Changes in terminology and management of over-the-counter cough therapy – time for a fresh perspective?

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Abstract

Coughing is one of the most common symptoms for which patients 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 (GORD). Terminology that includes 'wet' and 'dry' has become outdated and should be revisited. An understanding of the pathophysiology of coughs and how they manifest themselves enables the health professional to provide the necessary therapy.

Keywords: cough, antitussive, mucolytic, expectorant

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Introduction

Cough is a normal defence mechanism of the body and helps clear mucus and remove harmful particles and infective organisms from the larynx, trachea and large bronchi.[1] There are also other factors, like dysfunctional mucociliary clearance, that could lead to mucus accumulation, which may require clearance by coughing. Normally a cough is purported to be protective but excessive coughing may result in damage to the mucosa.

Coughing remains a common complaint and patients are often motivated to seek medical attention, with health professionals being requested to recommend therapies.[1,2,3]

It is not always necessary to treat an acute cough and if it is caused by a cold and flu it is usually self-limiting. If, however, the cough is persistent, it is important to see a doctor to determine the cause or aetiology and treat accordingly. This article will only focus on over-the-counter (OTC) cough medicines (schedule 0 to 2 medicines) that are available without prescription.[4]

Pathophysiology

Coughing is a result of 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. 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. These receptors are sensitive to either physical or chemical stimuli, such as heat, acid and capsaicin-related compounds.[1,5-8] Cough receptors are located in the middle ear, diaphragm, pleura and stomach, the external auditory canals, eardrums, paranasal sinuses, pharynx, diaphragm, pleura and pericardium. 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 (also known as the nucleus tractus solitarus [NTS]) that is located in the medulla oblongata. The central coordinating region for coughing is located in the upper brain stem and pons. 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, and laryngeal and bronchial muscles to produce the cough. Once a stimulus has triggered the cough reflex, the following phases become activated in a sequential manner:

- **Inspiratory phase:** The chest cavity expands and allows 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.[1,5-8]

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

Aetiology

Coughing can be classified as either acute or chronic. An acute cough is said to be a daily cough that lasts for a period of less than three weeks whilst a chronic persistent cough typically lasts

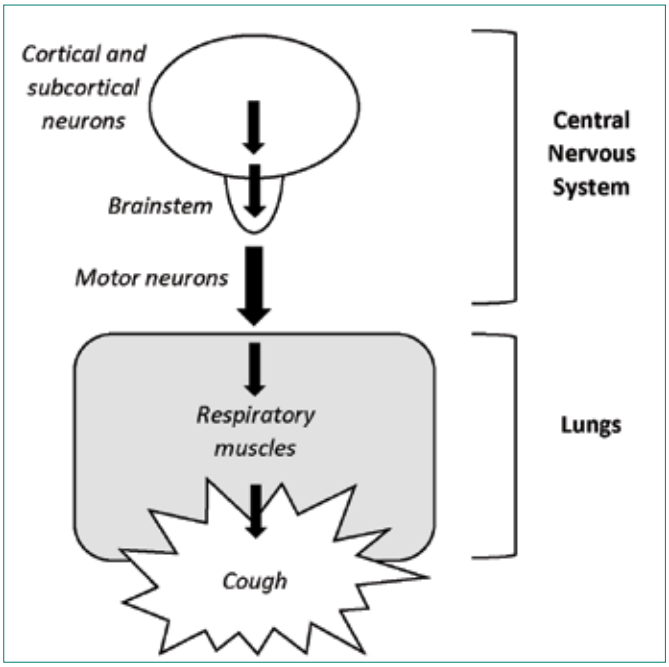

Figure 1. Simplified cough reflex pathway

more than eight weeks.[1,9] Coughing that lasts between 3–8 weeks (usually a product of bronchial sensitivity and hyperresponsiveness or post-infection) is referred to as subacute coughing. 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.[7] However, literature suggests that once the hyperresponsive phase has passed, coughs become self-limiting.[10] Chronic coughing lasts for a period of ≥ 3 months, but ≤ 2 years. Possible causes may be cancer, an effect of the smoking habit, GORD, asthma and certain medicines.[11]

