Burden and Mechanism of Chronic Cough in People Living with Idiopathic Pulmonary Fibrosis

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Interview Summary

Chronic cough is common and often debilitating in patients with idiopathic pulmonary fibrosis (IPF), affecting most people living with the condition. It is typically persistent and difficult to control, and can cause significant physical consequences, including pain, sleep disruption, and fatigue. In severe cases, it can cause vomiting and even rib fractures. Beyond the physical burden, chronic cough has a profound psychosocial impact, contributing to embarrassment, social withdrawal, and reduced quality of life. Despite this, it is frequently overlooked in clinical care. Limited effective treatment options mean it is often deprioritised in favour of more measurable aspects of disease, leaving many patients without adequate support or relief.

However, growing scientific understanding is beginning to change this landscape. Chronic cough is increasingly recognised not simply as a consequence of lung disease, but as a neuropathic condition involving dysregulation of peripheral and central nervous system (CNS) pathways. This shift in thinking is helping to identify new therapeutic targets and is driving the development of potentially more effective treatments.

As a result, the future of care in IPF may look very different, with the possibility of personalised medicine, multidisciplinary care, and a greater emphasis on recognising and managing the full impact of chronic cough on patients' lives.

This work will discuss the burden and mechanisms of chronic cough, as well as the future of IPF care, with two leading experts in the field and an Ohio grandfather, whose chronic cough forced him to retire from a job he loved.

INTRODUCTION

IPF is a form of interstitial lung disease.[1] It is a chronic, progressive lung disease that affects around 3 million people worldwide, and is more prevalent in those over the age of 50 years.[1,2] It is characterised by progressive scarring of the lungs and is often associated with cough, dyspnoea, and reduced quality of life.[1] Chronic cough, defined as a cough that lasts for more than 8 weeks, is common in IPF.[2,3] Affecting up to 85% of people living with the condition, cough can develop prior to a diagnosis of IPF and is often the initial reason people seek help from their doctor.[3-5] "Many of our patients report it as a dry, or non-productive, cough that is persistent throughout the day. Some, however, especially those who are former smokers or have concurrent airway disease, report a cough that can be productive of some clear sputum," said Tejaswini Kulkarni, Associate Professor of Medicine, Director of the Interstitial Lung Disease Program, and Associate Medical Director of the Lung Health Center, The University of Alabama at Birmingham, USA.

Patients often describe cough as the most burdensome aspect of their IPF, and it has a wide-ranging impact.[6] It can cause chest pain, light-headedness, syncope, sleep disturbance, vomiting, and even rib fractures. Patients also report embarrassment, and social and professional isolation.[3] "It is incredibly debilitating for people," said Matthew Drake, Head of the Division of Pulmonary, Allergy, and Critical Care; and the Edwards Professor of Pulmonary Medicine at the Oregon Health and Science University, Portland, USA. "This constant urge to cough throughout your day will prevent you from doing things like speaking in front of others, because you realise you are going to cough the minute you start to vocalise words." This is something Steve Ashton knows only too well. The grandfather of four and former police officer felt forced to abandon his second career as an accident reconstructionist due to chronic cough. "I used to teach and give presentations. But when you are at the podium and you just start coughing, it is humiliating," he explained.

Despite the impact chronic cough can have on physical and mental health, treatment options are limited.[3,5,7] There are no approved therapies to specifically target IPF cough; approved IPF medications, such as antifibrotics, have not been evaluated for cough.[5] Standard antitussives, including over-the-counter cough drops, neuromodulators, gabapentin, and pregabalin, and non-pharmacological approaches, including speech therapy or physiotherapy, are often ineffective.[5,7] In many cases, Kulkarni said, this had led to healthcare professionals simply not talking to patients about cough and its impact.

In recent years, however, advances in research have started to open a window to the mechanisms of chronic cough.[2] With this deeper understanding comes the potential for a new treatment landscape that may help to tackle this significant unmet need in IPF care, Kulkarni and Drake believe.

