Cough Suppressant and Pharmacologic Protussive Therapy

ACCP Evidence-Based Clinical Practice Guidelines

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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.

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Key words: antitussive; cough; cough suppressant; nonopioid; opioid; protussive

Abbreviation: URI = upper respiratory infection

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-generation system transmits excitatory information to spinal motoneurons innervating respiratory muscles. Drugs that may act on this effenter limb of the cough reflex pathway and paralytic agents that block the neuromuscular
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.

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 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,” “antiviral,” “protussive,” “guaifenesin,” “glycerol,” and “zinc.”

**Drugs That Affect Mucociliary Factors**

This topic was not addressed separately in the previous evidence-based guideline. 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 URI3 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 guideline1 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 nonselecting H1-receptor antag-

Table 1—Summary of Studies on the Effects of Mucociliary Drugs on Cough

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study/Year</th>
<th>Patients, No.</th>
<th>Age, * yr</th>
<th>Population</th>
<th>Dosing</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guaifenesin vs placebo</td>
<td>Robinson et al/1977</td>
<td>230</td>
<td>Mean, 38.1 (range not reported)</td>
<td>URI</td>
<td>200 mg po qid × 3 d</td>
<td>Improved cough severity and frequency (p &lt; 0.001)</td>
</tr>
<tr>
<td>Guaifenesin vs placebo</td>
<td>Kuhn et al/1982</td>
<td>65</td>
<td>18–30</td>
<td>URI</td>
<td>30 mL (20 mg/mL) po q 6 h × 2.5 d</td>
<td>No significant effect on cough frequency and severity</td>
</tr>
<tr>
<td>Guaifenesin vs placebo</td>
<td>Parvez et al/1996</td>
<td>60</td>
<td>18–77</td>
<td>Bronchiectasis, COPD</td>
<td>400 mg po qid × 14 d</td>
<td>Reduction in cough intensity (p &lt; 0.05)</td>
</tr>
<tr>
<td>Guaifenesin vs placebo</td>
<td>Thompson et al/1973</td>
<td>7</td>
<td>64 ± 2</td>
<td>Chronic bronchitis</td>
<td>600 mg po sd</td>
<td>No effect on cough frequency</td>
</tr>
<tr>
<td>Iodinated glycerol vs placebo</td>
<td>Petty/1990</td>
<td>361</td>
<td>29–83</td>
<td>Chronic bronchitis</td>
<td>60 mg po qid × 56 d</td>
<td>Cough frequency and severity reduced (p &lt; 0.05)</td>
</tr>
<tr>
<td>Iodinated glycerol vs placebo</td>
<td>Repsher/1993</td>
<td>32</td>
<td>Mean, 53.7 (range not reported)</td>
<td>Chronic bronchitis</td>
<td>60 mg po qid × 5 wk</td>
<td>Reduction in cough severity (p &lt; 0.025)</td>
</tr>
<tr>
<td>Iodinated glycerol vs placebo</td>
<td>Rubin et al/1996</td>
<td>26</td>
<td>Not reported</td>
<td>Chronic bronchitis</td>
<td>60 mg qid × 16 wk</td>
<td>No effect on cough symptoms</td>
</tr>
<tr>
<td>Ipratropium vs placebo</td>
<td>Ghafouri et al/1984</td>
<td>23</td>
<td>27–72</td>
<td>Chronic bronchitis</td>
<td>40 μg inhaled qid × 49 d</td>
<td>Reduction in cough frequency and severity (p &lt; 0.05)</td>
</tr>
<tr>
<td>Ipratropium vs placebo</td>
<td>Holmes et al/1992</td>
<td>14</td>
<td>47 ± 12</td>
<td>URI</td>
<td>80 μg inhaled qid × 21 d</td>
<td>Reduction in cough (p &lt; 0.05)</td>
</tr>
<tr>
<td>Oxytropium vs placebo</td>
<td>Lowry et al/1994</td>
<td>56</td>
<td>18–60</td>
<td>URI</td>
<td>200 μg inhaled tid × 10 d</td>
<td>No effect on cough</td>
</tr>
<tr>
<td>Tiotropium vs placebo</td>
<td>Casaburi et al/2000</td>
<td>470</td>
<td>65 ± 9</td>
<td>COPD</td>
<td>18 μg dry powder qd 13 wk</td>
<td>No effect on cough</td>
</tr>
<tr>
<td>Broncheshine vs placebo</td>
<td>Mossberg et al/1981</td>
<td>12</td>
<td>39–70</td>
<td>Asthma, chronic bronchitis</td>
<td>4–8 mg IV sd</td>
<td>No effect on cough clearance</td>
</tr>
<tr>
<td>Broncheshine vs placebo</td>