There are various types of cough depending on the origin and pathway of stimulation, which may be used to determine the diagnosis and tailor treatment. 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, and occurs in convulsive attacks with loud inspirational sounds likened to whooping. A cough that originates from the larynx is usually associated with hoarseness.[10] Restrained coughing occurs in children with dyspnoea or pleural pain and is often identifiable by a distinct effort by the child to suppress the cough reflex. A dry cough is a distinctive sign of upper respiratory involvement.[11,12]

Conversely, a productive or so-called wet cough signifies the likely involvement of lower respiratory tract disease. 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.[13]

Table I. Causes of productive versus non-productive cough[8]

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

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 determine the diagnosis. In the absence of clear aetiology, a chest X-ray must be performed. This test provides a static, structural image of 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 prescribing the best possible treatment plan. In the case of asthma, patient history of symptoms coupled with spirometry are used to confirm the diagnosis. In instances where GORD is the underlying pathology, an oesophageal pH test must be performed.[11]

New approach to an old problem

A new proposed treatment pathway for cough is outlined in Figure 2. This approach allows pharmacists and pharmacist's assistants to provide patients seeking advice for cough with appropriate advice. This includes addressing the following matters:

- How long have you had the cough?

If it is less than three weeks, then it is highly likely to be an acute cough related to a respiratory tract infection.

Although disruptive, an acute cough associated with an upper respiratory tract infection is self-limiting and rarely needs significant medical intervention, particularly the use of antibiotics. Patients can be reassured and advised of a range of options for symptom relief.

- Are there any associated symptoms, such as headache, fever or runny nose?

If so, pharmacists and pharmacist's assistants have the opportunity to adjust their recommendations according to any co-existing treatable symptoms.

- Having addressed these points, patients can be advised on OTC drugs currently available for cough, providing evidence of efficacy where it exists.
- Assessments should include a discussion about other symptoms. Important here are any 'red flag' symptoms, such as localised chest pain or coughing up blood, which potentially indicate more serious pathology. For instance, pleuritic chest pain (which may be described as pain on inspiration localised

