Cough Suppressant and Pharmacologic Protussive Therapy:

ACCP Evidence-Based Clinical Practice Guidelines

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Abstract

Background—Cough-suppressant therapy, previously termed *nonspecific antitussive therapy*, incorporates the use of pharmacologic agents with mucolytic effects and/or inhibitory effects on the cough reflex itself. The intent of this type of therapy is to reduce the frequency and/or intensity of coughing on a short-term basis.

Methods—Data for this review were obtained from several National Library of Medicine (PubMed) searches (from 1960 to 2004), which were performed between May and September 2004, of the literature published in the English language, limited to human studies, using combinations of the search terms "cough," "double-blind placebo-controlled," "antitussive," "mucolytic," "cough clearance," "common cold," "protussive," "guaifenesin," "glycerol," and "zinc."

Results—Mucolytic agents are not consistently effective in ameliorating cough in patients with bronchitis, although they may be of benefit to this population in other ways. Peripheral and central antitussive agents can be useful in patients with chronic bronchitis, but can have little efficacy in patients with cough due to upper respiratory infection. Some protussive agents are effective in increasing cough clearance, but their long-term effectiveness has not been established. DNase is not effective as a protussive agent in patients with cystic fibrosis. Inhaled mannitol is acutely effective in this patient population, but its therapeutic potential must be investigated further.

Conclusions—These findings suggest that suppressant therapy is most effective when used for the short-term reduction of coughing. Relatively few drugs are effective as cough suppressants.

Keywords

antitussive; cough; cough suppressant; nonopioid; opioid; protussive

In this section, the evidence supporting the use of cough-suppressant drugs in the treatment of chronic cough is reviewed. Therapies are systematically addressed in relation to their effects on anatomically defined elements of the nervous and muscular systems responsible for coughing. More specifically, cough is produced when sensory receptors in the airways (*ie*, the afferent limb of the cough reflex) are excited by mechanical and/or chemical stimuli. A common mechanical stimulus for these sensory receptors is accumulated mucus, and agents that alter mucociliary factors (*eg*, mucus volume, production, consistency, or ciliary activity) are considered as a separate category in this section. The excitability of the sensory receptors themselves can be modified by drugs, and compounds that suppress cough by this mechanism are defined as peripheral antitussive agents. Airway sensory afferents control the excitability of neural elements in the brainstem that produce cough, and drugs that act at this level of the CNS are classified as centrally acting antitussive agents. The brainstem cough-

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generation system transmits excitatory information to spinal motoneurons innervating respiratory muscles. Drugs that may act on this efferent limb of the cough reflex pathway and paralytic agents that block the neuromuscular junction are considered as separate categories in this document. Finally, the scope of this section includes those drugs that have protussive effects (*ie*, any drug that may increase cough clearance) in patients with disorders in which thickened or accumulated mucus contributes to morbidity.

In the previous evidence-based guideline, these types of cough therapy were termed *nonspecific*, to differentiate them from therapy-specific for a particular disease/disorder. We have changed that terminology to *suppressant therapy*. Many of the drugs that fall into this category bind to specific pharmacologic receptors, and have effects on well-identified elements of the CNS and peripheral nervous systems. They are intended to reduce coughing regardless of etiology. As such, it is considered most appropriate to term them as *suppressants*.

These types of drugs are intended to be used when the excitability and/or intensity of cough is elevated over what is required to defend the airways. Their actions presumably return a hyperresponsive cough reflex to its normal state. There is no evidence that cough-suppressant therapy can prevent coughing. An important point to note is that, unlike specific therapy, these drugs do not resolve the underlying pathophysiology that is responsible for the coughing.

The classification of drugs as suppressant or non-specific is based largely on their ability to suppress cough in animal models in which there is no underlying airway pathophysiology. Furthermore, many of these drugs decrease cough sensitivity in healthy humans who are challenged with inhaled irritants. The recommendations of the committee are restricted to the efficacy of these drugs in double-blind, placebo-controlled studies in humans with airway pathology. While the focus of this section is on studies published since the last consensus document, other older double-blind, placebo-controlled studies that were not included in the previous report have been added. This section also refers to other studies in humans and animals in which the results shed light on mechanistic issues related to the actions of these drugs.

Because of the strong track record of success of specific therapy,[1] suppressant therapies are necessary only in specific situations. In particular, their use is typically on a short-term basis for symptomatic relief of cough. As noted in our previous evidence-based guideline,[1] the use of these drugs is most appropriate when (1) the etiology of cough is unknown (precluding the use of specific therapy), (2) specific therapy requires a period of time before it can become effective,[1] or (3) specific therapy will be ineffective, such as in patients with inoperable lung cancer.

