ABOUT THE AUTHOR

Imran Satia M.A MB BChir (cantab) MRCP PhD

Dr. Imran Satia graduated in Medicine from the University of Cambridge in 2006. He gained his Membership of the Royal College of Physicians (London, UK) and completed his specialist training in general internal medicine and respiratory medicine. In 2017 he was awarded a PhD in the mechanisms of cough and was awarded the British Medical Association James Trust Award and the European Respiratory Society Respire 3 Marie Curie Post-Doctoral Fellowship. Imran is now on Faculty at McMaster University and the Firestone Institute for Respiratory Health working as an Assistant Professor in Respiratory Medicine. He consults on patients with asthma, refractory chronic cough, complex airways diseases and has a broad research interest in understanding the mechanisms and developing treatments for these troublesome conditions.

CURRENT PHARMACOLOGICAL AND NON-PHARMACOLOGICAL THERAPIES FOR CHRONIC COUGH

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INTRODUCTION

Chronic cough, defined as cough lasting 8 weeks or longer, affects approximately 10% of adults globally, but with large global variations with prevalence estimates ranging from 2-18%.[1] The prevalence of chronic cough in adults over the age of 45 in the Canadian Longitudinal Study of Ageing (CLSA) was 16%, the second highest in the world.[2] Interestingly, the prevalence and incidence is higher in English speaking compared with French speaking participants.[3] Cough is the leading cause for ambulatory and primary care visits to physicians and one of the most common reasons for referral to specialist care.[4,5] Chronic cough is associated with aging, smoking, higher body mass index, use of an ACE-inhibitor, and airways diseases. More recently, novel data has shown that symptoms of depression and psychological distress independently increase the risk of developing chronic cough by approximately 20%.[6] Data from clinical trials and observational cohort studies suggest that patients with chronic cough have a median cough frequency of 20 coughs/hr.[7] This may lead to distressing physical, psychological and social consequences such as urinary incontinence, exhaustion, fatigue, anxiety, frustration, embarrassment and social isolation, which all impairs quality of life.[8] Chronic cough can be challenging to treat, since most over-the-counter therapies are ineffective and current treatments for chronic cough are all considered 'off-label'.[9,10] Although most cases are due to a benign cause, chronic cough can represent a serious underlying condition. A recent Canadian consensus has identified a simplified approach which can aid in the management of chronic cough and provide treatment for refractory or unexplained chronic cough.[11] The guiding principles of this approach

include i) investigation to rule out serious underlying conditions, ii) objective testing to prevent over and under-diagnosis, iii) treatment of identifiable diseases and traits and iv) monitoring to ensure effectiveness of treatment, including minimization of side effects and appropriate titration of treatment.

WHAT IS REFRACTORY AND UNEXPLAINED CHRONIC COUGH?

After conducting a thorough history, examination, and appropriate investigations, an underlying disease may be detected in patients presenting with chronic cough. Treatment targeting this/these condition(s) may completely or partially resolve cough. In such cases, the chronic cough is considered 'explained' and a symptom of the underlying condition. In cases where an associated condition is found but does not fully resolve with appropriate treatment, the cough is considered to be "refractory chronic cough" (RCC). In cases where no underlying disease is identified, the cough is described as 'unexplained chronic cough'(UCC).[12] In patients with both RCC/UCC there are often clinical features of cough hyper-sensitivity syndrome.

WHAT IS COUGH HYPERSENSITIVITY SYNDROME?

Patients often describe sensations of 'tickle', 'irritation', or 'something stuck in the throat'. Cough is often triggered by changes in temperature, perfumes, aerosols, strong smells, talking, laughing, and singing.[13,14] Cough Hypersensitivity Syndrome is considered an umbrella term to describe the neuro-pathological mechanisms within the central and peripheral nervous system which may be implicated in RCC/UCC.[14] This has been described as "Cough Hypersensitivity Syndrome", as many patients cough after exposure to low levels of thermal, chemical, or mechanical stimulation.[14,15]

WHAT IS THE UNDERLYING NEUROPHYSIOLOGY CAUSING EXCESSIVE COUGH?

