When a cough persists

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Coughing is an essential defensive mechanism of the respiratory tract.^{1,2} It may also be an indication of an underlying disease, either respiratory or non-respiratory in origin.²

Based on the duration of the cough, the cough may be classified as acute, subacute or chronic.³ Classifying the cough helps the clinician identify likely diagnostic possibilities.³ A cough may also be considered to be productive (wet) or non-productive (dry).⁴

Classification of cough

Acute cough: generally lasts for less than three weeks and is often self-limiting, not requiring therapy.³ Acute coughs are most often due to upper respiratory tract infections and acute bronchitis.⁵ Repeated cases of acute cough may be indicative of an underlying chronic condition, and may warrant further investigation.⁶

Subacute cough: lasts between three weeks and eight weeks.³ Often, a subacute cough occurs post infection as a result of bronchial hyperresponsiveness.^{3,6}

Chronic cough: is a cough that lasts more than eight weeks.³ A chronic cough may be due to a multitude of factors, including gastro-oesophageal reflux, upper airway cough syndrome (UACS) and asthma.² Patients with a chronic cough often have a minimally productive or dry cough.²

Management of a subacute or chronic cough involves a systematic approach to identify the underlying cause.⁷ This may present as quite a challenge due to the myriad of possibilities, and in some cases, patients may not always respond to a specific therapy.⁷ Increased sensitivity of the cough reflex is sometimes noted in patients with a dry cough, and interestingly, women have been found to have a more sensitive cough reflex than men.⁴

Cough receptors are found in the epithelium of the respiratory tract (upper and lower), pericardium, oesophagus, diaphragm and stomach.⁸ They may also be found in the auditory canal and tympanic membrane.⁴ Stimulation of these receptors sends impulses via an afferent pathway (vagus nerve) to the "cough centre" in the medulla.^{3,4} Signals from there are then transmitted via the efferent pathway (vagus, phrenic and spinal motor nerves) to the expiratory musculature in effector organs (expiratory muscles, diaphragm, larynx, trachea and bronchi),

which results in the production of a cough.^{3,4} Although a cough arises via the activation of a reflex arc, this reflex can be initiated and suppressed voluntarily depending on which peripheral sensory nerves are stimulated.^{1,2} (See Figure 1.)

For patients who inadequately respond to specific treatment, and where no underlying cause can be determined, nonspecific suppressive treatment may be recommended.^{4,7} However, it must be noted that cough suppression is only warranted under certain circumstances, as coughing is the respiratory tract's defence mechanism that helps clear excessive secretions, irritating material and warns of harmful substances in the air.^{1,4}

When to consider antitussives

When a persistent dry cough is not responding to treatment or when coughing becomes persistent, hindering sleep, or interfering with a patient's daily activities, antitussive therapy may be considered.^{2,4,7} Productive coughs should not be

Figure 1: The Cough Reflex Arc^{4,8}

Adapted from: Padma L. Current drugs for the treatment of dry cough. J Assoc Physicians India. 2013;61(5 Suppl):9-13. and Mahashur AA, Banka R. Dry Cough: Presentation, Causes and Management Algorithm.[updated 24 Dec 2015; cited 29 Apr 2020].

routinely suppressed, as it may lead to a retention of mucus and stasis, possibly leading to the development of infection.⁹

Antitussives may be centrally or peripherally acting.⁸

Centrally acting antitussives

Centrally acting antitussive agents exert a depressive action on the medullary cough centre.⁸ This depressive action decreases the nerve impulse discharges to the effector organs that produce cough.^{2,8}

The most common centrally acting agents include codeine, dextromethorphan and pholcodine.² Potential for abuse restricts the use of codeine to short-term use only or for as long as is medically necessary.^{9,10}

Gabapentin has also been used "off-label" for coughs that are resistant to other tried therapies.⁷