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Drugs That Affect Mucociliary Factors

This topic was not addressed separately in the previous evidence-based guideline.[1] In disorders that have associated mucus hypersecretion, cough is elicited to enhance the clearance of accumulated secretions. One pharmacologic approach to treating these disorders is to alter the mucociliary factors. As described by Irwin et al,[2] there are several mechanisms by which this may occur, as follows: (1) the drug could be an expectorant,

increasing mucus volume; (2) the drug may suppress mucus production; (3) mucus consistency may be altered; and (4) ciliary function may be enhanced. These mechanisms need not be mutually exclusive. For example, it is unlikely that expectorants will alter mucus volume without also affecting its consistency. Antihistamines also may act to reduce coughing by the suppression of mucus production in URI.

Relatively few drugs have been shown to suppress cough by an action on mucociliary factors, and none of them consistently. Table 1 summarizes the effects of putative mucociliary drugs on cough. Of these, inhalation of ipratropium bromide has been shown to suppress subjective measures of cough in patients with URI[3] or chronic bronchitis.[4] However, oxitropium bromide did not alter subjective measures of coughing in subjects with URI.[5] Interestingly, tiotropium does not suppress cough in patients with COPD, although cough was a outcome measure in this study.[6] It should be noted that other studies evaluating the effects of tiotropium have not measured cough. The reasons for the inconsistent effects of anticholinergic agents in disorders in which mucus production should contribute to cough are not clear. The previous guideline[1] supported the use of inhaled ipratropium bromide for cough suppression in bronchitis. The results of these more recent studies on inhaled anticholinergic agents in bronchitis have caused us to maintain a recommendation that is focused on inhaled ipratropium bromide for relief of cough due to URI or chronic bronchitis.

The inconsistent actions of inhaled anticholinergic agents on cough due to URI also are relevant to the proposed mechanism of action of older, CNS penetrant, H1 antihistamines in the suppression of cough due to upper respiratory infection (URI). It is widely accepted that first-generation antihistamines appear to be more effective in the suppression of URI-induced cough than nonsedating H1-receptor antagonists because they have greater anticholinergic activity. The therapeutic effect of cholinergic blockade by the systemic administration of sedating antihistamines is likely to be restricted to the nasal airways. This concept is supported by the inconsistent action of inhaled anticholinergic agents on cough (*ie*, itis unlikely that systemically administered sedating antihistamines are acting in the lower airways). A related point is that only 7% of inhaled ipratropium bromide is systemically absorbed, and there is little evidence for the anticholinergic activity of this drug in nonpulmonary tissues when it is delivered in this manner.[7] Presumably, a systemically administered and selective anticholinergic agent would have the same efficacy on cough due to URI as the sedating antihistamine agents. However, a primary difference between first-generation and second-generation antihistamines is central penetration. It is equally plausible that first-generation antihistamines are more effective in the suppression of URI-induced cough because they act on H1 histaminergic and/or M1 muscarinic receptors located in the CNS. Indeed, Muether and Gwaltney[8] have proposed this exact mechanism to explain the greater effectiveness of first-generation antihistamines over that of second-generation antihistamines in blocking sneezing associated with natural or induced colds. While these two potential mechanisms are not mutually exclusive, it will be a challenge to sort out their relative roles in future studies.

The expectorant guaifenesin decreased subjective measures of cough due to URI,[9] and subjective and objectives indexes of cough due to bronchiectasis.[10] However, two other studies[11,12] found no effect of this drug on cough due to chronic bronchitis. Another expectorant, iodinated glycerol, has been found to be active in reducing subjective assessments of cough frequency and severity in patients with chronic bronchitis in two studies.[13,14] However, another study[15] found no significant benefit of iodinated glycerol on coughing in stable patients with chronic bronchitis. This drug has since been removed from the US market because of carcinogenicity concerns.[16] Bromhexine has been tested in patients with chronic bronchitis or bronchiectasis in several studies employing both subjective and objective indexes of cough. While this drug decreased sputum volume or

thickness, it was inactive to modify cough in three studies[17-19] and active in only one study.[20] The latter study consisted of a much larger patient population than those in the other studies, so it is possible that the effect of bromhexine on cough is small and requires a much larger group to be detected. Carbocysteine was inactive in one study[21] to alter the clearance of secretions or cough frequency in a small population of patients with chronic bronchitis and with or without radiologic evidence of emphysema. Another larger study[22] of patients with chronic bronchitis producing at least 25 mL of sputum daily showed significant reductions in objective measures of sputum viscosity after carbocysteine treatment. There were no significant changes in the subjective indexes of cough frequency or severity, but patients reported significantly better ease of expectoration while receiving therapy with carbocysteine.