<td>Olivieri et al/1991</td>
<td>88</td>
<td>52 ± 15</td>
<td>Bronchiectasis</td>
<td>30 mg po tid × 15 d</td>
<td>No effect on cough symptoms; reduction in sputum volume (p &lt; 0.01)</td>
</tr>
<tr>
<td>Broncheshine vs placebo</td>
<td>Thompson and Reeve/1972</td>
<td>14</td>
<td>39–70</td>
<td>Chronic bronchitis, asthma, COPD</td>
<td>16 mg bid po × 21 d</td>
<td>No effect on cough</td>
</tr>
<tr>
<td>Broncheshine vs placebo</td>
<td>Valenti and Manzocco/1989</td>
<td>237</td>
<td>Broncheshine group, 53 ± 13 placebo group, 54 ± 11</td>
<td>COPD</td>
<td>30 mg po bid × 14 d</td>
<td>Significant reduction in cough (p &lt; 0.01) and sputum volume (p &lt; 0.01)</td>
</tr>
<tr>
<td>Carbocysteine vs placebo</td>
<td>Edwards et al/1976</td>
<td>82</td>
<td>35–60</td>
<td>Chronic bronchitis</td>
<td>2.25 or 3 g tid × 10 d</td>
<td>No significant effect on cough frequency or severity; reduction in sputum viscosity (p &lt; 0.02)</td>
</tr>
<tr>
<td>Carbocysteine vs placebo</td>
<td>Thomson et al/1975</td>
<td>16</td>
<td>64 ± 9</td>
<td>Chronic bronchitis, emphysema</td>
<td>4 g qid × 4–7 d</td>
<td>No significant effect on cough frequency</td>
</tr>
<tr>
<td>Acetylcysteine/ isoproterenol vs placebo</td>
<td>Hirsch et al/1970</td>
<td>12</td>
<td>Not reported</td>
<td>Chronic bronchitis</td>
<td>4% aerosol tid × 5 wk</td>
<td>No effect on cough</td>
</tr>
<tr>
<td>Acetylcysteine vs placebo</td>
<td>Dueholm et al/1982</td>
<td>65</td>
<td>Men, 53 ± 2, women, 54 ± 2</td>
<td>Chronic bronchitis</td>
<td>4 mg inhaled bid × 16 wk</td>
<td>Significantly greater coughing than placebo (p &lt; 0.05)</td>
</tr>
<tr>
<td>Acetylcysteine vs placebo</td>
<td>Jackson et al/1984</td>
<td>121</td>
<td>Mean, 63</td>
<td>Chronic bronchitis</td>
<td>200 mg po tid × 12 wk</td>
<td>No difference on cough severity</td>
</tr>
<tr>
<td>Mercaptopothenyl sulphamate vs placebo</td>
<td>Clarke et al/1970</td>
<td>11</td>
<td>63 ± 8</td>
<td>Chronic bronchitis</td>
<td>10% aerosol tid × 3 d</td>
<td>No effect on cough frequency</td>
</tr>
<tr>
<td>Mercaptopothenyl sulphamate/ isoproterenol vs placebo</td>
<td>Hirsch et al/1970</td>
<td>12</td>
<td>Not reported</td>
<td>Chronic bronchitis</td>
<td>10% aerosol tid × 5 wk</td>
<td>No effect on cough</td>
</tr>
<tr>
<td>Hypertonic saline vs placebo</td>
<td>Pavia et al/1978</td>
<td>7</td>
<td>61 ± 10</td>
<td>Chronic bronchitis</td>
<td>7.1% saline solution inhaled sd</td>
<td>No effect on cough frequency</td>
</tr>
</tbody>
</table>

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

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 nonselecting H1-receptor antag-
This concept is supported by the inconsistent action of inhaled anticholinergic agents on cough (i.e., it is 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. 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 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 and objective and objective indexes of cough due to bronchiectasis. However, two other studies 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. However, another study 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. 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 and active in only one study. 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 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 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, mercaptoethane sulfonate, and hypertonic saline solution 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 mucociliatory 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.

**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

**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, one prominent drug, levodropropizine, acts at least in part by the activation of C-fiber sensory afferents that reflexively inhibit cough. One drug, caramiphen, has been considered as a centrally acting drug. However, according to a preclinical study, 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.

