

## Cough Preparations: to give or not

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**Received:** September 13, 2017; **Published:** September 21, 2017

### Abstract

Cough mixtures are frequently prescribed for cough associated with upper respiratory diseases. Many different cough mixture combinations are available making an informed, therapeutic sound choice, can be challenging to a pharmacist. Supportive evidence on the efficacy of cough mixtures is not yet convincing, cough mixtures alleviates symptoms of colds and flu. This review article aims to provide the pharmacist with knowledge and skills to make an appropriate informed choice of drug individualised for the right patient, at the right time.

**Key words:** *Cough mixture; Antitussives; Mucolytic; Guaifenesin; Codeine; Acetylcysteine*

Volume 1 Issue 5 September 2017

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### Introduction

Acute cough is the most often due to the common cold. It is the most common symptom, for which patients seek medical care. Between 35-40% of school age children still cough 10 days after the onset of a common cold [1]. Cough is an important defensive reflex that helps clear secretions, foreign particles and irritants from breathing passages and can be a symptom of upper or lower respiratory tract infection [2]. An acute cough following an upper respiratory tract infection is usually self-limiting, but can be difficult to control, and can be associated with impaired quality of life for patients [3]. Cough can be designated as acute (< 3 weeks in duration), prolonged acute cough (3 to 8 weeks in duration) or chronic (> 8 weeks in duration) [2]. In the majority of patients, acute cough is caused by upper respiratory tract infections (URTI), acute bronchitis or tracheo-bronchitis due to bacterial or more frequently viral infections Cough is treated symptomatically either through non-pharmacological or pharmacological interventions [2].

### Pharmacological Therapy

Cough mixtures may be a combination of different active ingredients. These active pharmaceutical ingredients can be classified in the following pharmacological classes: antitussives, antihistamines and mucoactive agents (mucolytic, expectorants, mucokinetics) [8]. In table 1 these classes are summarised into examples, reported action, common adverse effects and interactions.

Classification	Example	Reported action	Common adverse effects	Drug-drug; drug disease interactions, contra-indications
Antitussives (cough suppressants)	Pholcodine, noscapine	Centrally acting opioid derivative, directly suppressing medullary cough centre.	Dizziness, sedation, nausea, constipation, headache	Caution: Contra-indicated in children < 2 years. Contra-indicated in pregnancy. Risk of opioid dependence, potential abuse
	Dextromethorphan	Centrally active N-Methyl-D-aspartate (NMDA) receptor antagonist; directly suppresses medullary cough centre.	Sedation, dizziness, nausea(rare); respiratory depression, confusion, excitation (in overdose)	Drug-drug interactions: Alcohol, CNS drugs sedative action may be enhanced. Drug- disease interactions: Asthma, liver impairment, respiratory depression. Patient with history of opioid dependency Caution: Not recommended for children < 6 years Pregnancy: relative safe
	Codeine phosphate	Suppress cough reflex by suppressing the cough centre in medulla	Sedation, constipation, nausea	Caution: Risk of opioid dependence, potential abuse
Antihistamines				
	Diphenhydramine, Chlorpheniramine, diphenhydramine promethazine, triprolidine, diphenylpyraline	They reduce the cholinergic transmission of nerve impulses in the cough reflex. Reduce frequency of coughing	Sedation, headache, dizziness, nervousness, restlessness, irritability, palpitations, dry mouth, urine retention,	Drug-disease interaction: Contra-indicated in patients with narrow-angle glaucoma and prostatic hypertrophy due to anticholinergic/antimuscarinic properties. Drug-drug interaction: Potentiate effects of anxiolytics, hypnotics, analgesics, alcohol and other CNS depressants. Potentiate anticholinergic effects with sympathomimetic drugs.
Demulcents				
	Sucrose, honey alcohol	Coats the throat and soothes irritated mucous membranes.	Hyperglycemia in patients with Diabetes mellitus	Drug- disease interactions; Preparations with added sugar should not be used in patients with Diabetic Mellitus due to its influence on glucose levels,
<b>MUCOACTIVE AGENTS</b>				
Expectorants				
	Guaifenesin, Ammonium chloride, sodium citrate, glyceryl guaiacolate	Stimulates secretions and reduces mucus viscosity. Reduce bronchial sputum surface tension.	Drowsiness, dizziness, headache, rash	Drug-Disease interactions: Use with caution in patients with gastro-intestinal ulcers,
Mucoregulators	Carbocysteine	Regulate metabolism of mucus producing cells,	Nausea, vomiting, headache, diarrhoea	Drug-disease interactions: caution in asthmatics and history of peptic ulcers
Mucolytics				
	N-Acetylcysteine (NAC)	Depolymerize the mucin glycoprotein oligomers by hydrolysing the disulphide bonds in mucoproteins to reduce the viscosity of secretions.	Nausea, vomiting, bronchospasm, headache, fever, urticaria, skin rashes, abdominal pain and diarrhoea	Drug-disease interactions: caution in asthmatics and history of peptic ulcers

