

# Cough Mixtures – an overview

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## Abstract

Cough mixtures are frequently prescribed for cough associated with upper respiratory diseases. Many different cough mixture combinations are available making an informed, therapeutically sound choice challenging for the pharmacist. Supportive evidence on the efficacy of cough mixtures in the alleviation of symptoms of colds and flu is not yet convincing. 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.

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## Introduction

Acute cough is usually due to the common cold. It is the most common symptom for which patients seek medical care. In a South African study, 79% of the mothers in the study group took their children to the clinic for coughing.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> Cough can be designated as acute (< 3 weeks in duration), prolonged acute (3 to 8 weeks in duration) or chronic (> 8 weeks in duration).<sup>4</sup> 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.

In South Africa cough mixtures may be a combination of many different active ingredients, and there are more than 40 different cough mixtures listed in the Monthly Index of Medical Specialities (MIMS).<sup>5</sup>

## 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). In Table I these classes are summarised into examples, reported action, common adverse effects and interactions.

## Therapeutic application

### 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.<sup>6</sup> 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 causes exhaustion.<sup>11</sup> 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 tract infection. The use of cough suppressants in children under six years of age should be avoided due to its safety profile.

### Antihistamines

Antihistamines are added to many cough and cold remedies as both antitussives and to treat rhinorrhoea and nasal

**Table I:** Pharmacological treatment options<sup>6, 7, 8, 9, 10, 11</sup>

Classification	Example	Reported action	Common adverse effects	Drug-drug interactions; Drug-disease interactions, contra-indications
<b>Cough suppressants</b>				
<b>Antitussives (Cough suppressant)</b>	Pholcodine, noscapine e.g. Nitepax <sup>®</sup> , Pholtex <sup>®</sup>	Centrally acting opioid derivative, directly suppressing medullary cough centre	Dizziness, sedation, nausea, constipation, headache	<i>Caution:</i> Contra-indicated in children < 2 years Contra-indicated in pregnancy Risk of opioid dependence, potential abuse
	Dextromethorphan e.g. Benylin dry cough <sup>®</sup>	Centrally active N-Methyl-D-aspartate (NMDA) receptor antagonist; directly suppresses medullary cough centre	Sedation, dizziness, nausea (rare), respiratory depression, confusion, excitation (in overdose)	<i>Drug-drug interactions:</i> Alcohol, CNS drugs' sedative action may be enhanced <i>Drug-disease interactions:</i> Asthma, liver impairment, respiratory depression. Patient with history of opioid dependency <i>Caution:</i> Not recommended for children < 6 years <i>Pregnancy:</i> relatively safe (Category C)
	Codeine phosphate	Suppresses cough reflex by suppressing the cough centre in medulla	Sedation, constipation, nausea	<i>Caution:</i> Risk of opioid dependence, potential abuse
	Embelia Ribes, Hyssopus officinalis, adhatoda vasica, glycyrrhiza glabra, sysygium aromaticum eg. Kofcare	Anti inflammatory and anti-microbial	None	Hypersensitivity to any of the ingredients
<b>Antihistamines</b>				
	Diphenhydramine, chlorpheniramine, diphenhydramine promethazine, triprolidine, diphenylpyraline e.g. Expectalin <sup>®</sup> (Diphenhydramine); Expigen <sup>®</sup> (ammonium chloride)	Reduces the cholinergic transmission of nerve impulses in the cough reflex Reduces frequency of coughing	Sedation, headache, dizziness, nervousness, restlessness, irritability, palpitations, dry mouth, urinary retention	<i>Drug-disease interaction:</i> Contra-indicated in patients with narrow-angle glaucoma and prostatic hypertrophy due to anticholinergic/antimuscarinic properties <i>Drug-drug interaction:</i> Potentiates effects of anxiolytics, hypnotics, analgesics, alcohol and other CNS depressants Potentiates anticholinergic effects with sympathomimetic drugs
<b>Demulcents</b>				
	Sucrose, honey alcohol	Coats the throat and soothes irritated mucous membranes		<i>Drug-disease interactions:</i> Preparations with added sugar should not be used in patients with diabetes mellitus due to its influence on glucose levels
<b>Mucoactive agents</b>				
<b>Expectorants</b>				
	Guaifenesin, ammonium chloride, sodium citrate, glyceryl guaiacolate e.g. Benylin wet cough <sup>®</sup> (guaifenesin)	Stimulates secretions and reduces mucus viscosity. Reduces bronchial sputum surface tension	Drowsiness, dizziness, headache, rash	<i>Drug-disease interactions:</i> Use with caution in patients with gastro-intestinal ulcers
<b>Mucoregulators</b>	Carbocysteine e.g. Mucospect <sup>®</sup>	Regulates metabolism of mucus-producing cells	Nausea, vomiting, headache, diarrhoea	<i>Drug-disease interactions:</i> Caution in asthmatics, and history of peptic ulcers.
<b>Mucolytics</b>				
	N-Acetylcysteine (NAC) e.g. Solmuco <sup>®</sup>	Depolymerises the mucin glycoprotein oligomers by hydrolysing the disulphide bonds in mucoproteins to reduce the viscosity of secretions	Nausea, vomiting, broncho-spasm, headache, fever, urticaria, skin rashes, abdominal pain and diarrhoea	<i>Drug-disease interactions:</i> Caution in asthmatics, and history of peptic ulcers
	Bromhexine	Loosens and thins bronchial secretions by reducing surface tension and viscosity of mucus	Gastro-intestinal effects, allergic reactions, broncho-spasm, dizziness, headache	<i>Drug-disease interactions:</i> Caution in asthmatics, and history of peptic ulcers