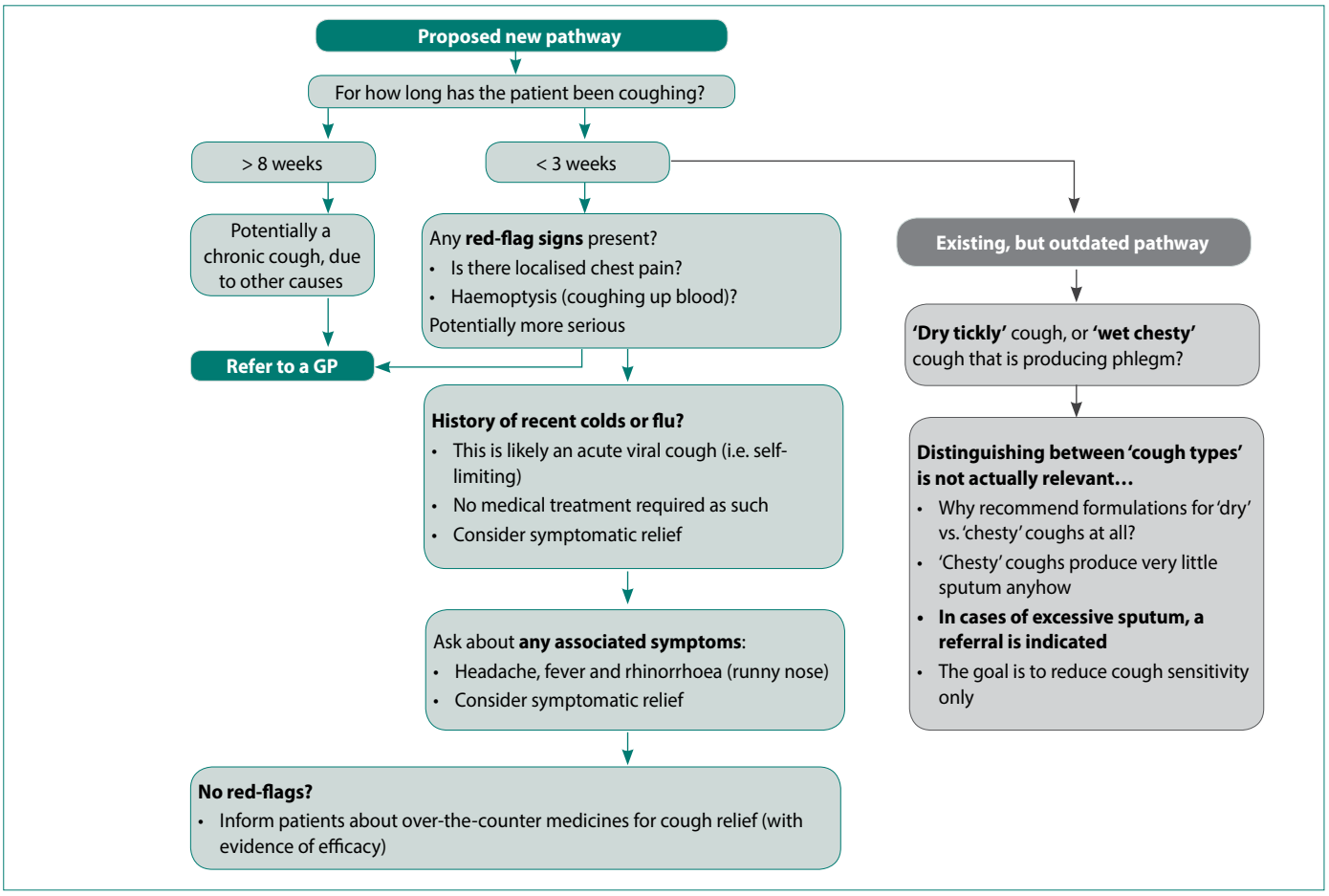

Figure 2. Proposed new treatment pathway for cough management from the age 12

to the chest, worsening when coughing, sneezing or moving around), may be a sign of pneumonia, and consultation with a doctor leading to an X-ray should be sought. Any such 'red flag' signs, or a cough persisting for longer than eight weeks (i.e. a chronic cough), require referral to a general practioner.

Note that the proposed treatment pathway (see Figure 2) only focuses on the treatment of adults and children aged over 12 years of age. Younger patients (aged 12 years and under) are not included in this new pathway. Further information relating to their management should be obtained from the British Thoracic Society guidelines.[14-16]

Antitussive therapy and key objective measures for cough medicine

Products have traditionally been recommended for different types of cough (dry, wet, etc). Typically, the recommendations included that expectorants be used for productive (wet) coughs while suppressants are routinely recommended for non-productive (dry) coughs.[14]

The current way of classification is directed towards brand diversification rather than rational antitussive pharmacotherapy. Furthermore, with so many branded OTC cough preparations available, it is likely to cause confusion amongst both counter staff and patients seeking the best therapy for symptom relief.