MECHANISM OF CHRONIC COUGH

Chronic cough is the most predominant and, in many cases, most burdensome part of living with IPF, said Drake.[2,6]

"For some, it may be even more troubling than shortness of breath, because it is so persistent," he added. In recent years, there has been a "seismic shift" in the scientific understanding of chronic cough. "We have recognised that it is not just a pulmonary problem: it is a consequence of dysfunction between the peripheral nerves in the airways and their connections to the brainstem," he said. In essence, it is a neuropathic problem that involves peripheral airway triggers, as well as how signals are sensed and responded to centrally, he went on.[7-9]

A cough happens when sensory nerves in the airways are activated by stimuli and send a signal to the CNS. This, in turn, triggers an alteration in the respiratory pattern to produce a cough. This reflexive pathway is intended to protect the lungs from foreign materials, and, in general, the stronger the stimuli, the stronger the urge to cough.[7] "Unlike acute cough, which is protective, chronic cough is maladaptive," said Drake, adding that chronic cough is caused by increased and amplified signals between the peripheral nervous system (PNS) and the CNS.[7-9] "The sensory nerves in the airways, those that travel up to our brain and trigger things like reflexive cough when we choke or aspirate something, are really central to chronic cough."[2,9] When these pathways become dysfunctional, it heightens their response to both noxious and innocuous stimuli and lowers the CNS's threshold for triggering cough, thereby leading to cough hypersensitivity, he explained.[9] "Patients who experience chronic cough describe having an urge to cough, or an actual production of a cough, in relation to innocuous stimuli: things like breathing cold air, laughing, or talking, will trigger a cough. This constant tickle in the throat, that urge to cough, is at the cornerstone of cough hypersensitivity. Mechanistically, we think this is due to changes in the threshold for nerve activation and successive nerve triggering."[9]

Expanding on this, Drake explained that, historically, airway sensory nerves have been classified as either nociceptors, those that respond to chemical signals, or mechanoreceptors, those that respond to physical deformation, pressure, or movement of the airways.[10] Advanced research techniques, such as single-cell genomics, however, have provided a deeper understanding of this complex network and revealed a variety of subtypes within those two main classifications.[10] "Not only has it shown us that we have this incredibly rich diversity of sensory nerves in the airways, but it has also allowed us to trace those connections to where they integrate with the brainstem, and understand how the brainstem interfaces with higher cortical neurones. In essence, it has given us a tremendous amount of information about how this system functions, both in health and how it begins to change and evolve in disease."[10]

Such work has uncovered a range of receptors and ion channels that contribute to chronic cough.[10] At the peripheral level, adenosine triphosphate, for example, which is released by injured or activated airway epithelial cells, acts on the nerve fibres through purinergic receptors, such as purinergic receptor P2X 3 (P2X3), that stimulate the cough reflex.[10,11] Transient receptor potential channels, which have been identified in airway sensory neurones, airway epithelial cells, and airway smooth muscle cells mediate chemosensitivity to various endogenous and exogenous triggers.[12,13] In addition, some subtypes of voltage-gated sodium channels, which are essential for the action potential in response to all stimuli, are predominantly expressed in cough-triggering airway nerves.[14] Drake also explained that opioid receptors, such as kappa and mu, play a pivotal role in both the peripheral and central neural pathways involved in cough. These can be found in high numbers in the CNS and PNS regions that regulate sensitisation.[7]

In turn, these discoveries have identified new treatment targets, and the therapeutic landscape is evolving rapidly.[2,10] Drake highlighted a dual opioid agonist/antagonist approach, which modulates both central

and peripheral neurotransmission involved in cough, via kappa opioid receptor agonism, while limiting side effects, such as respiratory depression and abuse liability, via mu opioid receptor antagonism.[7] "Here, the goal is not just stopping the triggering at the source in the airway, but also turning down the volume in the brainstem and cortex to address that key underlying problem of cough hypersensitivity," he said.

