

Advances in Optimizing the Diagnosis and Management of Refractory Chronic Cough

Toolkit for Healthcare Professionals

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You can access this activity's two patient cases and accompanying video content at www.ime.healthcare

Fast facts about CHRONIC COUGH¹⁻⁶

- It is defined as a cough that is persistent for **more than 8 weeks** – but can last 20+ years in 10–20% of cases.
- 2 in 3 affected individuals are **women**.
- It can be associated with vomiting, urinary incontinence (more commonly in women, yet rarely discussed), sleep disturbances and, if sufficiently severe, chest and intra-abdominal pain, rib fractures, and hernias.
- Many individuals with chronic cough develop **anxiety** and **depression**.
- **Cough syncope** occurs in approximately 10% of cases and can lead to fatal consequences.
- It is often **inadequately treated**.

What is...

Refractory chronic cough (RCC)?

Refractory chronic cough is a cough that persists despite investigation and treatment for the presumed associated common and uncommon conditions.^{2,7}

It may be referred to as **unexplained chronic cough (UCC)** when its cause remains entirely unexplained despite optimal investigation.^{2,7}

How do we diagnose RCC?

Primary Care chronic cough checklist^{6,10,12-15}

Identify “**red flags**” requiring **urgent investigation and referral** by:

- Getting a **detailed medical, family and social history**
- Addressing **modifiable risk factors**
- Assessing **cough intensity and impact on QoL**
- Requesting a **chest X-ray**
- Performing a **thorough physical examination**

Conditions commonly associated with chronic cough^{6,8}

- Asthma
- Non-asthmatic eosinophilic bronchitis
- Gastroesophageal reflux disease
- Upper airway cough syndrome
- Cough hypersensitivity syndrome
- A combination of the above

Chronic cough “red flags”⁹

- Hemoptysis
- Smoker >45 years of age with new cough, change in cough, or coexisting voice disturbance
- Adults 55–80 years with 30 pack-year smoking history and currently smoke or quit within the past 15 years
- Prominent dyspnea, especially at rest or at night
- Hoarseness
- Systemic symptoms
- Trouble swallowing when eating or drinking
- Vomiting
- Recurrent pneumonia
- Abnormal respiratory exam and/or chest X-ray

A **diagnosis of chronic cough can be delayed by several years**, during which individuals undergo **multiple (often repeated) visits, referrals, and extensive testing**.^{4,6,8}

CHEST and ERS guidelines recommend an **initial diagnostic workup** consisting of a **comprehensive clinical history, physical examination, and focused diagnostic testing**, followed by a **stepwise empirical therapeutic regimen**.^{4,9-11}

How do we treat RCC?

In view of the therapeutic area covered and currently available management options, this activity discusses the off-label use of opioids. Please note that **opioid use is associated with significant risks of addiction, abuse, and misuse, even at prescribed or recommended doses**. Merck does not promote or condone the use of any medication or procedure for an off-label use.

This educational activity provides information, in whole or in part, related to unlicensed or unapproved drugs. For full prescribing information, including indications, contraindications, warnings, precautions, and adverse events, please refer to the approved product labeling in your country/region. Please note that products may have different product labeling according to geographical location. In Europe, full prescribing information is available from the **European Medicines Agency**, and in the United States, from the **US Food and Drug Administration**.

Key guidelines on diagnosis and treatment of chronic cough

American College of Chest Physicians (ACCP/CHEST)^{9,11}

European Respiratory Society (ERS)¹⁰

To date, there are no agents indicated for RCC approved by the FDA or EMA.¹⁶

Current guidelines recommend the **off-label** usage of certain **neuromodulators**.^{10,11}

- However, many patients are unresponsive to these agents and/or unable to tolerate their adverse effects (e.g., fatigue, dizziness, xerostomia, sedation), leading to **treatment non-adherence or discontinuation**.^{16,17}

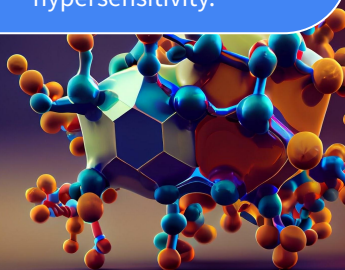
In addition, guidelines recommend **non-pharmacologic therapy** such as **multicomponent physiotherapy** or **speech and language therapy**, alone or in combination with pharmacologic agents.^{10,11}

Guideline pharmacotherapy recommendations for the treatment of RCC/UCC^{10,11}

Treatment	2016 CHEST	2020 ERS
Gabapentin	Recommended (Grade 2C)	Recommended (conditional recommendation, low-quality evidence)
Pregabalin	Not evaluated	
Low-dose morphine	Not recommended	Recommended (strong recommendation, moderate quality evidence)

What are P2X3 receptor antagonists?

P2X3 are ion channel receptors activated by ATP, released during airway cellular injury and inflammation, increasing peripheral neural excitability and contributing to cough reflex hypersensitivity.¹⁸



Gefapixant: Clinical trial data in RCC/UCC

- Gefapixant is the first and, so far, only agent to demonstrate efficacy in human clinical trials, **COUGH-1** (N=730; 12 weeks) and **COUGH-2** (N=1,314; 24 weeks).^{16,19}
- Gefapixant 45 mg BID **significantly reduced 24-hour cough frequency** (primary endpoint) versus placebo.¹⁹
- Cough frequency reduction evident at first evaluation (Week 4) and increased through Week 12 (COUGH-1) and Week 24 (COUGH-2).¹⁹
- In COUGH-2, the key secondary endpoint of change from baseline in awake cough frequency by Week 24 was significantly higher with gefapixant than placebo.¹⁹
- Pooled patient-reported outcomes (LCQ, VAS, CSD) collected over 52 weeks showed numerically greater improvements with gefapixant compared to placebo.²⁰
- **Safety:** Gefapixant had an overall acceptable safety profile. The most common adverse events were mild or moderate taste-related adverse events, reversible upon discontinuing therapy.^{19,20}

Abbreviations: ACCP, American College of Chest Physicians; ATP, adenosine triphosphate; BID, twice daily; CSD, Cough Severity Diary; EMA, European Medicines Agency; ERS, European Respiratory Society; FDA, Food and Drug Administration; LCQ, Leicester Cough Questionnaire; QoL, quality of life; RCC, refractory chronic cough; UCC, unexplained chronic cough; VAS, Visual Analog Scale.

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