Objective measures designed to assess cough include a cough challenge and cough counting. The cough challenge was introduced more than half a century ago as a tool for assessing cough reflex. The inhalation cough challenge facilitates the quantification of cough and the assessment of antitussive effects of specific therapies. To do this, tussive agents such as citric acid or capsaicin (the pungent extract of the *Capsicum* chili pepper genus) are delivered as nebulised solutions to determine cough reflex sensitivity. The effect of a drug on cough reflex sensitivity is then compared with that of placebo. Two methods are used: single dose (administering one concentration of the tussive agent) and dose-response using incremental dosing.[17]

When evaluating newer therapies, the cough challenge methodology is frequently used but the problem is that it does not always correlate with subjective measures. For instance, while morphine has been shown to be significantly effective in suppressing chronic cough in some patients, it does not appear to alter cough reflex sensitivity. By contrast, the most commonly prescribed OTC drug for cough, dextromethorphan, has been clearly demonstrated to suppress cough reflex hypersensitivity by cough challenge experiments. Thus, the methodology used in an individual experiment may determine whether there is a positive or negative outcome.[18,19]

Despite all of the measures mentioned in the sections above, and considering existing research, it remains difficult to evaluate the overall effectiveness of OTC medicines.[20]

The largest amount of data reviewed was for antitussives (six trials involving 1 526 adults and four trials involving 327 children), but the researchers also examined the evidence for expectorants, mucolytics, antihistamine-decongestant combinations, antihistamines and honey (which was shown to improve symptoms among children). Their finding, that there is no good evidence for or against the effectiveness of OTC medications in acute cough, confirms findings from two previous studies.[20,21]

This review will include the following available OTC therapies:

Antitussives

Dextromethorphan, codeine and hydrocodone are used to suppress the cough by decreasing the excitability of afferent nerves that stimulate the cough reflex, whereas some antitussives directly inhibit the medullary cough centre.[11,22] Only dextromethorphan has been demonstrated, using objective measures, to significantly suppress acute cough. Dextromethorphan was also shown to have a relatively slow onset of action, peaking after around two hours. The slow penetration, through the blood–brain barrier and consequent nervous system retention, may give the drug prolonged antitussive activity, still being significantly better than placebo after 24 hours.[23-27]

Although codeine is widely used and is often considered the archetypal antitussive, there is very little clinical evidence supporting significant antitussive action for orally administered codeine. Some studies have reported a small but significant effect while others report no effect on cough challenge or the sensation of urge to cough.[15]

The challenge with codeine involves dosing accuracy; codeine is bio-activated by CYP2D6 into morphine, which then undergoes further glucuronidation. Pharmacogenomics affect the rates of metabolism due to differences in cytochrome P450-dependent mono-oxygenase activity. Some patients are fast metabolisers, converting most of the codeine to morphine at first pass through the liver. However, in slow metabolisers, very little of the drug is converted, which makes efficacy an issue for slow metabolisers and toxicity a potential problem for fast metabolisers. In paediatrics, children who are fast metabolisers have been observed to have dangerous levels of sedation and suppression of respiration.[26-29]

Menthol produced by the plant *Mentha arvensis*, may be an ingredient of many OTC preparations, although few clinical studies have been performed to establish this. 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 analgesics and produce a euphoric effect, 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 to 20 mg every four to six 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 comprised of bacterial debris and pus, may precipitate therapeutic failure when not effectively cleared from the lower airway.

Pholcodine is comparable to dextromethorphan in terms of its efficacy in the management of patients with acute dry (non-productive) coughing. This agent, in a similar way to the other antitussives, has the ability to reduce the patient's mean daytime cough frequency, mean night-time coughing, as well as the intensity of the cough itself.[26-29]

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.[12,13] Although an antitussive, guaifenesin (200 to 400 mg orally every four hours) reduces the occurrence of coughs and is reserved for viscous secretions in patients with a dry, non-productive cough. Hydration of the airway is required to improve therapeutic outcomes. Other expectorants include bromhexine and ipecac.[30]

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. Bromhexine has been clearly shown to reduce mucus viscosity, thereby assisting the patient with sputum expectoration. In a more recent reappraisal of bromhexine, published in 2017,[30] the authors even showed that bromhexine augmented the actions of certain antibiotics when the latter were co-administered with this particular expectorant. This resulted in a more favourable clinical response to the antibiotic treatment. Bromhexine was found to be well tolerated with a favourable safety profile.