What is currently unclear is why this CNS/PNS dysfunction develops, said Drake. "We know that the sensory nerves in the airway grow and increase in their overall density, and we know that they become excessively prone to firing and sending those signals to the brainstem. We also know that changes in brainstem and cortical centres occur because of excessive firing, and that leads to this heightened activity level," he explained.[10] Why certain people develop these changes while others do not, however, "is not totally clear." It may be that some people are born with more nerves, or with differences in the nervous system connections, making them more susceptible, he said.[15] In IPF, Drake went on, it is possible that the fibrotic processes in the lungs contribute to excessive cough triggering.[16] There is also a suspicion that fibrosis promotes a feedback loop in which the more a person coughs, the more impact it has on the peripheral nerves in the airways, thereby amplifying peripheral responses.[17] "The consequence is that the brain is going to modulate the way it processes the signals centrally, to try to accommodate the excessive peripheral cough triggering." Such a combination, he went on, may have a maladaptive effect, leading to cough hypersensitivity and progressively worsening chronic cough triggering.[16,17]

CARING FOR A PATIENT WITH CHRONIC COUGH AND IPF

Regardless of the underlying mechanisms, chronic cough has a huge impact on the lives of people living with IPF.[3,6]

Kulkarni said the majority of the patients she saw in the clinic experience it. "It is not just a cough that might go away. This is something the patient has to live with. It can cause fatigue and disrupt sleep. When it is severe, it can cause chest discomfort or even incontinence in some."[3,6] The negative effects, she went on, often go beyond the physical. "The psychological and social impact is very significant and often overlooked,"[3] she explained. People can be embarrassed, avoid social situations, and, in some cases, develop anxiety and depression.[3,6] Such feelings were compounded during the COVID-19 pandemic, when coughing in public became a visible sign of infection, she explained. "A lot of patients tell us that cough probably impacts their quality of life more than shortness of breath."

Highlighting the burden, Kulkarni pointed to a survey of 197 people with IPF and non-IPF interstitial lung disease who experienced chronic cough.[18] A total of 63% reported they "often" or "almost constantly" had the urge to cough, while only 4% said coughing always relieved that urge. The most common triggers were respiratory related/sensation (22%) and exertion/physical activity/body position (22%), while 15% reported unknown triggers, and the cough was unpredictable. Normal everyday events such as talking or laughing (7%) or eating and drinking (7%) were also identified as triggers. Almost 80% reported that, once they started coughing, they continued coughing for more than 30 seconds. In terms of frequency, 35% reported daily coughing bouts, while around 30% reported coughing four or more times a week.[18]

The survey also demonstrated the significant impact cough had on their lives.[18] Almost half (48%) of patients reported that their cough interfered with activities of daily living "sometimes," "often," or "daily," while 46% experienced fatigue or exhaustion as a result of their cough. In 45% of respondents, cough "sometimes," "often," or "always" caused them to avoid social situations, while 16% said it

had significantly or extremely affected their ability to maintain physical or intimate relationships. When asked about the emotional impact of chronic cough, 71% reported feeling frustrated, 59% embarrassment, and almost a third (32%) anxiety.[18] The data show, said Kulkarni, that chronic cough in IPF is "not minor." "It has a profound impact on quality of life," she noted.

Participants' experience of healthcare with regard to their chronic cough was also explored in the survey.[18] The unmet need was clear in the findings. Of the 171 people who answered the question, 56% said they were currently using over-the-counter remedies, and 53% reported using inhalers or nebulisers. Other common treatments included benzonatate (22%), proton pump inhibitors (21%), and glucocorticoids (21%), while 11% reported no treatments and 2% reported speech or cough therapy. Yet 63% of participants said they had experienced no relief, or only partial/somewhat relief, with current or previous treatments. In addition, only 50% of participants said they felt "heavily involved in decisions about their cough treatment and care."[18]

Kulkarni said it was "really important" to routinely assess and proactively address cough, and to involve patients in the decision-making process. "We are challenged by the fact that we do not have many therapeutic options. Because of that, the amount of time spent talking to patients about cough is limited,"[3,5,7] she said, adding that healthcare providers tended to focus more on objective data, such as lung function, CT scans, and walk tests, simply because they were measurable. Another challenge is a lack of assessment tools. In the research setting, patient-reported measures such as the Leicester Cough Questionnaire (LCQ) and the Cough Visual Analogue Score (VAS) are often used to quantify severity.[19,20] Objective cough monitoring, which utilises wearable technology to measure cough frequency and intensity, is also common in trials.[21] There are several factors, however, that limit the use of such tools in routine clinical practice. Multi-item, structured questionnaire tools, for example, are often not practical from a time standpoint, and monitors are not validated for use in the clinic, Kulkarni explained.[22,23]

