Current Drugs for the Treatment of Dry Cough

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Abstract
Cough is one of the commonest symptoms of respiratory tract infections and is a frequent problem encountered in general practice as well as in hospital practice. A wide range of disease processes may present with cough and definitive treatment depends on identifying the cause and diagnosis. Specific treatment of the cause should control the cough, but this may not occur in all cases and in a sizeable proportion of patients, no associated cause can be found. An increased sensitivity of the cough reflex can be observed in patients with dry cough. Symptomatic relief must be considered when the cough interferes with the patient’s daily activities and this is effectively treated with antitussive preparations which are available as combinations of codeine or dextromethorphan with antihistamines, decongestants and expectorants.

Antitussives are used for effective symptomatic relief of dry or non-productive cough. First generation antihistamines like chlorpheniramine and centrally acting opioid derivatives like codeine are often used alone or in combination in the management of nonspecific cough. Sedation caused by these is valuable, particularly if the cough is disturbing the sleep. Although there is extensive experimental data on single agent antitussives and antitussive combinations, there is a major paucity of published literature on these combinations in nonspecific cough. Treatment of dry cough remains a challenge in some patients and this article reviews the scope of the current drugs and combination of Codeine and Chlorpheniramine in the effective management of dry cough.

Introduction

Cough is a reflex response to mechanical, chemical, or inflammatory irritation of the tracheobronchial tree which is mediated by sensory neurons in the airways reflexly through neurons present in the brainstem. It is a physiologic function to clear airways of obstructive or irritating material or to warn the brainstem of pulmonary pathology. It is a reflex mediated by sensory neurons in the airways reflexly through the vagus, phrenic, and spinal motor nerves. Additionally, this kind of chronic cough can lead to fatigue, especially in elderly patients. In such circumstances, the drug may be replaced with another without this side-effect profile (e.g., an Angiotensin receptor blocker instead of an ACE inhibitor) or add an antitussive agent that will reduce the frequency or intensity of the coughing.

Cough, apart from being classified as productive (wet) and non-productive (dry), can also be classified based on the location of the cough receptors and the receptor types present in these locations. Cough receptors are stimulated by triggers such as touch or chemical irritants. The receptors in larynx and tracheobronchial tree (e.g., TRPV1 and TRPA1) classes.7-11 The stimulation of a complex reflex arc is necessary for cough. This is set off by the irritation of cough receptors that exist not only in the epithelium of the upper and lower respiratory tracts, but also those in the pericardium, esophagus, diaphragm, and stomach. Receptors sensitive to acid, cold, heat, capsaicin-like compounds and other chemical irritants trigger the cough reflex by activating ion channels of the transient receptor potential vanilloid type 1 (TRPV1) and transient receptor potential ankyrin type I (TRPA1) classes. Mechanical cough receptors are stimulated by triggers such as touch or displacement. The receptors in larynx and tracheobronchial tree respond to both mechanical and chemical stimuli.

Impulses from stimulated cough receptors are carried to the “cough center” in the medulla via the vagus nerve, which is under some control by higher cortical centers. The finding that women are more prone to develop chronic cough than men are explained by the sex-related differences in cough reflex sensitivity.3,13-15 The efferent signals are carried from the cough center through the vagus, phrenic, and spinal motor nerves to expiratory musculature which results in the production of cough (Figure 1).

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**Current Drugs Used in Treatment of Dry Cough**

Treatment of cough mainly consists of treating the underlying cause. A productive cough should not be suppressed except in special circumstances (eg, when it exhausts the patient or prevents rest and sleep) and generally not until the cause has been identified. Suppressing a productive cough is less advisable because sputum needs to be cleared. Cough remedies are categorized as antitussives and expectorants. Mucolytics, proteolytic enzymes, antihistamines, and bronchodilators are sometimes used.

**Antitussives:** These drugs may be centrally or peripherally acting. Centrally acting antitussives inhibit or suppress the cough reflex by depressing the medullary cough center or associated higher centers. The most commonly used drugs in this group are dextromethorphan and codeine.

Dextromethorphan, a congener of the narcotic analgesic levorphanol, has no significant analgesic or sedative properties, does not depress respiration in usual doses, and is nonaddictive. No evidence of tolerance has been found during long-term use.