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. Mucin is a polyionic tangled formation with charged side chains that ensure the structure is maintained. They hydrolyse disulphide bonds reducing mucus viscosity. 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.[30- 34]

Antihistamines, ammonium chloride and demulcents

First-generation antihistamines such as diphenhydramine, promethazine, phenyltoloxamine (tablet) and triprolidine act

as cough suppressants by reducing cholinergic transmission of nerve impulses in the cough reflex.[35] Further to this it has been reported to reduce heightened cough reflex sensitivity in subjects with URTI-associated cough.[35]

Ammonium chloride is an acid-forming salt that is thought to exert an 'expectorant' effect by loosening sputum. It is usually used in combination with other expectorants and cough mixtures.

Demulcents are thought to reduce cough and cold symptoms by an action hypothesised to be a soothing effect on the mucous membrane. There is no trial that unequivocally demonstrates such an effect, and the term demulcent does not have a precise clinical definition. However, almost all OTC antitussive medications come in the form of syrups.

Antihistamines have been used in congestion and postnasal drip to reduce the frequency of coughing. These agents are mostly effective in allergic conditions. The combination of an antihistamine and a cough suppressant can be used for night-time cough.[36,37]

Bronchodilators

Bronchodilators increase cough clearance by increasing expiratory flow,[30] whereas agents such as terbutaline have a more pronounced enhancement of mucocilliary function. The effect of bronchodilators is more pronounced in asthma-related coughs when salbutamol and theophylline are used.[38] 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.[39]

In addition to its adrenergic effects, salbutamol has 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 mucocilliary clearance, making it a useful active ingredient in a suitable cough mixture. Furthermore, salbutamol is an excellent active ingredient, in combination with bromhexine, for a so-called tight chest.[32] Table II provides an overview of the drugs available for the management of cough.

Cough mixture stability

Cough syrups are pharmaceutical solutions that are susceptible to chemical degradation reactions (e.g. hydrolysis, oxidation, reduction, decarboxylation and epimerisation) due to chemical incompatibility, photodegradation reactions and changes in pH. Stability should be maintained throughout the duration of the product's shelf-life. This can be achieved by controlling the pH, moisture content and storage conditions (temperature, light and humidity) of the product. The packaging materials used in the container closure system are also critical for product stability. Glass and aluminium packaging is more resistant to oxidation, heat, sorption and permeability than plastic packaging material. Amber or opaque containers help prevent photo-oxidation.[40]

Cough mixture combinations, special populations and compounding in South Africa

Cough mixtures contain both pharmacologically active compounds and various excipients which cannot be regarded as simply inert. There are various cough mixture combinations available on the South African market (refer to Table III). Apart from the commercially available cough mixture combinations, healthcare providers often compound their own combinations of syrups that may include antihistamines, bronchodilators, mucolytics, 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 and it is therefore imperative to do thorough research on the various stability factors that should be considered before compounding just any cough mixture.[34,40-44]

Table II. Drugs used in the management of cough

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, dependence (codeine)
	Dextromethorphan	Centrally active *N*-Methyl- D-aspartate (NMDA) receptor antagonist; directly suppresses medullary cough centre.		
	Pholcodine	Centrally acting opioid derivative, directly suppressing the medullary cough centre.		
Expectorants	Guaifenesin, Bromhexine	Stimulates secretions and reduces mucus viscosity. Reduces bronchial sputum surface tension.	Cough alleviation, non-productive cough with viscous mucus.	Drowsiness, dizziness, headache, nausea, diarrhoea, rash
Mucolytics	N-Acetylcysteine	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 and diarrhoea.

Combination cough products contain more than one active ingredient to target more than one symptom at a time. They will typically contain a cough suppressant and an expectorant alongside agents that soothe the throat. They may also include decongestants to ease a stuffy nose; antihistamines to address allergies and a runny nose; or analgesics to relieve pain.[45] It is important to make use of a product that addresses all the relevant needs of the patient and to ignore those that are irrelevant. The duplicating of ingredients should be avoided and therefore it is important to look at the ingredients present in the combination formula when advising the patient on the use of multiple products.[46]

A doctor should be consulted before using any medication during pregnancy.