The current review expands on the previous one 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. This drug also is as effective as dihydrocodeine in suppressing cough due to lung cancer, although that study was not placebo-controlled. Moguisteine has been shown to be active in treating cough due to COPD. 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. 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 of inhaled sodium cromoglycate demonstrated significant suppression of cough in patients with lung cancer, presumably due to the suppression of mediator release.

**RECOMMENDATIONS**

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

**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, 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. Furthermore, cough can be voluntarily suppressed, indicating a prominent role for cortical pathways in its control. 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, 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

<table>
<thead>
<tr>
<th>Drug Study/Year</th>
<th>Patients, No.</th>
<th>Age Range, yr</th>
<th>Population</th>
<th>Dosing</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allegra and Bossi/1988</td>
<td>194</td>
<td>15–79</td>
<td>Acute and chronic bronchitis</td>
<td>1–10 mL po tid × 3 d</td>
<td>Reduced cough severity, reduced cough frequency by 72% (p &lt; 0.05)</td>
</tr>
<tr>
<td>Aversa et al/1993</td>
<td>87</td>
<td>18–75</td>
<td>COPD (n = 44), pulmonary neoplasm (n = 7), pulmonary fibrosis (n = 6), unknown (n = 13), other (n = 3)</td>
<td>200 mg po tid × 4 d</td>
<td>Reduced cough frequency 42% (p &lt; 0.03)</td>
</tr>
<tr>
<td>Adams et al/1993</td>
<td>108</td>
<td>18–69</td>
<td>URI</td>
<td>200 mg po tid × 3 d</td>
<td>Significant difference in nighttime cough severity (p &lt; 0.05)</td>
</tr>
</tbody>
</table>
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, suppressing cough counts by 40 to 60%. However, the antitussive effects of codeine in patients with chronic bronchitis were established in small patient populations. 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 in cough due to URI. Others have reported the suppression of cough due to URI by these drugs. As suggested by Pavesi et al, 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 conducted a metaanalysis of six separate studies of > 700 subjects, while Parvez et al studied > 300 subjects. However, it is unclear the extent to which the metaanalysis of Pavesi et al overlapped with the population reported by Parvez et al. The reports of Lee et al and Tukiainen et al 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.

### Table 3—Summary of Studies on the Actions of Central Cough Suppressants*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study/Year</th>
<th>Patients, No.</th>
<th>Age†</th>
<th>Population</th>
<th>Dosing</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine vs placebo</td>
<td>Aylward et al1/1984</td>
<td>8</td>
<td>54-65</td>
<td>Chronic bronchitis</td>
<td>7.5–30 mg po × 1 d sd</td>
<td>Reduced cough counts by 40% at 30 mg (p &lt; 0.05), no effect of lower doses</td>
</tr>
<tr>
<td>Codeine vs placebo</td>
<td>Freestone and Eccles9/1997</td>
<td>82</td>
<td>18–46</td>
<td>URI, LRI</td>
<td>50 mg po qd × 2 d</td>
<td>No difference in cough frequency, severity, or cough sound pressure differences</td>
</tr>
<tr>
<td>Codeine vs placebo</td>
<td>Sevelius and Colmore4/1966</td>
<td>10</td>
<td>65 ± 7</td>
<td>Chronic bronchitis</td>
<td>30 mg po tid × 1 d</td>
<td>Cough frequency reduced 47% (p &lt; 0.01)</td>
</tr>
<tr>
<td>Codeine vs placebo</td>
<td>Sevelius et al9/1971</td>
<td>12</td>
<td>55–72</td>
<td>COPD</td>
<td>7.5–60 mg po × 1 d</td>
<td>Reduced cough counts by 60% (p &lt; 0.004)</td>
</tr>
<tr>
<td>Dextromethorphan vs placebo</td>
<td>Lee et al9/2000</td>
<td>43</td>
<td>18–46</td>
<td>URI</td>
<td>30 mg po × 1 d</td>
<td>No difference in cough frequency, severity, or cough sound pressure differences</td>
</tr>
<tr>
<td>Dextromethorphan vs placebo</td>
<td>Pavesi et al9/2001</td>
<td>710</td>
<td>18–69</td>
<td>URI</td>
<td>30 mg po × 1 d</td>
<td>Cough frequency significantly reduced at 1 h (p &lt; 0.003), cough intensity not reduced</td>
</tr>
<tr>
<td>Dextromethorphan vs placebo</td>
<td>Tukiainen et al9/1986</td>
<td>108</td>
<td>Mean, 38 (range not reported)</td>
<td>URI</td>
<td>30 mg po tid × 4 d</td>
<td>No significant difference in cough frequency or severity</td>
</tr>
<tr>
<td>Dextromethorphan vs placebo</td>
<td>Aylward et al1/1984</td>
<td>8</td>
<td>54-65</td>
<td>Chronic bronchitis</td>
<td>7.5–60 mg po × 1 d sd</td>
<td>Reduced cough counts by 50% at 60 mg (p &lt; 0.05), 28% at 30 mg, no effect of 7.5 and 15 mg</td>
</tr>
<tr>
<td>Dextromethorphan vs placebo</td>
<td>Korpi et al9/1991</td>
<td>78</td>
<td>1–10</td>
<td>RI</td>
<td>7.5 mg to 15 mg in 5 or 10 mL tid × 3 d</td>
<td>No significant difference in cough frequency or severity</td>
</tr>
<tr>
<td>Dextromethorphan vs placebo</td>
<td>Parvez et al9/1996</td>
<td>451</td>
<td>18–69</td>
<td>URI</td>
<td>30 mg po × 1 d sd</td>
<td>Reduction in cough counts 19–36% (p &lt; 0.05), reduction in cough effort 41% (p &lt; 0.05)</td>
</tr>
<tr>
<td>Pipazethate vs placebo</td>
<td>Sevelius and Colmore4/1966</td>
<td>10</td>
<td>65 ± 7</td>
<td>Chronic bronchitis</td>
<td>5 mL po × 1 d</td>
<td>No significant difference in cough frequency</td>
</tr>
</tbody>
</table>