Cough can be under both voluntary and involuntary control, but the cough reflex is the archetypal airway defensive reflex to prevent aspiration of foreign bodies or inhalation of noxious chemicals like smoke. The vagus nerve projects sensory afferents to the upper and lower respiratory tract, which, when stimulated, transmits signals to the brainstem. These signals are projected to cortical neurons in the thalamus and primary somatosensory cortex. If the stimulus is great enough, coughing will occur via the spinal motor efferent nerves to the diaphragm, intercostal muscles, and glottis. Excessive cough in patients with RCC/UCC could thus be due to i) increased activation of the airway peripheral nerve terminals by chemical irritants/mucus/alarmins (e.g., extracellular ATP), ii) hypersensitivity and/or hyper-responsiveness of the afferent vagal nerve, brainstem, and higher cortical projections and iii) impaired voluntary control and/or descending inhibitory control pathways. Recent studies suggest patients with RCC have impairment in the descending inhibitory control neurons[16] and a relative lack of voluntary cough suppression[17] compared to healthy controls.

WHAT TREATMENTS ARE CURRENTLY USED FOR REFRACTORY OR UNEXPLAINED CHRONIC COUGH

There are currently no approved treatments for RCC/UCC, thus the therapies described below are considered 'off-label' (**Table 1**). The American College of Chest Physicians (ACCP) and European Respiratory Society (ERS) suggest speech and language therapy and neuromodulators should be considered as appropriate therapies/interventions for the treatment of RCC/UCC.

Speech and Language Therapy

Speech and language therapy provides a safe and effective adjunct or alternate therapy in patients who do not wish to take neuromodulator medications or for those who develop intolerable side effects.[18] However, access to adequately trained therapists in the management of RCC/UCC can be challenging, and patient compliance with exercises is difficult beyond the initial 4 visits that are recommended as part of the speech and language therapy care algorithm.

Treatment of Neuromodulation

Neuromodulator treatment includes low-dose morphine[19], gabapentin[20], and pregabalin[21]. All three therapies demonstrate improved symptom control and improved quality of life in randomised controlled trials; however, these trials have been small, and the doses used in the RCTs were associated with high rates of adverse events, such as dizziness, drowsiness, unsteadiness, and fatigue. One study using amitriptyline 10 mg at bedtime reported symptomatic improvement but lacked a placebo control or a validated tool to assess improvements in cough.[22] In clinical practice, most patients are unable to tolerate the high doses of neuromodulators used in RCTs, hence it is recommended to start gabapentin at 100 mg TID and titrate up to a maximum of 300 mg TID, or to start pregabalin at 50-75 mg BID and increase on a weekly basis up to 150 mg twice a day. The use of low-dose opioid therapy can be attempted after discussion with the patient on the potential benefits and harms of treatment. Low-doses, between 5-10 mg of slow- or modified-release morphine BID may be effective, and in those who achieve clinical response, the benefit is often apparent

within 3-7 days.[19] Another recent study showed that treatment for one week can reduce objective cough frequency by up to 72%.[23] Hence, if the patient does not demonstrate clinical benefit after a 1–2-week trial, low-dose morphine can be discontinued. If there is benefit, then the dose can be titrated to minimize side effects such as constipation, drowsiness, and sedation. A clinical audit in a tertiary cough clinic has shown that approximately 36% of patients demonstrate a complete or partial response to low-dose morphine and nearly two-thirds develop no side effects.[24] If cough severity improves and side effects are mild, changing the dose and timing may be useful. Alternative regimens include once daily dosing at night, alternate day dosing, or, when required, 3-4 hours before socializing, teaching or attending important public events. In patients who have been on treatment for longer periods, short periods 'off-treatment' can be carefully attempted to prevent tolerance.

WHAT DOES THE FUTURE HOLD FOR REFRACTORY AND UNEXPLAINED CHRONIC COUGH?