A Cochrane review reported a lack of robust evidence towards the efficacy of OTC cough medicine in children. Combination OTC cough medicine has not been FDA approved for use in children under two years of age due to severe life-threatening adverse effects, including death, and it should be used with caution when administered to children older than two.[47]

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. The Association of Compounding Pharmacists of South Africa (ACPSA) may also be able to provide direction on combining cough syrups.

Table III. Cough mixture combinations

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

The way forward – the ROCOCO trial

A potentially new medicine, Unicough, (CS1002) targeted to address cough-reflex hypersensitivity, has been evaluated in a real-world, randomised, controlled, multi-centre study. This formulation contains diphenhydramine, ammonium chloride and levomenthol in a cocoa-flavoured demulcent. The ROCOCO study is the largest clinical trial of a cough medicine conducted in the United Kingdom, and used an active comparator (simple linctus), while using validated endpoints in the correct population.

The Unicough group had a statistically significant reduction in sleep disruption throughout the eight-day trial, and there was a statistically significant improvement in cough frequency on days three, four and five.

Clinical findings show that 29.3% of patients in the Unicough group achieved cough resolution by day four, compared with just 17.3% of those taking the linctus. While 24.4% of those receiving Unicough were able to stop taking their medication by day four because their cough had got better, only 10.7% of the linctus group were able to stop taking their medication at this stage. However, this also highlights the challenges of investigating a condition that can naturally improve.[36,37,48,49]

Conclusion

An acute cough is usually self-limiting and is usually 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.

Terminology that includes 'wet' or 'dry' classification for cough has been ingrained in our approach to managing cough for far too long. There is one trigger for a common cough: increased sensitivity of the nerve endings in the throat. It may be time to revisit the classification of this terminology and use best practice approaches.

There is currently a wide range of OTC cough remedies from which to choose, but they are not all supported by proven clinical efficacy and are divided into unhelpful 'wet' and 'dry' categories. Treatment advice must be based on normalising the cough reflex. Education interventions for healthcare workers and patients should be targeted to include an improved understanding of the mechanism of cough hypersensitivity. This will bring rational treatment choices a step closer.

Perhaps a new way of thinking that includes assessing acute vs. chronic cough and assessing evidence is the way forward in the treatment and management of coughs.

References

1. Chung KF,Widdicombe J. Cough: setting the scene. In Chung KF, Widdicombe J. Pharmacology and Therapeutics of Cough. First edition. 2009:1-21. Heidelberg: Springer.
2. Kim V, Ramos F, Krahnke J. Clinical issues of mucus accumulation in COPD. International Journal of Chronic Obstructive Pulmonary Disease. 2014;9(1):139.
3. De Blasio F, Virchow J, Polverino M, et al. Cough management: a practical approach. Cough. 2011;7(1):7.
4. Medicines and related substances act. (1965). [online] Available at: https://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/legislations/acts/medicines_and_related_sub_act_101_of_1965.pdf [Accessed 8 May 2019].
5. Polverino M, Polverino F, Fasolino M, et al. Anatomy and neuro-pathophysiology of the cough reflex arc. Multidisciplinary Respiratory Medicine. 2012;7(1).
6. Scaglione F, Petrini O. Mucoactive agents in the therapy of upper respiratory airways infections: fair to describe them just as mucoactive? Clinical Medicine Insights: Ear, Nose and Throat. 2019;12:1-9.
7. Dicpinigaitis P, Morice A, Birring S, et al. Antitussive drugs – past, present, and future. Pharmacological Reviews. 2014 66(2):468-512.
8. Van Schoor J. An approach to recommending cough mixtures in the pharmacy. South African Pharmacy Journal, 2019;85(4):40-44
9. Herrier RN, Apgar DA, Boyce RW, Foster SL. Introduction to Patient Assessment for Pharmacists. 2015 McGraw-Hill.
10. Lechtzin N. Cough in adults – pulmonary disorders – MSD Manual Professional Edition. [online] MSD Manual Professional Edition. 2019.
11. Begic E, Begic Z, Dobraca A, Hasanbegovic E. Productive cough in children and adolescents - view from primary health care system. Medical Archives. 2017;71(1):66
12. Malesker M, Callaha-Lyon P, Ireland B, Irwin R. Correction to reference in: Treatment

