

A modern approach to cough management

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Abstract

Coughing is one of the most common symptomatic reasons for patients to consult their healthcare practitioners. Their coughing may be caused by various factors such as respiratory tract infections, asthma, inhaled irritants, postnasal drip syndrome and gastro-oesophageal reflux disease. Coughing can be classified as either acute or chronic cough, and acute coughing is usually self-limiting. Patients can present with either 'wet' (chesty or productive) or 'dry' (non-productive) coughs. Unfortunately, a cough is generally uncomfortable and may interfere with daily activities, including sleep. Understanding how coughs manifest enables the health professional to provide adequate therapy. Evidence suggests that cough mixtures' effectiveness is disputable, but many patients have reported good results; hence, the medication is used in various combinations. This article provides an overview of the pathophysiology, causes and treatment of acute cough.

Keywords: cough, antitussive, mucolytic, expectorant, NTS, NAC, asthma, GORD

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Introduction

Coughing is a reflexive physiological response to external stimuli that may be intermittent or persistent. It is intended to clear the airway of secretions (mucous, oedematous fluid and pus) and particles (inhaled material, infectious agents, harmful substances and foreign particles) that accumulate within the respiratory tract. Other factors, like dysfunctional mucociliary clearance, may lead to mucus accumulation, which may require clearance by coughing.¹ Normally, a cough is purported to be protective but excessive coughing may damage the mucosa. Patients are often motivated to seek medical attention, with health professionals being requested to recommend therapies because coughing remains a common complaint.^{2,3}

Pathophysiology

Coughing results from repeated stimulation of a complex cough reflex arc that originates from afferent impulses from sensory nerve fibres that lead to the cough centre located in the upper brain stem and pons and then back to the diaphragm, abdominal wall and inspiratory and expiratory muscles via the efferent pathway.^{3,4} This is initiated by particulates irritating the countless cough receptors that are located mainly in the trachea, bronchi and larynx, but also in the external auditory canals, eardrums, paranasal sinuses, pharynx, diaphragm, pleura, pericardium and stomach.^{3,4} These receptors are sensitive to either physical or chemical stimuli, such as heat, acid and capsaicin-related compounds.⁴ These receptors include rapidly-adapting receptors (RAR), slow-adapting stretch receptors (SARs) and C-fibres. A stimulatory signal is conveyed by an afferent pathway using the vagus nerve to the solitary tract nucleus or nucleus tractus solitarius (NTS) located in the medulla oblongata. The central coordinating region for coughing is located in the upper brain stem and pons.⁵ In response to stimuli, the medulla sends a signal via the efferent pathway in the vagus, phrenic, and spinal

motor nerves to expiratory musculature, mainly the diaphragm, laryngeal and bronchial muscles, to produce the cough.⁴ Once a stimulus has triggered the cough reflex, the following phases become activated sequentially:

- **Inspiratory phase:** The chest cavity expands and allows for air to flow inwards, resulting in the expansion and filling of the lungs, with a resultant increase in pressure, to a volume necessary for an effective cough to be produced.
- **Compression phase:** The larynx will close, and the respiratory muscles start contractile movements to further increase pulmonary pressure in anticipation of the expulsion event.
- **Expiratory phase:** Opening of the larynx, coupled with further contractions of the respiratory muscles, forcing out air at high velocity.^{4,6}

Refer to Figure 1 for an illustration of the cough reflex.