Other drugs such as acetylcysteine,[23-25] mercaptoethane sulfonate,[24,26] and hypertonic saline solution[27] have been found to be inactive against cough in subjects with chronic bronchitis. Bromhexine, mercaptoethane sulfonate, and carbocysteine are not approved for use in the United States.

In sum, these findings suggest an important conclusion regarding the actions of mucociliary agents on cough. While cough is important in the clearance of mucus from the airways, its frequency and intensity can be independent of mucus properties in patients with chronic bronchitis. It is important to note that this conclusion is specific to cough and does not lessen the potential benefit of therapy with mucolytic agents in patients with chronic bronchitis on other outcomes. In essence, the data suggest that other therapeutic modalities may be more useful to manage cough in patients with chronic bronchitis.

Drugs That Affect the Afferent Limb of the Cough Reflex

The classification of antitussive drugs as peripheral or central is based largely on preclinical studies. Peripherally acting suppressants lack the sedation potential that is often associated with centrally acting drugs, such as opioids, because they do not penetrate the CNS to an appreciable extent. It should be noted, however, that one centrally acting drug, dextromethorphan, is not sedating, so a central action does not guarantee sedation potential as a side-effect of cough suppression.

Peripherally active drugs are thought to act wholly on the sensory elements that contribute to cough. While the most widely accepted mechanism of action for this class of drugs is thought to be the frank suppression of pulmonary afferent activity,[28] one prominent drug, levodropropizine, acts at least in part by the activation of C-fiber sensory afferents that reflexively inhibit cough.[29] One drug, caramiphen, has been considered as a centrally acting drug. However, according to a preclinical study,[30] this drug should be classified as a peripherally acting drug. There are apparently no other published studies on the site of action of this drug, and the US Food and Drug Administration has removed this drug from the US market as an antitussive agent.[31]

The current review expands on the previous one[1] for peripheral drugs by citing several more studies on levodropropizine and adding moguisteine to this list of drugs (Table 2). Levodropropizine is very active (approximately 75% suppression) in reducing cough in patients with chronic or acute bronchitis.[32] This drug also is as effective as dihydrocodeine in suppressing cough due to lung cancer,[33] although that study was not placebo-controlled. Moguisteine has been shown to be active in treating cough due to COPD.[34] This drug also can suppress cough due to URI, although the effect was restricted to cough at night and the magnitude of suppression was limited.[35] Moguisteine and levodropropizine are not approved for use in the United States.

Cough due to lung cancer is also sensitive to peripherally acting suppressant drugs (reviewed elsewhere in the guidelines). A placebo-controlled trial[36] of inhaled sodium cromoglycate demonstrated significant suppression of cough in patients with lung cancer, presumably due to the suppression of mediator release.

Drugs That Affect the Central Mechanism for Cough

This class of compounds is thought to act at one or more sites in the CNS to suppress cough. The particular CNS elements that are sensitive to these drugs are unknown. Based on preclinical experiments,[37] the brainstem is thought to be the main region where antitussive agents act by a mechanism in which the motor control of cough is inhibited. However, the production of cough can be associated with sensation, termed the *urge to cough*, indicating that sensory information associated with cough affects suprapontine sites in the brain.[38] Furthermore, cough can be voluntarily suppressed, indicating a prominent role for cortical pathways in its control.[39] It is possible that some centrally acting drugs affect the excitability of cough by interacting with suprapontine pathways that mediate sensation or the voluntary suppression of this behavior. This issue has been addressed by Hutchings and Eccles,[40] who showed that the voluntary suppression of cough was not altered by codeine or the opioid antagonist naltrexone in healthy subjects. Their work suggests that endogenous opioids do not mediate the voluntary suppression of cough. Further work is necessary to address the role of these novel mechanisms in the actions of cough suppressants in patients with airway disease.

The most common patient population covered in the previous review was patients with chronic bronchitis, and a variety of centrally active drugs were deemed to be effective in patients with this disorder. Studies on patients with chronic bronchitis appear in the current review, but there also are a number of studies on patients with URI. The effects of these drugs on cough are summarized in Table 3. Pipazethate is not approved for use in the United States. The current review reveals that not all suppressant drugs are effective, especially in cough due to URI. Codeine and dextromethorphan (but not pipazethate) are active in cough due to chronic bronchitis/COPD,[41-43] suppressing cough counts by 40 to 60%. However, the antitussive effects of codeine in patients with chronic bronchitis were established in small patient populations.[41-43] Furthermore, there have been no double-blind placebo-controlled studies of the effects of codeine on cough due to acute bronchitis, although it is reasonable to presume that this drug is effective under these circumstances. There have been several studies that have indicated a lack of efficacy of codeine and dextromethorphan[44-47] in cough due to URI. Others[10,48] have reported the suppression of cough due to URI by these drugs. As suggested by Pavesi et al,[48] the reason for this discrepancy for dextromethorphan may be related to the limited efficacy (< 20% suppression) of this drug, requiring larger numbers of subjects to demonstrate a significant effect. Pavesi et al[48] conducted a metaanalysis of six separate studies of > 700 subjects, while Parvez et al[10] studied > 300 subjects. However, it is unclear the extent to which the metaanalysis of Pavesi et al[48] overlapped with the population reported by Parvez et al.[10] The reports of Lee et al[46] and Tukiainen et al[47] studied 43 and 108 subjects, respectively.