of Unexplained Chronic Cough: CHEST Guideline and Expert Panel Report. Chest, 2016;149(5):1353.
13. Brenner G, Stevens C. Pharmacology. Fourth Edition. Philadelphia, PA: Elsevier/Saunders; 2013.
14. Morice AH, Kantar A, Dicpinigaitis PV, et al. Treating acute cough: wet versus dry – have we got the paradigm wrong? ERJ OpenRes 2015; 1:00055-2015. doi: 10.1183/23120541.00055-2015.
15. Dicpinigaitis PV, Morice AH, Birring SS, et al. Antitussive drugs – past, present, and future. Pharmacol Rev 2014; 66:468–512. doi: 10.1124/pr.111.005116.
16. Shields MD, Bush A, Everard ML, et al. On behalf of the British Thoracic Society Cough Guideline Group. BTS guidelines: Recommendations for the assessment and management of cough in children. Thorax 2008; 63 Suppl 3: iii1–iii15. doi: 10.1136/thx.2007.077370.
17. Morice AH, Kastelik JA, Thompson R. Cough challenge in the assessment of cough reflex. Br J Clin Pharmacol 2001;52(4):365–375. doi: 10.1046/j.0306-5251.2001.01475.x.
18. Grattan TJ, Marshall AE, Higgins KS, et al. The effect of inhaled and oral dextromethorphan on citric acid induced cough in man. Br J Clin Pharmacol 1995;39:261–263. PMID: PMC136500.
19. Morice A, Kardos P. Comprehensive evidence-based review on European antitussives. BMJ Open Resp Res 2016;3:e000137. doi: 10.1136/bmjresp-2016-000137.
20. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. Cochrane Database Syst Rev 2014;(11):CD001831. doi: 10.1002/14651858.CD001831.pub5.
21. Smith MBH, Feldman W. Over-the-counter cold medications. A critical review of clinical trials between 1950 and 1991. JAMA 1993;269(17):2258–2263. doi: 10.1001/jama.1993.03500170088039.
22. Malesker M, Callaha-Lyon P, Ireland B, Irwin R. Correction to reference in: Treatment of Unexplained Chronic Cough: CHEST Guideline and Expert Panel Report. Chest, 2016;149(5):1353.
23. Pavesi L, Subburaj S, Porter-Shaw K. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a meta-analysis. Chest 2001;120(4):1121–1128. doi: 10.1378/chest.120.4.1121.
24. John A. Most common products with dextromethorphan. Livestrong.com. Available at: http://www.livestrong.com/article/199393-most-common-products-with-dextromethorphan/ [Accessed March 2017].
25. Smith JA, Earis JE, Woodcock AA. Establishing a gold standard for manual cough counting: video versus digital audio recordings. Cough 2002:6. doi: 10.1186/1745-9974-2-6.
26. Smith JA, Kitt M, Sher M, et al. Profound antitussive response to P2X3 blockade with AF-219 permits correlation of objective measure of cough with improvement in patient reported outcomes. Abstract A2866 2016. Available at: http://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2016.193.1_MeetingAbstracts.A2866 [Accessed March 2017].
27. Abdul-Manap R, Wright CE, Gregory A, et al. The antitussive effect of dextromethorphan in relation to CYP2D6 activity. Br J Clin Pharmacol 1999;48(3):382–387. doi: 10.1046/j.1365-2125.1999.00029.x.
28. Gasche Y, Daali Y, Fathi M, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med 2004;351(27):2827–2831. doi:10.1056/NEJMoa041888.