Explaining her own assessment and management method, Kulkarni said she used a stepwise approach. Assessment starts with taking a detailed history, looking at factors such as the duration of cough, the diurnal variations, and triggers. She attempts to identify any common contributors, such as gastro-oesophageal reflux, upper airway conditions, or medications.[5] She can then suggest treating the underlying cause. "If a patient says their cough is worse after they eat or lay down flat, for example, the cause may be reflux, rather than the IPF itself." Potential interventions include cough drops or over-the-counter cough medicines, and benzonatate, which reduces the cough reflex. However, efficacy is limited. Low-dose opioids are an option that may help some patients; however, they "come with [their] own challenges," said Kulkarni. "We have to be mindful of the potential side effects."[5]

Despite the challenges and the limited treatment options, there is still much to gain from having a conversation about cough in the clinic. Reflecting on her own experience, Kulkarni explained: "Even if you cannot eliminate the cough completely, improving it just slightly can have a meaningful difference to the patient's life," she said. Upcoming and ongoing clinical trials may be an option for some people, and, even where there are no suitable interventions, just having the conversation can help make the person feel validated. "At least they know that I have thought about it and am not ignoring it. Just that can have a psychological impact," she added.

LIVING WITH CHRONIC COUGH: A PATIENT PERSPECTIVE

Steve Ashton, a motorbike enthusiast and grandfather living in Cincinnati,

Ohio, USA, knows the impact of living with a chronic cough only too well. It had such a huge impact on his ability to speak that he gave up his business, and he routinely chooses to avoid social gatherings. "I have absolutely no control over the cough," he said. "When it comes, it comes, and I just have to bear with it until it is over. Sometimes it gets to the point where I physically get muscle aches in my back and shoulders, just from the cough itself."

Like many people living with the condition, he experienced a cough long before his IPF diagnosis, which came in 2021. He said he did not think much of it at first, but it got progressively worse over the course of 5–10 years. "There is a joke in the Cincinnati area that if you do not have a sinus infection, you are definitely not from Ohio," he said. "All my life, I have had coughs, and they have been treated as sinus infections." When he was finally diagnosed with IPF, he realised that he had been coughing for some time and that he had the same condition that had led to the death of both his mother and his youngest brother.

While he and Lucie, his wife of 48 years, are very active, regularly enjoying camping, hiking, and cycling, a chronic cough has had a huge impact on his life. After retiring from a 28-year law enforcement career in 2008, he was running an independent accident reconstruction franchise, which frequently involved giving talks and presentations, when he received his diagnosis. However, his cough forced him to retire at the end of 2024. "It was humiliating to stand at the podium in full uniform, trying to talk to 300 or 400 police officers, and just start coughing in the middle of it. I am a very professional person, and it pulled away at my pride," Ashton explained. "It got to a point where I was so embarrassed, I thought 'I just cannot do this anymore'. I loved what I was doing, but my personal perception was that people thought less of me." Describing the feeling, he said: "Picture yourself during the COVID era, when you go into a store, and everybody is wearing masks. The first person who coughs, everyone thinks 'Oh my God, we have to get away from you'." This embarrassment, as well as cough-related fatigue, has also significantly impacted his social life. "I feel like I have isolated myself," said Ashton. "I do not have the drive to go to see people, because I feel like I am becoming a zombie. I cannot function, and it is humiliating."

Despite the huge impact chronic cough has had on his life, Ashton said his healthcare team had never addressed the cough with him. "I would mention it to my pulmonologist, but it was like the cough was just a sidebar," he said. "I started to wonder, 'Did I really say that, or did I just think I said it?' It was like it went in one ear and out the other." Through patient forums, he has found an over-the-counter cough drop which he said, "helps a little," but "only sometimes." "I will take those when I'm driving or when it gets to the point where I can't have a conversation… but there really is nothing else I have found that can control it." He described the cough drop, as well as drinking mullein tea, as "very, very short stopgaps" that "do not address the issue behind" his chronic cough. "I wish there was something the medical field could do to prepare us for the way life is going to be."