The limited activity of these drugs against cough due to URI is not predictable based on our current understanding of the physiology and pharmacology of the cough reflex. Indeed, the fact that codeine can have a differential effect on cough based on specific pathology suggests that the central mechanisms for cough can differ significantly between disorders. In essence, cough may have the same mechanical function in different disorders, but the CNS mechanism responsible for its production may have a different neural organization, analogous to remodeling. This neural remodeling (also called *plasticity*) may alter the sensitivity of the central cough mechanism to various pharmacologic agents.

Centrally acting opioid cough suppressants, such as hydrocodone and dihydrocodeine, have also been shown to be effective in patients with cough due to lung cancer (reviewed elsewhere in this guideline). However, the evidence for these effects was obtained from studies that were not placebo-controlled.

Drugs That Affect the Efferent Limb of Cough Reflex

In this context, the efferent limb of the cough reflex is defined as a spinal action of the drug. While this definition appears to overlap with that of centrally acting drugs, it bears specific attention here. As defined above, our current definition of centrally acting antitussive drugs is restricted to those acting in the brainstem and/or at suprapontine sites. A drug that selectively suppressed the excitability of spinal pathways to abdominal muscle motoneurons would be expected to ameliorate intense expiratory efforts associated with repetitive coughing and would represent a useful adjunct to existing specific therapies. Of the drugs known to have central actions to inhibit cough, baclofen may be an example of a drug with this mechanism of action. It is well-known that this drug is a muscle relaxant with a spinal action.[49] Baclofen is a centrally acting cough suppressant in animals[50] and suppresses irritant-induced cough in humans.[51,52] Furthermore, this drug did suppress subjective measures of angiotensin-converting enzyme inhibitor-induced cough in an open-label study.[53] However, this drug has not yet been tested for activity in double-blind placebo-controlled studies of pathologic cough. The utility of this drug or others that may have solely a spinal action in the treatment of cough due to airway disease awaits further study.

Drugs That Affect the Skeletal Muscles

Neuromuscular blocking agents have been used in conjunction with anesthetics to suppress cough and thus to facilitate intubation. The depolarizing agent, succinylcholine, is most commonly used for this application but has a significant side effect profile.[54] Newer non-depolarizing agents have fewer side effects but do not possess the rapid onset and recovery associated with succinylcholine.[54-56] Erhan et al,[56] in a double-blind study, showed that anesthetics, especially propofol, can provide adequate cough suppression for intubation in the absence of neuromuscular blockade. However, a single-blind study[57] found treatment with a neuromuscular blocker (atracurium) plus propofol to be more effective than propofol alone in suppressing cough induced by intubation. The increased efficacy of neuromuscular blocking agents in combination with anesthetics in suppressing cough accounts for their use during intubation.

Other Drugs

Table 4 summarizes studies on the effects of zinc acetate or zinc gluconate on the common cold,[58-66] and two studies[63,67] evaluated cough with subjective measures. Mixed results were obtained, with some studies[58,59,61,63,67] indicating a positive effect of zinc preparations on the common cold and others[60,62,64-66] suggesting no benefit. Two metaanalyses[68,69] of these studies have been performed, and both concluded that there was insufficient evidence to support the use of zinc preparations in the treatment of the common cold. Various explanations for the divergent results of these studies have been proposed including widely variant dosages, inadequate blinding, and bioavailability issues.[70] Furthermore, zinc therapy can be associated with a significant side-effect profile, in particular bad taste and nausea.[70] Of these two preparations, only zinc acetate is approved for use in the United States.

Albuterol has been evaluated in two studies of acute (*ie*, < 4 weeks) cough[71,72] (Table 4). Cough was evaluated by subjective measurements in both studies. Bernard et al[71] studied nonasthmatic children in whom the exact cause of cough was not determined, but cough resolved within 7 days in both the placebo and treatment groups. Littenberg et al[72] studied

adults with either bronchitis or cough of undetermined origin. Albuterol had no significant effect on coughing in either study.