Mucokinetics				
Bronchodilators	Terbutaline, theophylline e.g. Alcophyllin <sup>®</sup> , Nuelin <sup>®</sup>	Improves cough clearance by increasing expiratory flow, reduction in volume of mucus secretion	Headache, fine tremor, insomnia, dizziness, tachycardia	<i>Drug-disease interactions:</i> Use with caution in patients with cardiac arrhythmias, ischaemic heart disease, uncontrolled hypertension or hyperthyroidism
	Ocimum Sanctum, adhatoda vasica, Ephedra gerardiana, e.g. Chest-eeze	Relief from painful and severe cough	None	Hypersensitivity to any of the ingredients

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.<sup>14</sup>

### Demulcents

Demulcents consist 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 trigger 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.<sup>14</sup>

### 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, 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 muco-kinetics (bronchodilators and surfactants).<sup>11</sup> In this article, we will only focus on the agents used in combination.

### Expectorants

Guaifenesin is the most common expectorant and the dose required to be effective is 100–200 mg per dose for adults.<sup>15</sup> 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.<sup>10</sup> Ammonium chloride, sodium citrate, glyceryl guaiacolate failed to show better efficacy than placebo in several randomised control trials (RCT).<sup>9</sup>

### Mucoregulators

Carbocysteine has long been on the market and is frequently used as a 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.<sup>11</sup>

### Mucolytics

Mucolytics decrease mucus viscosity. Evidence suggests that N-acetylcysteine (NAC) may also protect against free radical damage.<sup>11</sup> A systemic review found N-acetylcysteine (NAC) may decrease cough after six to seven days of therapy in children older than two years.<sup>15</sup>

### 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.<sup>10</sup> Bronchodilators work through their direct relaxation effect on airway smooth muscle cells. At present, three major classes of bronchodilators,  $\beta_2$ -adrenoceptor (AR) 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 with caution in patients with cardiac arrhythmia, diabetes and hyperthyroidism.<sup>15</sup> Theophylline has a narrow therapeutic index; serum levels

**Table II:** Cough mixture combinations available in South Africa<sup>5</sup>

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

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 increase the risk for toxic effects.<sup>12</sup>

### Cough suppressant/antitussive combinations

Two other classes of cough preparations commonly added to cough suppressants are decongestants ( $\alpha$ -adrenergic agonists on capillary blood vessels of nasal mucosa), and expectorants like ammonium chloride, sodium chloride, glyceryl guaiacolate and guaifenesin. 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 cough suppressant are illogical as they have opposing effects and should not be advocated.<sup>8</sup>

### Expectorant combinations

Expectorant combinations include decongestants, bronchodilators and cough suppressants. Combinations of expectorant and cough suppressant are not advisable, as they have opposing actions on the mucus, the one suppressing the cough and the other assisting with coughing out of mucus.<sup>18</sup> Combinations of decongestants, expectorants and bronchodilators could be of benefit for patients with blocked noses, wheeze and cough with mucus hypersecretion.

### Bronchodilator combinations

Theophylline (xanthine), and oriprenaline ( $\beta_2$ -adrenoceptor (AR) 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 are unavoidable. Combining muscarinic acetylcholine receptor antagonists and  $\beta_2$ -adrenoceptor agonists is a pharmacologically reasonable choice as muscarinic antagonists reduce the bronchoconstrictor effects of acetylcholine and  $\beta_2$ -adrenoceptor enhance the bronchial smooth muscle relaxation effect, thus bronchodilation. Antimuscarinic agents can suppress mucus/fluid secretions resulting in changes in surface tension.<sup>17</sup>

### 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.<sup>14</sup>

**Table III:** When to refer a patient with cough to the doctor

- 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 of foreign objects
- Drug-associated cough
- Coughing more than seven days
- Cough not responding to appropriate medication
- Infant or child who has a bark-like cough, stridor or hoarseness<sup>19</sup>

**Table IV**

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).

### Conclusion

Treatment with cough mixtures should be individualised for each patient and is indicated for short-term, symptomatic 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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