Dextromethorphan	<ul style="list-style-type: none"> Although structurally related to codeine, dextromethorphan is considered a non-opioid cough suppressant with an improved safety profile versus codeine.⁷ Unlike codeine, dextromethorphan does not have analgesic or sedative properties, and at regular doses, does not cause respiratory depression.⁸ Long-term use has not been shown to cause tolerance.⁸ Use with caution in patients with asthma, emphysema, respiratory depression and liver impairment.⁹ Dextromethorphan is contraindicated for use in patients taking monoamine oxidase inhibitors (MAOIs).⁹
Pholcodine	<ul style="list-style-type: none"> Pholcodine is an opioid cough suppressant, but unlike codeine, has little or no metabolism to morphine.⁹ It also has a longer elimination half-life than codeine and should therefore be dosed less frequently.⁹ As with dextromethorphan, caution should be exercised in patients with asthma, emphysema, respiratory depression and liver impairment.⁶
Gabapentin	<ul style="list-style-type: none"> American College of Chest Physicians (ACCP) guidelines recommend gabapentin (a neuromodulator) in the symptomatic treatment of unexplained chronic cough that is refractory to other measures.⁷ Dose is initiated at a low concentration (300 mg once a day) and increased gradually until the cough is relieved, adverse effects occur, or a maximum daily dose of 1 800 mg (in 2 divided doses) is achieved.⁷ Risks versus benefits should be discussed with the patient.¹¹ Adverse effects include nausea, diarrhoea, somnolence, nystagmus, weakness, tremor, emotional lability and peripheral oedema.⁷

Morphine and methadone, in the centrally acting antitussive group, are not used routinely, but rather in special cases (e.g. lung cancer), due to their side-effect profile and abuse potential.⁹

Peripherally acting antitussives

Peripherally acting antitussives work on the afferent or efferent nerves of the cough reflex and inhibit their responsiveness.²

On the afferent side, peripherally acting antitussives act as mild anaesthetics or analgesics on the respiratory mucosa, reducing the input of stimuli.⁴

On the efferent side, antitussives that work peripherally, may increase the effectiveness of the cough mechanism, making it easier to expectorate secretions (e.g. ipratropium bromide).^{4,7}

Peripherally acting antitussives may be further classified as demulcents, local anaesthetics (e.g. benzocaine or lidocaine), and humidifying aerosols.⁸

Demulcents	<ul style="list-style-type: none"> Can be in the form of syrups or lozenges.⁴ Useful for coughs originating in the pharyngeal area by soothing irritability.^{4,12} Examples include acacia, glycerine, liquorice, honey, Syrup Simplex.^{8,13}
Local anaesthetics	<ul style="list-style-type: none"> A few patients with refractory cough may benefit from inhaled lidocaine.⁷ Examples include lidocaine and benzocaine.²
Humidifying aerosols	<ul style="list-style-type: none"> Steam may help to liquify lung secretions and the warm moist air may soothe the airways.¹³ Although menthol or eucalyptus may be added to the water, it does not increase the clinical effect of using steam on its own.¹³

Inhaled ipratropium bromide, an anticholinergic, has been shown to ease cough.⁷ It is thought to exert its action on the efferent nerves of the cough reflex as well as by altering mucociliary factors, decreasing the stimulation of cough receptors.⁷

Combination ingredients

Antitussives may be found in combination with other active ingredients to treat multiple symptoms.¹³

First generation antihistamines, such as doxylamine, chlorpheniramine and diphenhydramine may work centrally and peripherally, decreasing cough frequency and drying up secretions, which may help to relieve cough with concomitant nasal symptoms, such as rhinorrhoea.^{4,8,13}

Antitussive agents, such as dextromethorphan are often available in combination with one of the above first generation antihistamines in a syrup form. Combining the demulcent effect of a syrup or lozenge with an antitussive, such as dextromethorphan, has been shown to be effective in cough suppression.¹³ Other ingredients, such as decongestants, antipyretics and expectorants may also be available in combination with antitussives.⁸

Certain combinations, such as antihistamines combined with expectorants do not make pharmacological sense, as they have opposing actions.⁶ There is no clear evidence that expectorants (e.g. guaifenesin) are effective in alleviating a dry

cough.⁴ Encouraging sufficient fluid intake assists in easing expectoration.⁴

Conclusion

While all possible effort should be made in determining the cause of a chronic dry cough, there are some patients that do not adequately respond to various treatment methods.⁷ For patients where a persistent cough is affecting their daily lives, antitussives may be considered.⁴ Although studies are limited, the patient may also benefit from nonpharmacological interventions, such as speech therapy, breathing exercises and cough suppression techniques.⁷

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