Codeine, which has antitussive, analgesic, and slight sedative effects, is especially useful in relieving painful cough. It also exerts a drying action on the respiratory mucosa that may be useful (eg, in bronchorrhea) or deleterious (eg, when bronchial secretions are already viscous). Nausea, vomiting, constipation, tolerance to antitussive as well as analgesic effects, and physical dependence can occur, but potential for abuse is low.

Other centrally acting antitussives include chlorphedianol, levopropoxyphene, and noscapine in the nonnarcotic group and hydrocodone, hydromorphone, methadone, and morphine in the narcotic group.

Peripherally acting antitussives may act on either the afferent or the efferent side of the cough reflex. On the afferent side, an antitussive may reduce the input of stimuli by acting as a mild analgesic or anesthetic on the respiratory mucosa, by modifying the output and viscosity of the respiratory tract fluid, or by relaxing the smooth muscle of the bronchi in the presence of bronchospasm. On the efferent side, an antitussive may make secretions easier to cough up by increasing the efficiency of the cough mechanism. Peripherally acting agents are grouped as demulcents, local anesthetics, and humidifying aerosols.

Demulcents are useful for coughs originating above the larynx. They form a protective coating over the irritated pharyngeal mucosa. They are usually given as syrups or lozenges and include acacia, licorice, glycerin, honey, and wild cherry syrups.

Local anesthetics (eg, lidocaine, benzocaine, hexylcaine hydrochloride, and tetracaine) are used to inhibit the cough reflex under special circumstances (eg, before bronchoscopy or bronchography). Benzonatate (100 mg po tid), a congener of tetracaine, is a local anesthetic; its antitussive effect may be due to a combination of local anesthesia, depression of pulmonary stretch receptors, and nonspecific central depression.

Expectorants: These drugs are intended to help expel bronchial secretions from the respiratory tract by decreasing their viscosity, thus facilitating removal, and by increasing the amount of respiratory tract fluid, thus exerting a demulcent action on the mucosal lining. Most expectorants increase secretions through reflex irritation of the bronchial mucosa. Some, like the iodides, also act directly on the bronchial secretory cells and are excreted into the respiratory tract.

The use of expectorants is highly controversial. No objective experimental data show that any of the available expectorants decreases sputum viscosity or eases expectoration. Data may be lacking partly because of inadequate technology for obtaining such evidence. Thus, the use and choice of expectorants are often based on tradition and the widespread clinical impression that they are effective in some circumstances.

Adequate hydration is the single most important measure that can be taken to encourage expectoration. If it is unsuccessful, using an expectorant in addition may produce the desired result.

Guaiifenesin (100 to 200 mg po q 2 to 4 h) is the most commonly used expectorant in OTC cough remedies. It has no serious adverse effects, but there is no clear evidence of its efficacy.

Many other traditional expectorants (eg, ammonium chloride, terpin hydrate, creosote, squill) are found in numerous OTC cough remedies. Their efficacy is doubtful, particularly in the dosages of most preparations.

**Less commonly used drugs:** Mucolytics (eg, acetylcysteine) have free sulfhydryl groups that open mucoprotein disulfide bonds, reducing the viscosity of mucus. As a rule, their usefulness is restricted to a few special instances such as liquefying thick, tenacious, mucopurulent secretions (eg, in chronic bronchitis and cystic fibrosis). Acetylcysteine is given as a 10 to 20% solution by nebulization or instillation. In some patients, mucolytics may aggravate airway obstruction by causing bronchospasm. If this occurs, these patients may inhale a nebulized sympathomimetic bronchodilator or take a formulation containing acetylcysteine (10%) and isoproterenol (0.05%) before taking the mucolytic.

Proteolytic enzymes (eg, pancreatic dornase) are useful only when grossly purulent sputum is a major problem. They seem to offer no advantage over mucolytics. Local irritation of the buccal and pharyngeal mucosa and allergic reactions commonly follow repeated doses. Dornase alfa, the new highly purified recombinant human deoxyribonuclease I (rhDNase), seems likely to become important in the treatment of cystic fibrosis, although its place has not been defined.

Antihistamines have little or no use in treating cough. Their drying action on the respiratory mucosa may be helpful in the early congestive phase of acute coryza but may be deleterious, especially to patients with a nonproductive cough resulting from retained viscous airway secretions. They may also be beneficial in chronic cough due to postnasal drip associated with allergic sinusitis.