Over the counter, non-prescription medications are commonly used to treat acute cough and other symptoms associated with the common cold. The combination medications contain antitussives, expectorants, sympathomimetics, and/or antihistamines; many are carried in a demulcent vehicle. Unfortunately, with the exception of an older antihistamine-decongestant combination,[73] many have never been shown to be effective, many have never been studied in combination, and some drugs in the combination products are indicated only for other conditions. Fortunately, one is not limited to having to take one of these combination medications because there are available effective cough suppressant medications that work in a variety of different ways. For further information, readers are encouraged to refer to section on Cough and the Common Cold in this guideline.

Pharmacologic Protussive Therapy

Protussive therapy is intended to enhance cough effectiveness to promote the clearance of airway secretions. The most common disorders in which this type of therapy is indicated include cystic fibrosis, bronchiectasis, pneumonia, and postoperative atelectasis.[2] In these disorders, mechanical methods to loosen mucus or pharmacologic tools that increase cough clearance may be useful to increase the effectiveness of coughing. Mechanical protussive procedures are covered in another section of this guideline. These approaches require the cough motor control system to be competent. It should be noted that there are several prominent disorders in which cough is impaired and the resultant accumulation of secretions contributes significantly to morbidity. Cough can be impaired after stroke or spinal injury. The impairment of cough after stroke can contribute to aspiration, and this topic has been reviewed elsewhere in this guideline. Therapeutic approaches to the impairment of cough after spinal injury have been restricted to mechanical methodologies intended to harvest accumulated secretions (*eg*, suctioning of the airway in tracheostomized patients) or to enhance cough airflows.[74] There are currently no pharmacologic therapies for the enhancement of cough in disorders in which the motor system for this behavior is impaired.

Pharmacologic Enhancement of Cough Clearance

The previous evidence-based guideline[1] cited randomized, double-blind, placebo-controlled studies showing that hypertonic saline solution and erdosteine (which is not approved for use in the United States) were effective agents for increasing cough clearance in patients with bronchitis, and that amiloride was effective for this function in patients with cystic fibrosis. Ineffective agents (in bronchitic patients) included carbocysteine, mercaptoethane sulfonate, bromhexine, and guaifenesin. Terbutaline was also shown to be effective in combination with chest physiotherapy and postural drainage in patients with bronchiectasis.

The current guideline includes two new studies that investigated the effects of recombinant DNase on cough clearance[75] and mucociliary clearance[76] in subjects with cystic fibrosis (Table 5). Both studies also recorded subjective measures of spontaneous cough. Neither study demonstrated a significant action of recombinant DNase over placebo, although Robinson et al[75] suggested that their study may have been underpowered given the large intersubject variability that they encountered.

A double-blind placebo-controlled study[77] showed that the inhalation of dry-powder mannitol increased cough clearance in patients with cystic fibrosis (Table 5). In this study, mannitol was as effective as hypertonic saline solution in increasing mucociliary clearance. The long-term effectiveness and safety of mannitol must be confirmed before it should be considered as a treatment for cystic fibrosis patients.

Conclusions

Relatively few drugs are effective for the nonspecific suppression of cough. Our current recommendations largely confirm and extend the findings of the previous panel.[1] Most notably, the current guidelines expand on the previous consensus by recommending that the use of suppressants be guided by the physician's specific knowledge of the disorder that is eliciting cough.

The previous guideline[1] identified a number of different drugs as effective cough suppressants, particularly in patients with chronic bronchitis. These drugs included codeine, dextromethorphan, ipratropium bromide, and diphenhydramine. The previous guideline also included the following several drugs that are not available in the United States: caramiphen; levodropropizine; the acetylsalicylic acid pro-drug guaimesal; the phosphodiesterase inhibitor and antidopaminergic agent glaucine; and the analgesic viminol. The current recommendations have been revised to narrow recommended inhaled anticholinergic agents to a single drug, ipratropium bromide, for cough due to URI or bronchitis. The current guideline supports the use of codeine only in chronic bronchitis and not in cough due to URI. The previous guideline also recommended naproxen and dexbrompheniramine/ pseudoephedrine for cough due to colds.

Protussive agents that were recommended previously were relatively few in number, and the present guideline is essentially unchanged in this regard, with the exception that recommendations regarding cystic fibrosis have been limited to adult patients. See Chang and Glomb (these guidelines)[78] on evaluating cough in pediatric patients for specific recommendations regarding that group.