Aetiology

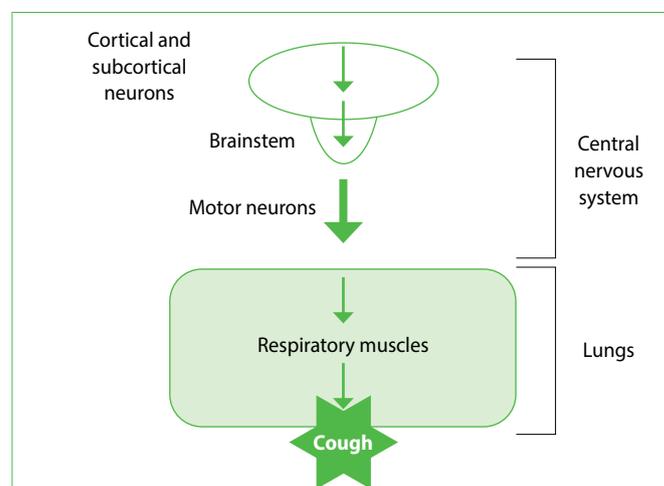


Figure 1: Simplified cough reflex pathway⁷

Coughing can be classified as either being acute or chronic. An acute cough is a daily cough that lasts for fewer than three weeks, whilst a chronic persistent cough typically lasts more than eight weeks.^{3,8} Coughing that lasts between 3–8 weeks (usually a product of bronchial sensitivity and hyper-responsiveness or post-infection) is referred to as subacute coughing.^{3,6} Subacute coughs may precipitate an infection if not adequately resolved. Unfortunately, there is inadequate data to determine accurate and directed therapy, hence in practice, inhaled corticosteroids and leukotriene modifiers have been used. However, literature signifies that once the hyper-responsive phase has passed, coughs become self-limiting.⁹ Chronic coughing lasts for three months or more, but not more than two years. Possible causes may be cancerous, an effect of the smoking habit, gastro-oesophageal reflux disease (GORD), asthma and certain medicines.¹⁰

There are various types of coughs depending on the origin and pathway of stimulation, which may be used to determine the diagnosis and tailor the treatment of the condition. A pharyngeal cough is usually dry and not particularly strong (i.e. a so-called dry cough). A dry cough does not produce any mucus and is often painful. A pharyngeal cough occurs in convulsive attacks with loud inspirational sounds likened to whooping. A cough that originates from the larynx is usually associated with hoarseness of the voice.¹⁰ Restrained coughing occurs in children with dyspnoea or pleural pain and is often identifiable by the child's distinct effort to suppress the cough reflex. A dry cough is a distinctive sign of upper respiratory involvement.¹¹

Conversely, a productive or so-called wet cough signifies the likely involvement of lower respiratory tract disease.¹² It is mainly characterised by its exudative nature, whereby phlegm is produced. Phlegm is a type of mucus produced in the lower respiratory tract. In some instances, the colour and texture may determine the nature of the pathology. The presence of blood in the phlegm or sputum may represent physical damage to the mucosal lining. Refer to Table I for a comparison of the causes of wet (productive) versus dry (non-productive) cough.

Productive cough (wet cough)	Non-productive cough (dry cough)
Chronic bronchitis	Postnasal drip
Air pollutants/irritants	Viral infection (common cold)
Allergic conditions, including asthma	Gastro-oesophageal reflux disease (GORD)
Aspiration	Medication-induced coughing (e.g. ACE-inhibitors)
Lung cancer	Heart failure
Pneumonia or tuberculosis	Psychological causes

Diagnosis

A physical examination of the patient should focus on history and signs of possible sinusitis, postnasal drip and rhinitis. The physician must perform chest auscultations during a cough to assist with the diagnosis of various disease states. In the absence of a clear

aetiology, the physician must have a chest X-ray performed.¹⁰ This test provides a static, structural image of the lungs to demonstrate abnormalities (e.g. over-secretion of mucus or inflammation of the mucosal lining). The elimination of possible differential diagnoses is significant in directing the best possible treatment plan. In the case of asthma, the patient's history of symptoms coupled with spirometry is used to confirm the diagnosis. In the instance when GORD is the underlying pathology, then an oesophageal pH test must be performed.¹⁰

Treatment

It is paramount that the underlying condition is correctly managed because a cough tends to be a symptom of underlying pathology rather than a disease condition. The use of mucolytics, expectorants, antitussives, bronchodilators and antihistamines are used to manage a cough.¹⁰ A cough is designed to expel irritants from the airways.¹³