*LR = lower respiratory tract infection; RI = respiratory infection.
†Values are given as range or mean ± SD, unless otherwise indicated.

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Recommendations

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

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 animals50 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.

Recommendation

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

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 study57 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.

Recommendation

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

Other Drugs

Table 4 summarizes studies on the effects of zinc acetate or zinc gluconate on the common cold,58–66 and two studies63,67 evaluated cough with subjective measures. Mixed results were obtained, with some studies58,59,61,63,67 indicating a positive effect of zinc preparations on the common cold and others60,62,64–66 suggesting no benefit. Two metaanalyses68,69 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 (i.e., < 4 weeks) cough71,72 (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, 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.

**Recommendations**

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 recommendation, 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

**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. 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.

RECOMMENDATION

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

PHARMACOLOGIC ENHANCEMENT OF COUGH CLEARANCE

The previous evidence-based guideline1 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 clearance75 and mucociliary clearance76 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 al75 suggested that their study may have been underpowered given the large intersubject variability that they encountered.

A double-blind placebo-controlled study77 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.

Table 5—Influence of Protussive Drugs on Cough or Cough Clearance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study/Year</th>
<th>Patients, No.</th>
<th>Age, yr</th>
<th>Population</th>
<th>Dosing</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNase vs placebo</td>
<td>Laube et al75/1996</td>
<td>20</td>
<td>18–44</td>
<td>Cystic fibrosis</td>
<td>2.5 mg inhaled bid × 6 d</td>
<td>No effect on cough frequency</td>
</tr>
<tr>
<td>DNase vs placebo</td>
<td>Robinson et al76/2000</td>
<td>13</td>
<td>25 ± 5</td>
<td>Cystic fibrosis</td>
<td>2.5 mg inhaled qd × 7 d</td>
<td>No effect on cough clearance</td>
</tr>
<tr>
<td>Mannitol vs placebo</td>
<td>Robinson et al77/1999</td>
<td>12</td>
<td>30 ± 9</td>
<td>Cystic fibrosis</td>
<td>300 mg dry powder sd</td>
<td>Increase in cough clearance (p &lt; 0.01)</td>
</tr>
</tbody>
</table>

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

Recommendations

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

Conclusions

Relatively few drugs are effective for the nonspecific suppression of cough. Our current recommen-
dations largely confirm and extend the findings of the previous panel. 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 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: carmiphen; levodropropizine; the acetylsalicylic acid pro-drug guameasal; the phosphodiesterase inhibitor and antidopaminergic agent glaucine; and the analgesic vaminol. 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 dextromethorphan/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) on evaluating cough in pediatric patients for specific recommendations regarding that group.

### 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 mogustaine, 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 recommendation: 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

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