Abbreviation

URI   upper respiratory infection

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Summary of Recommendations

1. In patients with chronic bronchitis, agents that have been shown to alter mucus characteristics are not recommended for cough suppression. Level of evidence, good; benefit, none; grade of recommendation, D

2. In patients with cough due to URI or chronic bronchitis, the only inhaled anticholinergic agent that is recommended for cough suppression is ipratropium bromide. Level of evidence, fair; benefit, substantial; grade of recommendation, A

3. In patients with chronic or acute bronchitis, peripheral cough suppressants, such as levodropropizine and moguisteine, are recommended for the short-term symptomatic relief of coughing. Level of evidence, good; benefit, substantial; grade of recommendation, A

4. In patients with cough due to URI, peripheral cough suppressants have limited efficacy and are not recommended for this use. Level of evidence, good; benefit, none; grade of recommendation, D

5. In patients with chronic bronchitis, central cough suppressants, such as codeine and dextromethorphan, are recommended for the short-term symptomatic relief of coughing. Level of evidence, fair; benefit, intermediate; grade of recommendation, B

6. In patients with cough due to URI, central cough suppressants have limited efficacy for symptomatic relief and are not recommended for this use. Level of evidence, good; benefit, none; grade of recommendation, D

7. In patients with chronic or acute cough requiring symptomatic relief, drugs that affect the efferent limb of the cough reflex are not recommended. Level of evidence, low; benefit, none; grade of recommendation, D

8. In patients requiring intubation during general anesthesia, the use of neuromuscular blocking agents is recommended to suppress coughing. Level of evidence, good; benefit, substantial; grade of recommendation, A

9. In patients with acute cough due to the common cold, preparations containing zinc are not recommended. Level of evidence, good; benefit, none; grade of recommendation, D

10. In patients with acute cough due to the common cold, over the counter combination cold medications, with the exception of an older antihistamine-decongestant, are not recommended until randomized controlled trials prove that they are effective cough suppressants. Level of evidence, fair; benefit, none; grade of reccommendation: D

11. In patients with acute or chronic cough not due to asthma, albuterol is not recommended. Level of evidence, good; benefit, none; grade of recommendation, D

12. In patients with neuromuscular impairment, protussive pharmacologic agents are ineffective and should not be prescribed. Level of evidence, good; benefit, none; grade of recommendation, D

13. In patients with bronchitis, hypertonic saline solution and erdosteine are recommended on a short-term basis to increase cough clearance. Level of evidence, good; benefit, substantial; grade of recommendation, A

14. In adult patients with cystic fibrosis, amiloride is recommended to increase cough clearance. Level of evidence, good; benefit, substantial; grade of recommendation, A

15. In adult patients with cystic fibrosis, while recombinant DNase does improve spirometry it is not recommended to increase cough clearance. Level of evidence, good; benefit, none; grade of recommendation, D

Table 1

Summary of Studies on the Effects of Mucociliary Drugs on Cough

Drug	Study/Year	Patients, No.	Age,* yr	Population	Dosing	Results
Guaifenesin vs placebo	Robinson et al[9]/1977	239	Mean, 38.1 (range not reported)	URI	200 mg po qid × 3 d	Improved cough severity and frequency (p < 0.001)
Guaifenesin vs placebo	Kuhn et al[11]/1982	65	18–30	URI	30 mL (20 mg/mL) po q 6 h × 2.5 d	No significant effect on cough frequency and severity
Guaifenesin vs placebo	Parvez et al[10]/1996	60	18–77	Bronchiectasis, COPD	400 mg po qid × 14 d	Reduction in cough intensity (p < 0.05)
Guaifenesin vs placebo	Thomson et al[12]/ 1973	7	64 ± 2	Chronic bronchitis	600 mg po sd	No effect on cough frequency
Iodinated glycerol vs placebo	Petty[14]/1990	361	29–83	Chronic bronchitis	60 mg po qid × 56 d	Cough frequency and severity reduced (p < 0.05)
Iodinated glycerol vs placebo	Repsher[13]/1993	32	Mean, 53.7 (range not reported)	Chronic bronchitis	60 mg po qid × 5 wk	Reduction in cough severity (p < 0.025)
Iodinated glycerol vs placebo	Rubin et al[15]/1996	26	Not reported	Chronic bronchitis	60 mg qid × 16 wk	No effect on cough symptoms
Ipratropium vs placebo	Ghafouri et al[4]/1984	23	27–72	Chronic bronchitis	40 μg inhaled qid × 49 d	Reduction in cough frequency and severity (p < 0.05)
Ipratropium vs placebo	Holmes et al[3]/1992	14	47 ± 12	URI	80 μg inhaled qid × 21 d	Reduction in cough (p < 0.05)
Oxitropium vs placebo	Lowry et al[5]/1994	56	18–60	URI	200 μg inhaled tid × 10 d	No effect on cough
Tiotropium vs placebo	Casaburi et al[6]/2000	470	65 ± 9	COPD	18 μg dry powder qd 13 wk	No effect on cough
Bromhexine vs placebo	Mossberg et al[17]/ 1981	12	39–70	Asthma, chronic bronchitis	4–8 mg IV sd	No effect on cough clearance
Bromhexine vs placebo	Olivieri et al[18]/1991	88	52 ± 15	Bronchiectasis	30 mg po tid × 15 d	No effect on cough symptoms; reduction in sputum volume (p < 0.01)
Bromhexine vs placebo	Thompson and Reeve[19]/1972	14	39–70	Chronic bronchitis, asthma, COPD	16 mg bid po × 21 d	No effect on cough
Bromhexine vs placebo	Valenti and Marenco[20]/1989	237	Bromhexine group, 53 ± 13; placebo	COPD	30 mg po bid × 14 d	Significant reduction in cough (p < 0.001) and