	Bromhexine	Loosen and thin bronchial secretions by reducing surface tension and viscosity of mucus.	Gastro-intestinal effects, allergic reactions, bronchospasm, dizziness, headache	Drug-disease interactions: caution in asthmatics, and history of peptic ulcers
Mucokinetics				
Bronchodilators	Terbutaline, theophylline	Improve cough clearance by increasing expiratory flow, reduction in volume of mucus secretion	Headache, fine tremor, insomnia, dizziness, tachycardia	Drug- Disease interactions: use with caution in patients with cardiac arrhythmias, ischemic heart disease, uncontrolled hypertension or hyperthyroidism

**Table I:** Pharmacological treatment options [6-11].

### Antitussives/cough suppressants

Central antitussive agents can be useful in patients with chronic bronchitis, but have little efficacy in patients with cough due to upper respiratory infections. Dextromethorphan appears to have little serious toxicity [12]. The safe dosage range seems to be considerably higher for dextromethorphan than for codeine. Use of these drugs is most appropriate in specific therapy such as patients with inoperable lung cancer and in cases in which an unproductive cough interferes with sleep or cause exhaustion [11]. The underlying cause of the dry cough should first be established to exclude conditions such as asthma and congestive heart failure. Peripheral and central antitussive agents can be useful in patients with chronic bronchitis, but have little efficacy in patients with cough due to upper respiratory infection. The use of cough suppressants in children under six years should be avoided due to its safety profile [12].

### Antihistamines

Antihistamines are added to many cough and cold remedies as both antitussives and to treat rhinorrhoea and nasal congestion. Although some antihistamines may have an antitussive action, their clinical efficacy has not been well documented. The anticholinergic (atropine-like) action of antihistamines frequently causes a drying sensation in the throat and nasal passages and may result in thickening of bronchial secretions [9].

### Demulcents

Demulcents consists of sugar, honey, lemon or glycerol and act by increasing saliva production and swallowing, thereby interfering with the cough reflex, or by coating the peripheral sensory receptors that triggers the cough. Demulcents may help reduce coughing associated with a dry irritated throat. Some cough syrups contain up to 40% alcohol and should never be used [10].

### Mucoactive agents

The main purpose of mucoactive agents is to increase the ability to decrease mucus hypersecretion and/or increase the ability to expectorate sputum. In a review article by Balsamo (2010) mucoactive drugs are classified according to their mechanism of action into expectorants (guaifenesin, hypertonic saline); mucoregulators (carbocysteine, anticholinergic agents, glucocorticosteroids, macrolide antibiotics); mucolytics (N-acetylcysteine) and mucokinetics (bronchodilators and surfactants). For the focus on this article, we will only focus on the agents used in combination [13].

### Expectorants

Guaifenesin is the most common expectorant and the dose required to be effective is 100-200 mg per dose for adults [14]. It has no mucolytic action but may reduce bronchial sputum surface tension. Guaifenesin can stimulate the cholinergic pathway and increase mucus secretion from the airway submucosal glands [13]. Ammonium chloride, sodium citrate, glyceryl guaiacolate failed to show better efficacy than placebo in several randomised control trials (RCT) [8].

### Mucoregulators

Carbocysteine has long been on the market and frequently used as single agent or in combination with other cough preparations. Carbocysteine may modulate airway inflammation by reducing the production of cytokines in rhinovirus infections. Additional evidence shows that carbocysteine inhibits the adherence of bacteria and viruses to ciliated epithelial cells *in vitro* [13].

