



# Cough and Cold

## Therapeutic Class Review (TCR)

June 25, 2014

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## FDA-APPROVED INDICATIONS<sup>1</sup>

Cough and cold formulations are available for use in the treatment of the signs and symptoms of the common cold, sinusitis, allergies, and cough. They come in various combinations as simple cold formulations, narcotic cough and cold formulations, and non-narcotic cough and cold formulations. The cold formulations are available as prescription generics which are combined in one of the following manners with several of the available ingredients: antihistamine-only, antihistamine-decongestant, decongestant-expectorant, and expectorant-only. There are many narcotic cough and cold formulations available as prescription generics which are combined in one of the following manners with several of the available ingredients: antitussive-anticholinergic, antitussive-antihistamine-decongestant, antitussive-decongestant-expectorant, and antitussive-expectorant. Lastly, there are many non-narcotic cough and cold formulations that are available as prescription generics which are combined in one of the following manners with several of the available ingredients: antitussive-antihistamine, antitussive-antihistamine-decongestant, antitussive-antihistamine-decongestant-expectorant, antitussive-decongestant, antitussive-decongestant-expectorant, and antitussive-expectorant.

Current products are listed in Appendix A.

## OVERVIEW

The common cold is a viral illness that affects persons of all ages, prompting frequent use of over-the-counter (OTC) and prescription medications and alternative remedies.<sup>2</sup> Adults in the United States experience two to four colds per year. At least 200 identified viruses are capable of causing the common cold.<sup>3</sup> The viruses often implicated include rhinoviruses, coronaviruses, parainfluenza viruses, respiratory syncytial virus, adenoviruses, and enteroviruses. Although histologic effects on the nasal epithelium may vary, any of the viruses can cause vasodilation and hypersecretion, which leads to the common cold syndrome, which includes nasal congestion, nasal discharge, postnasal drip, throat clearing, sneezing, and cough.

The 2006 ACCP Evidence-Based Clinical Practice Guidelines on the Diagnosis and Management of Cough state that patients with acute cough associated with the common cold can be treated with a first-generation antihistamine and decongestant preparation.<sup>4</sup> There are a variety of prescription and over-the-counter (OTC) cough and cold combination products. The focus of this review will be on the prescription products with emphasis on the component ingredients. There are also numerous generic products available.

## PHARMACOLOGY

Drug Type	Mechanism of Action	Examples
Anticholinergics	Competitively blocks the muscarinic receptors, primarily M2 and M3, and causing the drying effect on mucus membranes.	homatropine, methscopolamine, scopolamine
Antihistamines (first generation)	Competitively antagonize the effects of histamine on H <sub>1</sub> -receptors in the GI tract, uterus, large blood vessels, and bronchial smooth muscle. Blockade of H <sub>1</sub> -receptors also suppresses the formation of edema, flare, and pruritus that result from histaminic activity. H <sub>1</sub> -antagonists also possess anticholinergic properties in varying degrees.	brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dexbrompheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, hydroxyzine, promethazine, pyrilamine, triprolidine
Antitussives (opiate)	Directly act on receptors in the cough center of the medulla. These agents may also have a drying effect on the respiratory tract and increases the viscosity of bronchial secretions. Cough suppression can be achieved at lower doses than those required to produce analgesia. The most significant adverse effect associated with opiate agonist use is respiratory depression which results from a decreased sensitivity to carbon dioxide in the brainstem. Opiates cause generalized central nervous system (CNS) depression. Additive sedative effects are possible with other agents that can lead to CNS depression.	codeine, dihydrocodeine, hydrocodone
Antitussives (non-opiate)	Dextromethorphan is a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors in the brain and spinal cord. It acts on the cough center in the medulla to raise the threshold for coughing by decreasing the excitability of the cough center. It is the d-isomer of levorphanol but has none of the analgesic, respiratory depressive, or sedative effects associated with opiate agonists.  Carbetapentane and chlophedianol appear to work directly on the cough center of the medulla, thereby suppressing the cough reflex. Carbetapentane has atropine-like and anesthetic actions, producing a drying effect of respiratory mucus secretion. In addition, it possesses mild bronchodilatory actions, and does not affect respiratory volume.	carbetapentane, chlophedianol, dextromethorphan
Decongestants	Phenylephrine possesses both direct and indirect sympathomimetic effects, primarily as a postsynaptic alpha-adrenergic agonist, producing potent vasoconstriction. An indirect effect due to the release of norepinephrine plays a small role in the overall action of phenylephrine. Constriction of blood vessels leads to reduced blood flow to the nose, decreased amount of blood in the sinusoid vessels, and decreased mucosal edema, which relieves nasal congestion. Phenylephrine does not affect the beta receptors in the heart or lungs.  Pseudoephedrine is a sympathomimetic amine that causes the release of norepinephrine, leading to vasoconstriction and a decrease in nasal and sinus congestion.	phenylephrine, pseudoephedrine*
Expectorants	Loosens and thins sputum and bronchial secretions to ease expectoration.	guaifenesin, potassium guaiacolsulfonate

\* Many products containing pseudoephedrine have been reformulated due to increased regulatory restrictions on the sale and distribution of the drug, likely due to its notable use as a precursor in the illicit synthesis of methamphetamine.

## PHARMACOKINETICS

Due to the various product formulations and varying component ingredients in the cough and cold products, the specific product information should be consulted to evaluate pharmacokinetics.