Bronchodilators (eg, ephedrine and theophylline) may be useful if cough is complicated by bronchospasm. Atropine is undesirable because it thickens bronchial secretions. The anticholinergic drug ipratropium bromide can often ameliorate an irritating type of cough and does not adversely affect mucus secretions. Inhaled corticosteroids have become a mainstay in the treatment of cough in asthma.

**Management of Cough:** Focus on combination of antitussive preparations.
trials on patients with various airway disorders such as chronic cholinergic drugs are often used alone or in combination.16... and chronic cough in humans.25,26 There is a linear relationship between a codeine dosage of 7.5 to 60 mg/d and a decrease in the frequency of chronic cough.27 Codeine (60 mg) significantly reduced the cough frequency compared to placebo (p<0.001), and also produced a greater reduction in cough intensity than placebo and lower doses of codeine (20 and 30 mg; p<0.001).28 Eddy et al. opine that a multimodal action of codeine, including antitussive, analgesic and sedative effects is an advantage in special cases: an analgesic effect could be desirable, when cough is associated with pain and a sedative action could help if the patient is apprehensive or if the cough was initiated or enhanced by central stimuli (nervous cough).29 Codeine has also shown to be effective in the management of chronic cough caused due to various etiologies.30 Importantly, the danger of development of dependence to Codeine at doses used to suppress cough is very small.29 Furthermore, addiction is uncommon in individuals with no existing vulnerability to addiction.32 Compared to animals, codeine is less toxic to humans, possibly because it produces less respiratory depression. Dependence is far less frequent in humans, compared to that with morphine and also abstinence syndrome is less intense.33

Chlorpheniramine Maleate (The importance / role of First generation Anti-histamines in management of cough)

First generation anti-histamines like chlorpheniramine reduce the cholinergic transmission of nerve impulses in the cough reflex, hence, reduce the frequency of cough and dry up the secretions, making them ideal for treating cough concomitant with rhinorrhea.34 Additionally, sedation, which otherwise is considered a side-effect of these drugs can be valuable in this situation, particularly if the cough is disturbing the sleep.25 Table 1 describes the possible mechanisms by which these antihistamines suppress cough.35

As discussed previously, since cough is an entirely vagus-mediated phenomenon36, the difference in the antitussive effects of the first- and second-generation antihistamines is explained by their relative anticholinergic activity. Although both these groups of drugs are competitive antagonists to histamine at the H1-receptor site, the first-generation antihistamines also demonstrate competitive antagonism of acetylcholine at neuronal and neuromuscular muscarinic receptors. Additionally, first-generation antihistamines, cross the blood–brain barrier due to their lipophilicity, whereas the relatively lipophobic second-generation antihistamines do not.37 This concept is further supported by recent animal data demonstrating that the antitusive actions of antihistamines are not directly related to H1-receptor blockade.38 Of interest is that this study showed an independence of the antitusive actions of antihistamines and their sedative effects.

There have been very few clinical trials examining the antitusive effects of antihistamines. In healthy volunteers, the first-generation antihistamine, diphenhydramine, inhibited cough induced by citric acid.39 In contrast to this, the non-sedating, second-generation antihistamine, terfenadine, was ineffective in suppressing capsaicin-induced cough.40 Another second-generation agent, loratadine, was also ineffective in healthy volunteers; however, it did suppress cough induced by ultrasonically nebulized distilled water in patients with nasal disease and unexplained chronic cough.41 Several studies have shown that rhinitis/postnasal drip syndrome (PNDS) is one of the most common causes of chronic cough.42,43 First generation antihistamines are known to be

<table>
<thead>
<tr>
<th>Mechanism</th>
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<tr>
<td>Peripheral</td>
<td>Prevent the production of cough which is an effect of histamine receptors on sensory afferents</td>
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<tr>
<td>Direct</td>
<td>Nasal mucus secretion induced by histamine receptors promotes cough and that induced by cholinergic mechanisms produce cough by a mechanical action on pharyngeal or laryngeal mechanoreceptors that elicit cough</td>
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<tr>
<td>Indirect</td>
<td>Block the histamine H1 receptors in the central nervous system which may directly promote the production of cough. May bind to nonhistaminergic receptors in the central nervous system that control cough excitability.</td>
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<tr>
<td>Central</td>
<td>Block the histamine H1 receptors in the central nervous system and this decrease the nasal mucus secretion. May bind to nonhistaminergic receptors that regulate mucus secretion. Induce sedation that could result in a reduction in cough excitability.</td>
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Single Agents may not be effective, Combination may be essential for better control:

Many antitussive preparations are available are combinations of codeine or dextromethorphan with antihistamines, decongestants, expectorants, and/or antipyretics.1 In India, several such cough mixtures containing an anti-histaminic and an opioid derivative claiming increased efficacy are available. However, whatever knowledge is available on these cough mixtures is mostly based on the experience of the practicing clinicians and there is a paucity of published clinical trials.

