cough showed a positive effect on QoL measured with the Cough Quality of Life Questionnaire. However, only 20% of the screened subjects completed the study and the potential side-effects of thalidomide can be severe [43]. Thalidomide has anti-inflammatory and anti-angiogenic effects, similar to currently used anti-fibrotic drugs. Its side-effect profile with dizziness and neuropathy suggests that it might also have effects on

TABLE 2 Cough measurements in idiopathic pulmonary fibrosis (IPF) patients

Cough measurement tool	Description	Validation studies and MCID	Advantages	Disadvantages
Subjective				
Visual analogue scale [56]	100 mm scale with extremes no cough to worst possible cough severity	Not validated in IPF	Easy to use Repeatable Responsive	Not validated in IPF or chronic cough
Cough quality-of-life questionnaire [57]	28-item cough-specific quality-of-life questionnaire with six domains	Validated in IPF (n=23) MCID in IPF: change of five points on a 28–112 scale [57]	Comprehensive questionnaire Reliable Valid instrument for assessing impact of cough	Need more studies in IPF: MCID evaluated with a retrospective anchor scale
Leicester cough questionnaire [15]	19-item self-administered chronic cough quality-of-life questionnaire with three domains	Evaluated in IPF: high correlation found with cough visual analogue scale, cough symptom score and objective cough frequency in IPF [10, 22] MCID in chronic cough: 1.3	High reliability Valid instrument for assessing impact of cough Ability to detect a response to change	Need more studies in IPF: MCID evaluated in chronic cough
Objective				
Cough challenge test [58]	Measurement of cough reflex sensitivity by inhalation of nebulised tussive agents (most common citric acid or capsaicin)	Not validated in IPF No MCID Standardised methodology published by ERS [14]	Useful for testing effect of new cough therapies on cough reflex sensitivity and for obtaining mechanistic insights	Doesn't measure efficacy of therapy or predict response in patients Limited availability
Cough monitor [59]	Microphone and recording device measuring cough in a pre-specified time slot	Validated cough monitors for chronic cough High correlation found with subjective cough measurements [10]	Measures cough frequency accurately	Currently limited to research and trails Benefit in routine clinics is not clear

MCID: minimal clinically important difference; ERS: European Respiratory Society.

sensory nerves. Although these results advocate the need for further investigations, thalidomide should not be considered a routine treatment of cough in IPF, even as a second-line therapy, until further evaluation of the benefit/risk ratio has been undertaken.

The majority of IPF patients are treated with one of the two new anti-fibrotic drugs, pirfenidone or nintedanib [62]. Although the effect of these drugs on cough has not yet been evaluated, there are some indications of a possible effect on cough. AZUMA et al. [63] showed, in a subgroup analysis of the phase three trial in Japan, that pirfenidone seemed to reduce cough in patients with a forced vital capacity >70% and arterial oxygen saturation measured by pulse oximetry <90% predicted. Using a nonvalidated cough score, a Dutch group also observed a reduction in cough with pirfenidone use [64]. In a guinea pig model, the capsaicin-induced cough reflex sensitivity was inhibited by pirfenidone in a dose-dependent manner [65]. This effect was accompanied by a reduction of bronchoalveolar lavage mediators promoting cough sensitivity [65]. No data currently exist on the effect of nintedanib on cough.

Future trials

Progress has been made in the treatment of "general" chronic cough. A combination of pregabalin and speech therapy has been found to improve cough and QoL more than speech therapy alone [66]. Gabapentin, a neuromodulator, was shown to improve cough severity, cough frequency and QoL of patients with chronic cough [67]. Physiotherapy aimed at suppressing cough improved sleep and cough frequency [68]. Very recently AF-219, a P2X3 receptor antagonist, showed very promising phase two results in chronic cough [69].

Many trials in IPF are emerging that assess the effect of these treatments or other novel medications on cough as either a primary or exploratory end-point, illustrating the need for better cough treatment in patients with IPF. Among these trials are studies on pirfenidone, AF-219, azithromycin, PA101, GSK2126458, laparoscopic anti-reflux surgery, supplemental oxygen, omeprazole and cognitive behavioural therapy (clinicaltrials.gov; searched using the terms "cough" and "IPF"; date last accessed: August 17, 2015).

Conclusion

Chronic cough in IPF is a major problem for patients and treating physicians. The pathogenesis of cough is most likely "multifactorial" and influenced by mechanical, biochemical and neurosensory changes. Comorbidities also have an important role, in particular GORD. While progress has been made in gaining insight into the pathogenesis of cough in IPF, more research is needed to find effective therapies. Clinical trials of cough treatment in IPF have only recently started, with either compounds developed for "general" chronic cough or new compounds in development for IPF, which are also evaluated for their potential effect on cough. It is crucial that validated cough measurements are included in these trials. Hopefully these new studies will ultimately lead to adequate treatment of cough, thereby improving quality of life in patients with IPF.

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