29. Food and Drug Administration. FDA Drug Safety Communication: safety review update of codeine use in children; new boxed warning and contraindication on use after tonsillectomy and/or adenoidectomy. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm [Accessed March 2017].
30. Albrecht H, Dicpinigaitis P, Guenin E. Role of guaifenesin in the management of chronic bronchitis and upper respiratory tract infections. Multidisciplinary Respiratory Medicine. 2017;12(1).
31. Zanasi A, Mazzolini M, Kantar A. A reappraisal of the mucoactive activity and clinical efficacy of bromhexine. Multidisciplinary Respiratory Medicine. 2017;12(7):1-14.
32. Anonymous. Pulmonology: Cough treatment. Specialist Forum. 2017;17(6):28-30.
33. Hanson C. Cough mixtures – an overview: review. Professional Nursing Today. 2018;22(2):28-32.
34. Barnes AR. Chemical stability in dosage forms. In Aulton ME, Taylor KMG. 2018. Aulton's Pharmaceutics – the design and manufacture of medicines. Fifth edition. 2018 China: Elsevier.
35. Herrier RN, Apgar DA, Boyce RW, Foster SL. Introduction to Patient Assessment for Pharmacists. 2015 McGraw-Hill.
36. Behera D. Textbook of Pulmonary Medicine (2nd edition). Jaypee Brothers Medical Publishers (P) Ltd. 2010:20.
37. Eccles R. Mechanisms of the placebo effect of sweet cough syrups. Respir Physiol Neurobiol 2006;152:340–348. doi: 10.1016/j.resp.2005.10.004.
38. Albert RH. Diagnosis and treatment of acute bronchitis. Am Fam Physician 2010;82(11):1345–1350. PMID: 21121518.
39. Tyrell D, Fielder M. Cold wars: the fight against the common cold. Oxford University Press, 2002.
40. Vally M, Irhuma M. Management of cough: a practical approach. Safpj.co.za. 2016;58(4):35-39.
41. Dicpinigaitis,. P. Clinical perspective – cough: an unmet need. Current Opinion in Pharmacology. 2015;22:24.
42. Rowe RC, Sheskey PJ, Quinn ME. Handbook of pharmaceutical excipients. Sixth Edition 2009. Pharmaceutical Press.
43. Murdan S. Solutions. In Aulton ME, Taylor KMG. 2018. Aulton's Pharmaceutics – the design and manufacture of medicines. Fifth Edition. 2018. China: Elsevier.
44. Marshall P. Product stability and stability testing. In Aulton ME, Taylor KMG. 2018. Aulton's Pharmaceutics – the design and manufacture of medicines. Fifth Edition. 2018. China: Elsevier.
45. WebMD. 2017. OTC Medicines for cough. WebMD medical reference. https://www.webmd.com/cold-and-flu/otc-meds#1 [Accessed 20 Apr. 2019].
46. Brazier Y. 2017. Cough and cold medications: use them safely. MedicalNewsToday. https://www.medicalnewstoday.com/articles/16181.php [Accessed 20 Apr. 2019].
47. Woo T. (2008). Pharmacology of cough and cold medicines. Journal of Pediatric Health Care, 22(2), pp.73-79.
48. Birring SS, Brew J, Kilbourn A, et al. Rococo study: a real-world evaluation of an over-the-counter medicine in acute cough (a multicenter, randomized, controlled study). BMJ Open 2017;7:e014112. doi: 10.1136/bmjopen-2016-014112.
49. MHRA Public Assessment Report. Unicough 14mg/135mg/1.1mg in 5ml oral solution (diphenhydramine hydrochloride, ammonium chloride, levomenthol). Available at: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con553668.pdf [Accessed May 2019].