Drug	Study/Year	Patients, No.	Age,* yr	Population	Dosing	Results
			group, 54 ± 11			sputum volume (p < 0.01)
Carbocysteine vs placebo	Edwards et al[22]/1976	82	35–60	Chronic bronchitis	2.25 or 3 g tid × 10 d	No significant effect on cough frequency or severity; reduction in sputum viscosity (p < 0.02)
Carbocysteine vs placebo	Thomson et al[21]/1975	16	64 ± 9	Chronic bronchitis, emphysema	4 g qid × 4–7 d	No significant effect on cough frequency
Acetylcysteine/ isoproterenol vs placebo	Hirsch et al[24]/1970	12	Not reported	Chronic bronchitis	10% aerosol tid × 5 wk	No effect on cough
Acetylcysteine vs placebo	Dueholm et al[23]/1992	65	Men, 53 ± 2; women, 54 ± 2	Chronic bronchitis	4 mg inhaled bid × 16 wk	Significantly greater coughing than placebo (p < 0.05)
Acetylcysteine vs placebo	Jackson et al[25]/1984	121	Mean, 63	Chronic bronchitis	200 mg po tid × 12 wk	No difference on cough severity
Mercaptoethane sulphonate vs placebo	Clarke et al[26]/1979	11	63 ± 8	Chronic bronchitis	10% aerosol tid × 3 d	No effect on cough frequency
Mercaptoethane sulphonate/ isoproterenol vs placebo	Hirsch et al[24]/1970	12	Not reported	Chronic bronchitis	10% aerosol tid × 5 wk	No effect on cough
Hypertonic saline vs placebo	Pavia et al[27]/1978	7	61 ± 10	Chronic bronchitis	7.1% saline solution inhaled sd	No effect on cough frequency

*Values are given as mean ± SD or range, unless otherwise indicated.

Table 2

Summary of Studies on the Actions of Peripheral Cough Suppressants

Drug	Study/Year	Patients, No.	Age Range, yr	Population	Dosing	Results
Levodropropizine vs placebo	Allegra and Bossi[32]/1988	194	15–79	Acute and chronic bronchitis	1–10 mL po tid × 3 d	Reduced cough severity, reduced cough frequency by 72% (p < 0.05)
Moguisteine vs placebo	Aversa et al[34]/1993	87	18–75	COPD (n = 44), pulmonary neoplasm (n = 7), pulmonary fibrosis (n = 6), unknown (n = 13), other (n = 3)	200 mg po tid × 4 d	Reduced cough frequency 42% (p < 0.03)
Moguisteine vs placebo	Adams et al[35]/1993	108	18–69	URI	200 mg po tid × 3 d	Significant difference in nighttime cough severity (p < 0.05)

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Table 3

Summary of Studies on the Actions of Central Cough Suppressants[*]

Drug	Study/Year	Patients, No.	Age[†]	Population	Dosing	Results
Codeine vs placebo	Aylward et al[41]/1984	8	54–65	Chronic bronchitis	7.5–30 mg po × 1 d sd	Reduced cough counts by 40% at 30 mg ($p < 0.05$), no effect of lower doses
Codeine vs placebo	Freestone and Eccles[44]/1997	82	18–46	URI, LRI	50 mg po qd × 2 d	No difference in cough frequency, severity, or cough sound pressure differences
Codeine vs placebo	Sevelius and Colmore[42]/1966	10	65 ± 7	Chronic bronchitis	30 mg po tid × 1 d	Cough frequency reduced 47% ($p < 0.01$)
Codeine vs placebo	Sevelius et al[43]/1971	12	55–72	COPD	7.5–60 mg po × 1 d	Reduced cough counts by 60% ($p < 0.004$)
Dextromethorphan vs placebo	Lee et al[46]/2000	43	18–46	URI	30 mg po × 1 d	No difference in cough frequency, severity, or cough sound pressure differences
Dextromethorphan vs placebo	Pavesi et al[48]/2001	710	18–69	URI	30 mg po × 1 d	Cough frequency significantly reducedat 1 h ($p < 0.003$), cough intensity not reduced
Dextromethorphan vs placebo	Tukainen et al[47]/1986	108	Mean, 38 (range not reported)	URI	30 mg po tid × 4 d	No significant difference in cough frequency or severity
Dextromethorphan vs placebo	Aylward et al[41]/1984	8	54–65	Chronic bronchitis	7.5–60 mg po × 1 d sd	Reduced cough counts by 50% at 60 mg ($p < 0.05$), 28% at 30 mg, no effect of 7.5 and 15 mg
Dextromethorphan vs placebo	Korppi et al[45]/1991	78	1–10	RI	7.5 or 15 mg in 5 or 10 mL tid × 3 d	No significant difference in cough frequency or severity
Dextromethorphan vs placebo	Parvez et al[10]/1996	451	18–69	URI	30 mg po × 1 d sd	Reduction in cough counts 19–36% ($p < 0.05$), reduction in cough effort 41% ($p < 0.05$)
Pipazethate vs placebo	Sevelius and Colmore[42]/1966	10	65 ± 7	Chronic bronchitis	5 mL po × 1 d	No significant difference in cough frequency