In the absence of any licensed treatments, new treatments are desperately needed for RCC/UCC. Over the last 7 years, there have been successful studies demonstrating blockade of P2X3 ion channels found on peripheral airways nerves may be a successful strategy to reduce coughs.[25-27] Gefapixant is an oral, non-opioid, peripherally acting P2X3 antagonist which met its primary outcome in two phase 3 studies at a dose of 45 mg BID. Subjects in these studies had been diagnosed with RCC/UCC for at least 1 year prior to study entry, showed no abnormalities on chest radiology contributing to the cough (within 5 years of the study and after the onset of chronic cough), and had cough severity visual analog scale scores of ≥ 40 mm at both the screening and baseline visits. The primary endpoint in both studies was 24-hour cough frequency and safety/tolerability. The placebo adjusted estimated relative reduction in cough frequency was approximately 18% in COUGH-1 and 15% in COUGH-2.[25] These reductions were lower than expected due the significant placebo effect, the reasons for which are yet to be fully understood. The most prevalent side-effect was taste disturbance which was experienced by 60% and 69% of subjects at the highest dose of 45 mg compared with 3% and 8% of subjects in the placebo arm in COUGH-1 and COUGH-2 respectively. The putative mechanism is due to cross-selectivity against the hetero-trimer P2X2/3 which is thought to transmit taste from the tongue. Nonetheless, gefapixant has now been approved in Japan and Switzerland and is currently under-review by the U.S Food and Drug Administration (FDA), Health Canada and European Medicines Agency (EMA). Another P2X3 antagonist is currently under development by Bellus Health with its lead molecule BLU-5937 recently passing phase 2b with a placebo run-in study showing an approximate 34% reduction in 24-hour cough frequency with only a 6% taste disturbance.[26] Another P2X3 antagonist, sivopixant did not meet its primary endpoint in the phase 2b dose-finding study, but the optimum dose is still unknown.[27]

CONCLUSIONS

Chronic cough is a common troubling symptom that can severely affect the physical, social, and psychological well-being of patients. Current guidelines recommend treatment of any identifiable conditions, but if the cough is refractory or unexplained, speech and language therapy along with neuromodulator treatment, such as low dose opioids, pregabalin, and gabapentin, can be trialed. Clinicians should monitor and minimize the dose and length of treatment with centrally acting neuromodulator treatment to limit side effects and tolerability in a respiratory or specialized cough clinic. Emerging therapeutic agents such as the novel oral P2X3 antagonists may provide hope to patients in the years to come.

Name/Dose	Mechanism	Pros	Cons
Speech Therapy	Teaches cough suppression, avoid triggers, laryngeal exercises, hydration	No side effects Patient led	Access, Cost, Requires patient motivation Limited subjective improvement beyond initial 3-4 month treatment period, operator dependent 1 study of 24-hr cough frequency
Low-Dose Morphine 5-10 mg M/R BID	mu-opioid receptors	Fast onset 1-2 week trial	Nausea, drowsiness, unsteadiness, stigma, constipation 1 RCT with subjective endpoint
Pregabalin 150 mg BID	$\alpha 2\delta$-2 subunit of presynaptic voltage-gated calcium channels	Can start very low doses and titrate up	Drowsiness, hallucinations, suicidal ideation, weight gain, hair loss, difficult weaning off, 150 mg BID rarely tolerated 1 RCT with speech therapy, no improvement on spontaneous objective cough frequency
Gabapentin 300 mgTID	$\alpha 2\delta$-1 and $\alpha 2\delta$-2 (low affinity)	Can start very low doses and titrate up	Unsteadiness, dry mouth, nausea, sleepiness 1 RCT with subjective endpoint Cough monitoring for 1-hour only
Amitriptyline 10 mg -25 mg OID	TCA, serotonin/ noradrenaline reuptake inhibitor	Might also help with depression, anxiety	Tremor, dry mouth, weight gain, 1 uncontrolled study with unvalidated subjective endpoint

Table 1: Current Guideline Recommended Treatment Options for Refractory and Chronic Cough. OID; once per day BID; twice per day, RCT; randomised controlled trial, TCA; tricyclic anti-depressant

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