In terms of triggers, he said there seemed to be "no rhyme or reason for it." "It just comes and goes on its own," he went on, adding that each coughing fit could last for anything from 60 seconds to 3 minutes. "It just comes on like a regular cough, but it physically hurts more than a normal cough, and I can hear the wheezing when I cough dramatically." Asked what he would like to change about his cough, he said he wished it would go away. "If there was some way of managing it, it would give me a piece of my life back. I would love to get back out in public and enjoy life." Even reducing the cough by 10%, he added, "would be better than nothing."

FUTURE OF CHRONIC COUGH MANAGEMENT

Ashton's story may sound very familiar to pulmonologists who work with people living with IPF. The future, however, could

look very different, said Drake. "One of the biggest shifts in the field of chronic cough recently is really conceptual. It says that chronic cough is not just a symptom of other diseases, but a neuropathic disorder: changes in the nervous system that regulate cough lead to a persistent and chronic disease that is incredibly debilitating," he explained.[7-9] "This reframing is important scientifically in terms of how we are thinking about developing new therapeutic strategies, but it is also going to be fundamentally important for the way we address chronic cough clinically."

As the evidence base deepens, and new agents make their way through pipelines and out into clinical practice, there is a potential for personalised treatments, he went on. "I am hopeful for a day when we have multiple options in this space, and that we will be able to do things like phenotype various forms of cough in a really precise way. Then we would be able to treat patients in a really targeted way, based on biomarkers or other clinical features." Kulkarni agreed. "As we develop a deeper understanding of the mechanisms of chronic cough, IPF, and its impact on patient outcome, I hope to see a shift towards more targeted, personalised treatments," she said. "This may be the treatment of comorbidities, or specific treatment [for] cough, or its direct impact." She hopes a new generation of chronic cough treatments would "truly have an impact on cough while minimising the side effects seen with the currently available options."[5] Drake said the scientific community was currently in the process of "moving down this really transformative pathway." "It is a very exciting time to be in the field, and I think we are going to be looking at this in a very different way in 5 or 10 years' time," he added.

As the research continues to develop, Kulkarni said she would like to see better tools for measuring cough make their way into clinical practice and for IPF care to move towards a multidisciplinary approach that places more emphasis on the patient's perspective. "I hope we will learn more about speech therapy and involve that in our multidisciplinary approach, and maybe even getting [the] palliative care team involved earlier to help with the symptoms." Without this holistic approach, there is a danger of overreliance on objective data such as forced vital capacity, which does not necessarily reflect how the person feels or how the condition is impacting their lives, she believes. "We are just making the numbers look good, without truly having a holistic impact on how the patient feels. Trying to get this multidisciplinary approach, combined with, hopefully, better treatment options in the future, could really help us change that."

CONCLUSION

Summing up, Kulkarni said that chronic cough in IPF is far more than an inconvenient symptom. It profoundly affects patients' physical, emotional, and social wellbeing, and frequently overshadows breathlessness in terms of day-to-day burden.[2,5,6,19] Ashton's personal experience of living with chronic cough clearly illustrates how it can erode confidence, limit professional and social participation, and lead to isolation, anxiety, and reduced quality of life.

Despite this, chronic cough has historically been under-recognised and insufficiently addressed in clinical practice.[3] Limited treatment options coupled with inconsistent assessment and a tendency to prioritise objective disease markers have contributed to a gap in care.[3,19,20] However, recent advances in understanding the underlying mechanisms, particularly the recognition of chronic cough as a neuropathic disorder involving dysregulated peripheral and central neural pathways, mark an important turning point.[8-10]

Ultimately, understanding the mechanisms and the burden of chronic cough matters, said Drake.

"The fact is that, in the clinic, chronic cough is a very, very prevalent concern. Patients suffer with this for months and years, and we have few to no effective therapeutics for targeting this incredibly debilitating

disease." It prevents patients from being social, from working, and from living their lives in the way they want, he said.

Now, that could all be about to change. "We are potentially on the cusp of new therapies.

There is a lot of enthusiasm about those that are coming through the pipeline, and that we might finally be able to offer something to the millions of patients who have really been suffering."

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