Antitussives

Dextromethorphan, codeine and hydrocodone are used to suppress the cough by decreasing excitability of afferent nerves that stimulate the cough reflex (i.e. menthol), whereas some directly inhibit the medullary cough centre.¹³ Menthol is classified as a locally-acting antitussive and may be administered as a throat spray or lozenge. Opioid agonist antitussives are centrally-acting, meaning that they directly inhibit the cough centre in the medulla oblongata, but they are better as analgesics and produce a euphoric effect,¹³ hence their routine use has become increasingly undesirable. Dextromethorphan is an isomer of a very potent opioid, but at lower dosages it does not produce analgesia, euphoria or drowsiness. Codeine (10–20 mg every 4 to 6 hours) and hydrocodone are available in tablet and syrup form. Unfortunately for the patient, suppressing a wet infectious cough is not recommended because the sputum, usually comprising of bacterial debris and pus, may precipitate therapeutic failure when not effectively cleared from the lower airway.¹⁰

Pholcodine is comparable to dextromethorphan in terms of its efficacy in the management of patients with acute dry (non-productive) coughing. Similarly to the other antitussives, this agent can reduce the patient's mean daytime cough frequency, mean nighttime coughing, and the intensity of the cough itself.¹⁴

Expectorants

Guaifenesin can assist with the expulsion of mucus and particulates from the lungs. It is postulated that this agent reduces adhesiveness and surface tension of secretion found in the respiratory tract.¹² Although an antitussive, guaifenesin (200–400 mg orally every 4 hours) reduces the occurrence of coughs and is reserved for viscous secretions in patients with a dry, non-productive cough.¹⁵ Hydration of the airway is required to improve therapeutic outcomes.¹¹ Other expectorants include bromhexine and ipecac.⁸

There are significant differences between physiological and pathological mucus in the airways. Airway pathology results in the creation of a more viscous sputum that is significantly more difficult for the patient to expel from the lungs.¹⁶ Bromhexine has been clearly shown to reduce mucus viscosity, thereby assisting the patient with sputum expectoration.^{16,17} In a more recent reappraisal of bromhexine, published in 2017, the authors even showed that bromhexine augmented certain antibiotics' actions when the latter was co-administered with this particular expectorant. This resulted in a more favourable clinical response to antibiotic treatment.¹⁶ Bromhexine was found to be well tolerated with a favourable safety profile.¹⁶

Mucolytics

These agents are intended to reduce the surface tension and mucus viscosity of the lower airway secretions. N-acetyl cysteine (NAC) also possesses antioxidant properties and is classified as a classic mucolytic. NAC depolymerises the mucin glycoprotein oligomers by hydrolysing the disulphide bonds that link the mucin monomers through free thiol (sulfhydryl) groups.¹⁵ Mucin is a polyionic tangled formation with charged side chains that ensure the structure is maintained. They hydrolyse disulphide bonds reducing mucus viscosity.¹⁸ Literature has not provided evidence that NAC provides beneficial effects in the expulsion of mucus. Oral NAC is rapidly broken down and is not present in mucus. Peptide mucolytics depolymerise the DNA-polymer (i.e. dornase alfa) or the F-actin network and are most effective when sputum is rich in DNA pus.¹⁵

Antihistamines

First-generation antihistamines include diphenhydramine, promethazine, phenyltoloxamine (tablet) and triprolidine. These antihistamines act as a cough suppressants by reducing cholinergic transmission of nerve impulses in the coughing reflex.

Non-sedative antihistamines lack cholinergic effects hence are less effective for cough therapy.⁸ Antihistamines have been used in congestion and postnasal drip to reduce the frequency of coughing. These agents are most effective in allergic conditions.¹⁹ The combination of an antihistamine and a cough suppressant can be used for nighttime coughing. Antihistamines suppress coughing, but combined use with an expectorant that promotes coughing would not be therapeutically plausible.⁸ Table III briefly summarises the treatment indications of the main groups of medication used to manage wet and dry cough.

