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▶ Drugs for Cough

Acute cough (<3 weeks in duration) generally does not require pharmacologic treatment, especially in children. Suppression of productive cough may be harmful.¹ Management of patients with cough should include elimination of any precipitating factor (e.g., cigarette smoking) and treatment of any underlying cause such as upper airway cough syndrome, gastroesophageal reflux disease, asthma, or other pulmonary disease.

Cough suppressants are widely available over the counter (OTC) and by prescription, often in combination with an expectorant, an H₁-antihistamine, and/or a decongestant.^{2,3}

HONEY – A single nocturnal dose (10 g) of honey can relieve airway irritation and decrease cough.⁴ In comparative studies, honey has been about as effective in suppressing cough as dextromethorphan.³ It should not be used in children <1 year old because it contains spores of *Clostridium botulinum* that can cause infantile botulism.

DEXTROMETHORPHAN – An OTC derivative of morphine with no analgesic or addictive properties at recommended doses, dextromethorphan can reduce cough severity. Clinical trials comparing it with codeine for treatment of chronic cough have produced conflicting results. Dextromethorphan has not been shown to be effective or safe in young children.^{1,5}

Adverse Effects – Dextromethorphan can cause confusion, excitement, irritability, nervousness, and, in high doses, nausea, vomiting, and headache. Extremely high doses of dextromethorphan can cause euphoria and dissociative effects.

CODEINE AND HYDROCODONE – The opioid agonists codeine and hydrocodone are effective in suppressing cough. Codeine is a weak opioid agonist that must be converted by CYP2D6 to morphine for most of its analgesic and antitussive effects. About 10% of the population are CYP2D6 poor metabolizers;

Highlights

- ▶ Acute cough generally does not require pharmacologic treatment, especially in children.
- ▶ Suppression of productive cough may be harmful.
- ▶ Honey can relieve airway irritation and decrease cough.
- ▶ The OTC antitussive dextromethorphan can reduce cough severity. It is not recommended for children <4 years old.
- ▶ Codeine and hydrocodone are effective for suppression of cough, but even in low doses they can decrease mental alertness and cause constipation. In high doses, they can cause sedation, respiratory depression, and physical dependence.
- ▶ Benzonatate, a local anesthetic available as a liquid-filled capsule, is dangerous and should not be used.
- ▶ The expectorant guaifenesin can facilitate removal of viscous mucus by coughing.
- ▶ H₁-antihistamines do not suppress cough; they may reduce postnasal drip. First-generation H₁-antihistamines can impair school and driving performance.
- ▶ Decongestants do not suppress cough; they may reduce postnasal drip. OTC phenylephrine is no more effective than placebo for treatment of nasal congestion.

for them, codeine may be ineffective. CYP2D6 ultra-rapid metabolizers may be at greater risk for toxicity. Opioid-containing cough products are generally available only by prescription in the US (a few states and some other countries, including Canada, permit OTC sale of some codeine products).

Adverse Effects – Even in low doses, codeine and hydrocodone can decrease mental alertness and cause constipation. In high doses, they can cause sedation, respiratory depression, and physical dependence. The FDA recently required changes in the labeling of all cough and cold products that contain codeine or hydrocodone because of concerns about the risk of respiratory depression and death in children; these products are no longer indicated for use in patients <18 years old.⁶ Codeine/promethazine cough syrup, often in combination with soda, candy, or alcohol, has become a recreational drug of choice among young adults.

BENZONATATE (*Tessalon Perles*, and generics) – A polyglycol derivative structurally related to the local anesthetics procaine and tetracaine, benzonatate is a prescription alternative to opioids for suppression of severe cough. It suppresses the cough reflex