### Mucolytics

Mucolytics decrease mucus viscosity. Evidence suggests that N-acetylcysteine (NAC) may also protect against free radical damage [13]. A systemic review found N-acetylcysteine (NAC) may decrease cough after six to seven days of therapy in children older than two years [14].

### Mucokinetics/bronchodilators

Mucokinetics increase mucociliary clearance by acting on the cilia in airways. The  $\beta_2$  adrenergic agonists, such as terbutaline also enhance mucociliary function and may be of benefit in patients with cystic fibrosis [13]. Bronchodilators work through their direct relaxation effect on airway smooth muscle cells. At present, three major classes of bronchodilators,  $\beta_2$ -adrenoceptor agonists, muscarinic receptor antagonists, and xanthines are available and can be used individually or in combination.

Orciprenaline and terbutaline are moderately selective  $\beta_2$  adrenergic receptor agonists and should be used in caution in patients with cardiac arrhythmia, diabetes and hyperthyroidism [15]. Theophylline has a narrow therapeutic index; serum levels slightly outside the target ranges may lead to serious toxicity or lack of efficacy. Unpredictable and erratic elimination kinetics, especially in children and elderly patients increases the risk for toxic effects [11].

### Cough suppressant/antitussive combinations

Another two classes of cough preparations commonly added to cough suppressants are decongestants ( $\alpha$  adrenergic agonist on capillary blood vessels of nasal mucosa such as pseudoephedrine and ephedrine hydrochloride) and expectorants such as ammonium chloride, sodium chloride, glyceryl guaiacolate and guaiphenesin. These combinations' therapeutic goal is probably to relieve symptoms of a blocked nose (congestion), dry cough, expectoration of phlegm and bronchoconstriction (wheeze). Products combining an expectorant and a cough suppressant is illogical as they have opposing effects and should not be advocated [8].

### Expectorant combinations

Expectorant combinations include decongestants, bronchodilators and cough suppressants. Combinations with expectorant and cough suppressant is not advisable, as it has opposing actions on the mucus, the one suppressing the cough and the other assisting with coughing out of mucus [16]. Combinations of decongestants, expectorants and bronchodilators could be of benefit for patients with blocked noses, wheeze and cough with mucus hypersecretion, so called "wet cough" [13].

### Bronchodilator combinations

Theophylline (xanthine) and orciprenaline ( $\beta_2$ -adrenoceptor agonists) as bronchodilators are frequently combined with mucolytics such as bromhexine. Oral bronchodilators should be administered at higher doses than the dose in the cough mixtures, to be effective for bronchospasm. At this dose, systemic side effects such as tremor, insomnia and tachycardia is unavoidable.

Combining muscarinic acetylcholine receptor antagonists is a pharmacological reasonable choice as muscarinic antagonists reduce the bronchoconstrictor effect of the acetylcholine while  $\beta_2$ -adrenoceptor agonists enhance the bronchial smooth muscle relaxation and result in bronchodilation. Antimuscarinic agents can suppress mucus/fluid secretions resulting in changes in surface tension [18].

Inhaled bronchodilators are the agent of choice for bronchodilation and to provide relief of cough due to upper respiratory infections of chronic bronchitis [9].

- Presence of thick yellow sputum or green phlegm, indicating possible bacterial infection
- Fever > 38.6°C
- Night-time coughing
- Weight-loss (unintentional)
- History or symptoms of underlying chronic disease
- Aspiration foreign objects
- Drug associated cough
- Coughing more than 7 days
- Cough not responding to appropriate medication.
- Infants or child who has a bark-like cough, stridor or hoarseness

**Table II:** When to refer a patient with cough to the doctor? [16]

### Choice of drug therapy

When cough alone is a major problem, using a full dose of a single drug aimed at a specific component of the cough reflex is preferred [10].

Component of cough reflex	Drug therapy
Non-productive cough	Antitussive-dextromethorphan preferred to codeine
Bronchoconstriction associated with cough	Bronchodilators (inhaled) combined with expectorants
Cough originating from pharyngeal region	Demulcent syrups combined with cough suppressant (dextromethorphan)

**Table III:** The cough reflex and drug therapy [9].

### Conclusion

Cough mixtures should be individualised for each patient and is indicated for short time, symptomatically treatment of acute cough. Some cough mixtures are illogical and should be avoided. Assessing a patient's symptoms and providing appropriate treatment recommendations is an important service pharmacists provide.

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