Antitussives or more often, referred to as cough suppressants are used for effective symptomatic relief of dry or non-productive cough. First generation anti-histamines like chlorpheniramine, centrally acting opioid derivatives like codeine and anticholinergic drugs are often used alone or in combination.16

Codeine Amongst the many anti-tussive agents available for the management of cough, Codeine, is one of the most frequently used centrally acting cough suppressant and has been widely regarded as the ‘gold standard’ cough suppressant drug since a long time. This perception was based on its efficacy in animal models17-20 as well as several older placebo-controlled clinical trials on patients with various airway disorders such as chronic bronchitis or chronic obstructive pulmonary disease.21,22

Codeine and other centrally acting cough suppressants like pholcodeine and dextromethorphan act directly on the cough centre in the brain and reduce the discharge of nerve impulses to the muscles that cause coughing.23 These drugs can cause sedation and constipation in some patients

Besides their anti-tussive action, opioids like codeine also exhibit proven analgesic action. In fact, these agents cause cough suppression at lower doses than that required for analgesia. A 10- or 20-mg oral dose of codeine, produces a demonstrable antitussive effect, although ineffective for analgesia and higher doses produce even more cough suppression.24

Of the centrally acting antitusives, codeine and dextromethorphan are the most commonly used. In adults, both these drugs have been shown to inhibit fictive cough in animal models, and suppress artificially induced, disease-related
effective in the treatment of cough in patients with nasal disease. These drugs inhibit the release of histamine and leukotrienes produced by eosinophils and mast cells. Chronic cough in individuals with no asthma has been shown to be associated with airway inflammation by the presence of eosinophils and metachromatic cells and epithelial damage. First generation antihistamines are therefore, especially helpful in non-asthmatic cough.

Recent guidelines published by the American College of Chest Physicians (ACCP) recommend the use of a first-generation antihistamine in combination with a decongestant for the treatment of chronic cough due to PNDS, considering the observed ineffectiveness of the newer second-generation, relatively non-sedating antihistamines in acute cough associated with the common cold.

### Combination of Codeine and Chlorpheniramine

An Indian study compared pholcodiene plus promethazine (CS-1) with dextromethorphan plus chlorpheniramine (CS-2) and codeine plus chlorpheniramine (CS-3) in pediatric population. The details of the number and percentage of patients achieving clinical end-points for the symptoms are summarized in Table 2. A greater percentage of patients in the CS-3 group achieved the clinical endpoint for cough episodes by day 7 compared to those in the CS-1 group.

All three cough preparations were comparable for night awakenings (table-2). The authors concluded from this study that all the three combinations studied were equi-efficacious in awakening (table-2). The authors concluded from this study that all the three combinations studied were equi-efficacious in awakening (table-2). The authors concluded from this study that all the three combinations studied were equi-efficacious in awakening (table-2). The authors concluded from this study that all the three combinations studied were equi-efficacious in awakening (table-2). The authors concluded from this study that all the three combinations studied were equi-efficacious in awakening (table-2). The authors concluded from this study that all the three combinations studied were equi-efficacious in awakening (table-2). The authors concluded from this study that all the three combinations studied were equi-efficacious in awakening (table-2). The authors concluded from this study that all the three combinations studied were equi-efficacious in awakening (table-2). The authors concluded from this study that all the three combinations studied were equi-efficacious in awakening (table-2)

### Summary and Conclusions

Cough is one of the most common symptoms encountered in clinical practice. There are many over-the-counter combination syrups available for the management of cough. These are the mainstay of therapy in case of nonspecific cough and may act as adjuvant in addition to treatment of the specific cause, in case of cough associated with other conditions.

Opioids and older or first generation antihistamines have been used in the management of cough since a long time, and have shown some benefit. Codeine and chlorpheniramine maleate are archetypal drugs belonging to these two classes respectively. Their combination may be useful as an antitussive in the management of nonspecific cough. However, there is a major paucity of published literature on this combination and therefore, a large-scale randomized trial on the efficacy and safety of this combination is warranted.

### References