Table 1. Some FDA-Approved Combination Products for Cough

Drug	Some Formulations	Usual Adult Dosage	Cost ¹
Dextromethorphan-Containing Combinations²			
Dextromethorphan/guaifenesin – <i>Robitussin Maximum Strength Cough & Chest Congestion DM</i> (Pfizer) ^{3,4}	20/400 mg per 20 mL soln	20 mL q4h (max 6 doses/24 hrs)	\$8.40/237 mL
Dextromethorphan/brompheniramine/ pseudoephedrine – generic	10/2/30 mg per 5 mL soln	10 mL q4h (max 6 doses/24 hrs)	83.70/473 mL
Codeine-Containing Combinations^{2,5}			
Codeine polistirex/chlorpheniramine polistirex – <i>Tuzistra XR</i> (Vernalis) ⁶	14.7/2.8 mg per 5 mL ER susp ⁷	10 mL q12h (max 2 doses/24 hrs)	539.10/473 mL
Codeine/promethazine – generic ⁸	10/6.25 mg per 5 mL soln	5 mL q4-6h (max 6 doses/24 hrs)	27.00/473 mL
Codeine/phenylephrine/promethazine – generic ⁸	10/5/6.25 mg per 5 mL soln	5 mL q4-6h (max 6 doses/24 hrs)	170.60/473 mL
Hydrocodone-Containing Combinations^{2,5,9}			
Hydrocodone polistirex/chlorpheniramine polistirex – <i>Tussionex Pennkinetic</i> (UCB) generic	10/8 mg per 5 mL ER susp	5 mL q12h (max 2 doses/24 hrs)	157.60/115 mL 57.80/118 mL
<i>Tussicaps</i> (Bausch Health)	5/4, 10/8 mg ER caps	1 cap q12h (max 2 doses/24 hrs)	36.40/cap
Hydrocodone/chlorpheniramine <i>Vituz</i> (Hawthorn)	5/4 mg per 5 mL soln	5 mL q4-6h (max 4 doses/24 hrs)	17.70/240 mL
Hydrocodone/chlorpheniramine/ pseudoephedrine – <i>Zutripro</i> (Cypress) generic	5/4/60 mg per 5 mL soln	5 mL q4-6h (max 4 doses/24 hrs)	353.80/240 mL ¹⁰ 75.20/240 mL ¹⁰
Hydrocodone/guaifenesin – <i>FlowTuss</i> (Mission)	2.5/200 mg per 5 mL soln	10 mL q4-6h (max 6 doses/24 hrs)	297.20/280 mL ¹⁰
Hydrocodone/guaifenesin/pseudoephedrine – <i>Hycofenix</i> (Mission)	2.5/200/30 mg per 5 mL soln	10 mL q4-6h (max 4 doses/24 hrs)	320.10/280 mL ¹⁰
Hydrocodone/homatropine ¹¹ – generic	5/1.5 mg per 5 mL soln 5/1.5 mg tabs	5 mL q4-6h (max 3 doses/24 hrs) 1 tab q4-6h (max 6 doses/24 hrs)	70.00/473 mL 0.80/tab

ER = extended-release

1. Approximate WAC. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. December 5, 2018. Reprinted with permission by First Databank, Inc. All rights reserved. ©2018. www.fdbhealth.com/policies/drug-pricing-policy.
2. Combinations may include an expectorant (guaifenesin), an H₁-antihistamine (brompheniramine, chlorpheniramine, promethazine, triprolidine) and/or a decongestant (phenylephrine, pseudoephedrine).
3. Available without a prescription.
4. Not recommended for use in patients ≤12 years old.
5. Not recommended for use in patients <18 years old.
6. Classified as a schedule III controlled substance by the DEA.
7. Equivalent to 20 mg of codeine phosphate and 4 mg of chlorpheniramine per 5 mL.
8. Classified as a schedule V controlled substance by the DEA.
9. Classified as a schedule II controlled substance by the DEA.
10. Lowest retail price according to goodrx.com. Accessed December 6, 2018.
11. Homatropine is an anticholinergic agent added in a subtherapeutic amount to suppress deliberate overdose.

by anesthetizing stretch receptors in the lower respiratory tract. Benzonatate is available as a liquid-filled capsule, which must be swallowed whole. It is not indicated for use in children <10 years old.