[*]
LR = lower respiratory tract infection; RI = respiratory infection.

[†]Values are given as range or mean ± SD, unless otherwise indicated.

Table 4

Influence of Other Drugs on Cough

Drug	Study/Year	Patients, No.	Age,* yr	Population	Dosing	Results
Zinc acetate vs placebo	Prasad et al[67]/2000	50	37 ± 11	Common cold	42.96 mg po q2–3 h during the day	Reduction in duration of coughing by 3 d (p < 0.001)
Zinc gluconate vs placebo	Mossad et al[63]/1996	100	38 ± 8	Common cold	13.3 mg po q2 h during the day	Reduction in duration of coughing by 2.5 d (p < 0.04)
Zinc gluconate vs placebo	Eby et al[59]/1984	65	11–63	Common cold	46 mg po loading dose, then q2 h while awake for maximum 9 d	Higher percent of subject asymptomatic after 7 d (p < 0.0005)
Zinc gluconate vs placebo	Smith et al[64]/1989	110	> 18	Common cold	23 mg po q2 h while awake for 7 d	No effect on duration of symptoms, 8% reduction in symptom severity (p > 0.02)
Zinc gluconate vs placebo	Godfrey et al[61]/1992	73	18–40	Common cold	23.7 mg po q2 h while awake for 7 d	Significantly shorter duration of symptoms (p < 0.025)
Zinc gluconate vs placebo	Weismann et al[66]/1990	130	18–65	Common cold	4.5 mg po q1.5 h for 10 d	No effect on symptom duration or severity
Zinc gluconate vs placebo	Al-Nakib et al[58]/1987	12	18–50	Rhinovirus-induced cold	23 mg po q2 h while awake for 6 d	Reduction in clinical symptom score on days 4 and 5 postchallenge (p < 0.05)
Zinc gluconate vs placebo	Farr et al[60]/1987	32 (part 1); 45 (part 2)	21 ± 1	Rhinovirus-induced cold	23 mg po q2 h while awake for 5 d in part 1 and 8 d in part 2	No effect on severity or duration of symptoms
Zinc gluconate vs placebo	Macknin et al[62]/1998	249	6–16	Common cold	10 mg po q2–3 h while awake for 2 d	No effect on duration of symptoms
Zinc gluconate, zinc acetate vs placebo	Turner and Cetnarowski[65]/2000	273 (part 1); 281 (part 2)	18–65	Rhinovirus induced (part 1); common cold (part 2)	5 or 11.5 mg zinc acetate, 13.3 zinc gluconate q2–3 h while awake for 14 d	Significantly shorter duration of symptoms by zinc gluconate in part 1 (p < 0.035), no effect in part 2 of either formulation
Albuterol vs placebo	Bernard et al[71]/1999	59	1–10	Nonasthmatic, otherwise undetermined	0.1 mg/kg po tid × 7 d	No effect on cough
Albuterol vs placebo	Littenberg et al[72]/1996	104	19–74	Nonasthmatic, nonpneumonia, non-COPD, otherwise undetermined	4 mg po tid × 7 d	No difference in cough severity

*
Values are given as the mean ± SD or range.

Table 5

Influence of Protussive Drugs on Cough or Cough Clearance

Drug	Study/Year	Patients, No.	Age,[*] yr	Population	Dosing	Results
DNase vs placebo	Laube et al[75]/1996	20	18–44	Cystic fibrosis	2.5 mg inhaled bid × 6 d	No effect on cough frequency
DNase vs placebo	Robinson et al[74]/2000	13	25 ± 5	Cystic fibrosis	2.5 mg inhaled qd × 7 d	No effect on cough clearance
Mannitol vs placebo	Robinson et al[76]/1999	12	30 ± 9	Cystic fibrosis	300 mg dry powder sd	Increase in cough clearance ($p < 0.01$)

[*] Values are given as the range or mean ± SD.