Bronchodilators

There is a scarcity of data supporting enhanced mucociliary clearance due to bronchodilators but increase cough clearance by increasing expiratory flow.¹⁵ Agents such as terbutaline have a more pronounced enhancement of mucociliary function. The effect of bronchodilators is more pronounced in asthma-related coughs whereby salbutamol and theophylline are used.⁶ Other agents, including β_2 -adrenoceptor agonists, muscarinic receptor antagonists, and xanthines, are sometimes used in combination. Theophylline has a narrow therapeutic index which may lead to toxicity in vulnerable populations.¹⁸

In addition to its adrenergic effects, salbutamol has, however, also been shown to inhibit the release of bronchoconstrictive agents from mast cells in the lower airway, reducing the severity of bronchial oedema. In addition, some evidence does suggest its positive effect on mucociliary clearance, making it a useful active ingredient in a suitable cough mixture. Furthermore, salbutamol makes for an excellent active ingredient, in combination with bromhexine, for a so-called tight chest.¹⁷

Cough mixture stability

Cough syrups are pharmaceutical solutions that are susceptible to chemical degradation reactions (e.g. hydrolysis, oxidation,

Table II: Drugs used in the management of cough^{9,16,18}

Pharmacological group	Pharmacological active ingredients	Mode of action	Indication	Side effects
Antitussives	Codeine	Suppresses cough reflex by suppressing the cough centre in the medulla	Non-productive cough	Sedation, constipation, nausea, dizziness, respiratory depression, confusion
	Dextromethorphan	Centrally active N-Methyl-D-aspartate (NMDA) receptor antagonist; directly suppresses medullary cough centre		
	Pholcodine	Centrally-acting opioid derivative, directly suppressing medullary cough centre		
Expectorants	Guaifenesin, Bromhexine	Stimulates secretions and reduces mucus viscosity Reduces bronchial sputum surface tension	Cough alleviation of a non-productive cough with viscous mucus	Drowsiness, dizziness, headache, nausea, diarrhoea, rash
Mucolytics	N-acetyl cysteine	Depolymerises the mucin glycoprotein oligomers by hydrolysing the disulphide bonds in mucoproteins to reduce the viscosity of secretions	Respiratory conditions with viscous mucus	Nausea, vomiting, bronchospasm, headache, fever, urticaria, skin rashes, abdominal pain, diarrhoea

reduction, decarboxylation and epimerisation) due to chemical incompatibility, photodegradation reactions and changes in pH. Stability should be maintained throughout the products' shelf-life. This can be achieved by controlling the pH, moisture content and storage conditions (temperature, light and humidity) of the product.²⁰ The packaging materials used in the container closure system is also critical for product stability. Glass and aluminium packaging is more resistant to oxidation, heat, sorption and permeability than plastic packaging material.²¹ Amber or opaque containers help prevent photooxidation.²¹

Cough mixture combinations and compounding in South Africa

Cough mixtures contain both pharmacologically active compounds and various excipients, which cannot be regarded as simply inert.^{21,22} There are various cough mixture combinations available on the South African market (Table III).¹⁸ Apart from the commercially available cough mixture combinations, healthcare providers often compound their own combinations of syrups that may include antihistamines, bronchodilators, mucolytic, corticosteroids and herbal cough syrups without them having any stability data on the compounded combination. Degradation due to chemical incompatibility occurs between formulation ingredients that react with one another. Therefore, it is imperative to do thorough research on the various stability factors that should be considered before compounding just any cough mixture.^{21,23}

Official monographs can be consulted for information on active ingredients, whilst the Handbook of Pharmaceutical Excipients contains monographs with comprehensive information on the safety, handling and physical and chemical properties of excipients.^{22,24} The Association of Compounding Pharmacists of South Africa (ACPSA) may also be able to provide direction on combining cough syrups.

Table III: Cough mixture combinations¹⁸

Antihistamine + decongestant + cough suppressant
Antihistamine + expectorant + bronchodilator
Antihistamine + decongestant + expectorant + cough suppressant
Antihistamine + expectorant
Bronchodilator + expectorant
Bronchodilator + mucolytic

Conclusion

Apart from a more serious aetiology such as the prevalent SARS-Cov-2, an acute cough is usually self-limiting and is mostly a result

of either a common cold or an allergic condition. Treatment of a cough must be directed at symptomatic relief. Sensitisation of the cough reflex is a common feature in these patients, irrespective of the underlying cause. Although a large variety of cough preparations are available and commonly used, evidence for the efficacy of some of their active ingredients remains limited.

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