

Insight Brief

Chronic Cough in Interstitial Lung Disease: Current Insights and Emerging Innovations

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Introduction

Chronic cough is a significant and distressing symptom for many patients with Interstitial Lung Disease (ILD), impacting their physical and emotional well-being. Estimates indicate that the prevalence of chronic cough in ILD varies widely—up to 33% in scleroderma-associated ILD and 50% to 80% in idiopathic pulmonary fibrosis (IPF).¹ This symptom profoundly influences quality of life, affecting physical activity, social engagement, and overall lifestyle. Recent findings suggest that chronic cough may even serve as an early indicator of disease progression,² reinforcing the need for comprehensive cough assessment in ILD management. This insight brief provides an accessible, research-driven overview of cough in ILD for professionals in related fields.

Understanding Interstitial Lung Disease (ILD) and cough

ILD encompasses a diverse range of over 200 lung disorders characterized by scarring of lung tissue, resulting in reduced oxygen transfer to the bloodstream. Major subtypes include IPF, sarcoidosis, and connective tissue disease-associated ILD, with causes varying from environmental exposures to autoimmune disorders. In ILD, cough is predominantly dry and unproductive, originating from the architectural distortion impact on airways, and lung irritation rather than mucus accumulation. For patients, the persistent nature of this cough leads to lifestyle changes aimed at avoiding triggers and coping with its disruptive effects on everyday life.

Chronic cough as a prevalent and significant symptom in ILD

Studies have shown that the frequency and intensity of cough can serve as early indicators of disease progression, preceding other ILD symptoms.² For instance, in fibrotic forms of ILD, where scarring and fibrosis are more advanced, patients tend to report a higher cough burden. This cough burden translates into restrictions in social interactions, physical activity, and

overall quality of life, with patients often experiencing fatigue, anxiety, and social embarrassment.

Mechanisms behind cough in ILD

The persistent cough in ILD is driven by a combination of factors:

- **Nerve sensitization:** Chronic scarring in ILD heightens nerve sensitivity, leading to an exaggerated cough response to mild irritants. This hypersensitivity results in what's termed "cough hypersensitivity syndrome," where even minimal stimuli like speaking or inhaling can trigger a cough.³
- **Structural lung changes:** In ILD, lung tissue thickens and scars, which further irritates the lung's nerve endings, creating a feedback loop of chronic irritation and cough.
- **Central nervous system involvement:** Some researchers propose that the brain's perception of cough may adapt over time in ILD patients, responding to even slight irritants as potential threats, which compounds cough severity and frequency.⁴

Together, these mechanisms create a challenging symptom that does not respond well to typical cough suppressants, as they fail to address these unique structural and neurological drivers of cough in ILD.



Measuring the impact of cough: patient-reported outcomes and biomarkers

To understand the true impact of cough, healthcare providers increasingly rely on patient-reported outcomes (PROs), such as Visual Analog Scales (VAS) and Numeric Rating Scales (NRS), to capture cough severity and its effects on quality of life. These tools enable patients to quantify their experience, giving clinicians insights that go beyond clinical observations alone. Patients frequently report symptoms such as exhaustion, social embarrassment, and even urinary incontinence due to intense coughing fits.

In recent years, researchers have also identified potential biomarkers that correlate with cough severity and disease progression. Biomarkers like Krebs von den Lungen-6 (KL-6) have shown promise in detecting disease activity, particularly in connective tissue disease-associated ILD.⁵ Other biomarkers under investigation include CCL18 and surfactant D, although these are not yet widely adopted in clinical practice. By enabling earlier detection and closer monitoring, biomarkers could support more personalized treatment strategies for ILD-associated cough.

The link between cough frequency and disease severity

Evidence increasingly supports a correlation between cough frequency and disease severity.⁶ Studies demonstrate that patients with higher cough frequencies often show more extensive fibrosis or scarring in HRCT scans. This correlation highlights the importance of regular and comprehensive cough assessment in ILD management, particularly in monitoring disease progression in patients with high cough burdens.

Technological advancements in cough monitoring

Innovative technologies, such as cough monitors using artificial intelligence (AI), are beginning to play a role in ILD management. These monitors offer an objective way to measure cough frequency and intensity, providing

real-time data that can inform treatment adjustments and better understand symptom patterns. These AI-driven tools are particularly useful in tracking the effectiveness of interventions over time, offering a more dynamic approach to symptom management and patient care.

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Pharmacological approaches: new therapeutics on the horizon

Although traditional treatments like opioids and cough suppressants are still used, their efficacy in ILD is limited and often comes with side effects. In recent years, research has focused on novel therapeutic agents to alleviate cough in ILD patients, particularly those with refractory symptoms:

- Gefapixant is a P2X3 antagonist that has shown promise in clinical trials for its antitussive effects. However, it failed to meet endpoints in an IPF trial.⁷ Other agents in this class may still show effectiveness but are currently at the research stage.
- Neurokinin inhibitors such as Orvipitant are also under investigation for their potential to modify cough reflex pathways, providing a more targeted approach for ILD-associated cough. Though still in experimental stages, they represent a promising new avenue for treating this challenging symptom.

These pharmacological advancements are paving the way toward more effective cough management strategies in ILD, aiming to address the neurological basis of cough rather than simply suppressing it.

Non-pharmacological approaches: speech therapy and behavioral techniques

Non-pharmacological interventions, like speech therapy, can also provide some relief for ILD patients. Speech therapy focuses on teaching patients controlled breathing and cough-suppression techniques, which can reduce the frequency and intensity of coughing fits, especially in social contexts. Though it requires a long time to implement and show effect, it remains the one that provides the most consistent results for patients amongst non-pharmacologic interventions. Other strategies, such as the use of humidifiers or breathing exercises, may also benefit some patients by minimizing cough triggers and easing lung irritation.

The social and psychological impact of chronic cough

Chronic cough in ILD goes beyond a mere physical symptom, influencing patients' social lives, mental health, and overall well-being. Many patients experience isolation due to the embarrassment and discomfort associated with constant coughing, avoiding social situations and even public outings. This isolation can lead to feelings of loneliness and, over time, increase the risk of depression and anxiety. Healthcare providers play a vital role in supporting these patients, helping them access resources like counseling or support groups to manage the emotional toll of their condition.

A multifaceted approach to cough management

Given the complex nature of ILD-associated cough, effective management often requires a combination of pharmacological and non-pharmacological strategies, tailored to each patient's unique needs. This multifaceted approach includes:

1. **Patient education:** Teaching patients about the nature of their cough and available coping strategies can empower them to manage symptoms more effectively.

2. **Targeted pharmacological treatments:** Emerging agents like gefapixant and neurokinin inhibitors offer new hope for effective symptom relief.

3. **Behavioral interventions:** Techniques like speech therapy and cough suppression exercises can help patients control cough in specific situations, reducing social and emotional disruptions.

4. **Continuous monitoring and support:** Ongoing assessment of cough severity and impact, whether through PROs or AI-based cough monitors, provides valuable data to adjust treatments as the disease progresses.

Conclusion: advancing research and care for ILD-associated cough

Chronic cough remains a prominent, unresolved issue in ILD, impacting the lives of countless patients and underscoring the need for ongoing research. With new insights into the mechanisms of cough hypersensitivity, promising biomarkers, and emerging therapeutics, the field is moving closer to effective, individualized treatments. For research professionals and clinicians, the current emphasis on comprehensive assessment, personalized interventions, and patient education marks a step forward in managing this challenging symptom, ultimately enhancing the quality of life for those with ILD.

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