Adverse Effects – Benzonatate can cause nausea, dizziness, headache, sedation, a feeling of numbness in the chest, mental confusion, and visual hallucinations. Chewing or sucking the liquid-filled capsules, which look like candy, can cause laryngospasm, bronchospasm, and circulatory collapse. Ingestion of a small handful of capsules has caused seizures, cardiac arrhythmias, and death in adults.⁷ The FDA has warned that taking even a single capsule can be fatal for young children.⁸ The risks associated with use of benzonatate clearly outweigh its benefits.

GUAIFENESIN – The expectorant guaifenesin increases the volume of secretions in the respiratory tract, facilitating removal of viscous mucus by coughing. Clinical trials comparing it to placebo for treatment of cough have produced conflicting results.⁹ Guaifenesin is available by prescription in combination with an opioid, and OTC both alone and in combination preparations. Guaifenesin extended-release tablets are not recommended for use in children <12 years old.

Adverse Effects – In recommended doses, guaifenesin is generally considered safe. High doses can cause dizziness, drowsiness, headache, nausea, and vomiting. Continued use of high doses has been associated with development of kidney stones.

ANTIHISTAMINES – H₁-antihistamines do not suppress cough. Their antimuscarinic activity might reduce

coughing in some patients by reducing postnasal drip.¹⁰ They are available in many combination products that include an antitussive.

Adverse Effects – First-generation H₁-antihistamines such as diphenhydramine can cause dry mouth, dry eyes, blurred vision, constipation, bladder outflow obstruction leading to urinary retention, and CNS impairment with or without sedation. They can interfere with learning and memory, impair performance on school examinations, decrease work productivity, and increase the risk of on-the-job accidents. When these drugs are taken at night, adverse effects on wakefulness and psychomotor performance can persist the next day. A single 50-mg dose of diphenhydramine caused more errors on a driving simulation test than a blood alcohol level of 0.1%.¹¹

DECONGESTANTS – Decongestants do not directly suppress cough, but they may help reduce coughing by reducing postnasal drip. They are often available OTC in combination products that include an antitussive. Decongestants are not recommended for use in children <4 years old and they should not be used with or within 14 days of a monoamine oxidase (MAO) inhibitor.

OTC **phenylephrine** is no more effective than placebo for treatment of nasal congestion.¹² Access to products containing **pseudoephedrine** or **ephedrine** is restricted because of their potential for abuse: they are kept behind the pharmacy counter, a valid photo ID is required, and there is a limit to the amount that can be purchased in a single day or in a 30-day period. **Phenylpropanolamine** is no longer available in the US for human use because it was associated with an increased risk of hemorrhagic stroke in women who took it as an appetite suppressant.

Adverse Effects – Oral decongestants increase heart rate and blood pressure. They can cause transient excitability, insomnia, headache, nervousness, confusion, dizziness, nausea, and urinary retention. Dry nose and throat and rebound nasal congestion can occur.

SHORT-ACTING BRONCHODILATORS – The short-acting beta₂-adrenergic agonist (SABA) albuterol (*Proventil HFA*, and others) and the antimuscarinic ipratropium (*Atrovent HFA*, and others) have been used alone and in combination to treat cough that has a bronchospastic component.

Adverse Effects – Inhaled SABAs can cause paradoxical bronchospasm, tremor, tachycardia, QT interval prolongation, hyperglycemia, hypokalemia, and hypomagnesemia (especially if used in high doses).

Ipratropium can cause dry mouth, pharyngeal irritation, increased intraocular pressure, and urinary retention.

CORTICOSTEROIDS – Oral and inhaled corticosteroids have been used for treatment of cough in patients without asthma. In a randomized trial in 401 nonasthmatic adults with acute lower respiratory infection, oral prednisolone was not significantly more effective than placebo in reducing the duration of cough or cough severity.¹³ Controlled trials of inhaled corticosteroids for suppression of cough unrelated to asthma have produced conflicting results.^{14,15}

Adverse Effects – Local adverse effects of inhaled corticosteroids include oral candidiasis (thrush), dysphonia, and reflex cough and bronchospasm. Clinically relevant effects on hypothalamic-pituitary-adrenal (HPA) axis function generally do not occur with low- or medium-dose inhaled corticosteroids. ■

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