## CONTRAINDICATIONS/WARNINGS

In January 2007, the Centers for Disease Control and Prevention (CDC) warned caregivers and healthcare providers of the risk for serious injury or fatal overdose from the administration of cough and cold products to children and infants less than two years of age.<sup>5</sup> This warning followed an investigation of the deaths of three infants less than six months of age that were attributed to the inadvertent inappropriate use of these products. The symptoms preceding these deaths have not been clearly defined, and there is a lack of conclusive data describing the exact cause of death. The report estimated that 1,519 children less than two years of age were treated in emergency departments during 2004 and 2005 for adverse events related to cough and cold medications.

In October 2007, the FDA Nonprescription Drug Advisory Committee and the Pediatric Advisory Committee recommended that nonprescription cough and cold products containing pseudoephedrine, dextromethorphan, chlorpheniramine, diphenhydramine, brompheniramine, phenylephrine, clemastine, or guaifenesin not be used in children less than six years of age. In January 2008, the FDA issued a Public Health Advisory recommending that OTC cough and cold products not be used in infants and children less than two years old. An official ruling regarding the use of these products in children older than two years has not yet been announced. The FDA recommends that if parents and caregivers use cough and cold products in children older than two years, labels should be read carefully, caution should be used when administering multiple products, and only measuring devices specifically designed for use with medications should be used. While some combination cough/cold products containing these ingredients are available by prescription only and are not necessarily under scrutiny by the FDA, clinicians should thoroughly assess each patient's use of similar products, both prescription and nonprescription, to avoid duplication of therapy and the potential for inadvertent overdose.

In January 2008, a FDA panel recommended that nonprescription cold medicines should not be given to children under two years old due to the risk of serious and potentially life-threatening adverse reactions. In October 2008, manufacturers of cough and cold products voluntarily modified their labels to increase the age recommended warnings for use in children and infants to less than four years of age versus the previous warning in children and infants less than two years of age, making this a more stringent warning than the FDA advisory. Manufacturers also, introduced new child-resistant packaging and new measuring devices for use with the products.<sup>6,7</sup> The impact of these actions was evaluated. In addition, a retrospective review of OTC cough and cold medication ingestions reported to U.S. poison centers between 2000 and 2010 revealed that unintentional ingestions of these medications decreased by 33.4 percent and therapeutic errors by 46 percent. Health care facility referral declined for unintentional ingestions (28.9 percent < two years of age, 19.9 percent two-five years of age, [p<0.0001] and therapeutic errors in children < two years of age [(59.2 percent, p<0.0001)].<sup>8</sup> In addition, among children less than two years of age, emergency department (ED) visits related to cough and cold medication decreased from 4.1 percent of all adverse drug event ED visits before the 2007 voluntary market withdrawal of infant cough and cold medications by manufacturers to 2.4 percent afterward. Similarly, among children aged two to three years, ED visits related to cough and

cold medication adverse drug events decreased from 9.5 of all adverse drug event ED visits before the labeling revision announcement to 6.5 percent afterward.<sup>9</sup>

Some pyrilamine products (e.g., Deconsal CT, V-Tann Suspension, Ryna 12, Pyrex PD Suspension, etc.) may contain phenylalanine. These products should not be used in patients with phenylketonuria (PKU).

## DRUG INTERACTIONS<sup>10</sup>

Drug Type	Anticholinergics	Antihistamines	Antitussives (opiate)	Antitussives (non-opiate)	Decongestants	Expectorants
CNS depressants (e.g., alcohol, sedatives, anxiolytics, etc.)	--	✓	--	--	--	--
MAOIs	--	✓	--	--	--	--
Tricyclic antidepressants	✓	✓	--	--	--	--
Alpha blockers	--	--	--	--	✓	--
Beta blockers	--	--	--	--	✓	--
Centrally acting antihypertensives	--	--	--	--	✓	--
Antidiabetic agents	--	--	--	--	✓	--
Ototoxic medications (e.g., aminoglycosides)	✓	✓	--	--	--	--

Concurrent administration of methscopolamine nitrate with either sildenafil or vardenafil has been shown to potentiate hypotension due to the nitrate. Therefore, the concurrent use of sildenafil or vardenafil with products containing methscopolamine nitrate is not recommended.

## ADVERSE EFFECTS<sup>11,12</sup>

Drug Type	Anticholinergics	Antihistamines	Antitussives (opiate)	Antitussives (non-opiate)	Decongestants	Expectorants
Drowsiness	✓	✓	✓	✓	✓	✓
Xerostomia	✓	✓	--	--	✓	--
Nausea	✓	--	✓	✓	✓	✓
Tachycardia/ Palpitations	✓	--	--	--	✓	--
CNS depression	✓	✓	✓	✓	✓	--
Respiratory depression	✓	--	✓	✓	--	--

✓ = Reported

Adverse effects are reported above as a class effect due to the multiple ingredients contained in the products. Adverse effects have been taken from package inserts or other reliable databases and are not meant to be comparative or all inclusive.

## SPECIAL POPULATIONS<sup>13,14</sup>

### Pediatrics

Many of the products in this category are approved for use in children as young as two years of age. Please consult the individual prescribing information for specific product information.

### Pregnancy

Pregnancy category depends upon the component ingredients. Many are Pregnancy Category C, but consult the individual package inserts for specific product information.

### Renal Impairment

Dosage adjustment may be warranted; however, specific guidelines in renal impairment are not available. Consult the individual package inserts for additional information.

### Hepatic Impairment

Specific guidelines for dosage adjustments in patients with hepatic impairment are not available. Lower doses may be warranted due to metabolism of any one of the ingredients in a given product.

### Geriatrics

The elderly are more susceptible to the anticholinergic effects of antihistamines. Reduced initial dosages may be needed.

**DOSAGES<sup>15,16</sup>**

Drug (Products containing drug)	Maximum Recommended Daily Dose		Availability
	Adult	Child	
<b>Anticholinergics</b>			
homatropine	9 mg	Ages: six to twelve years: 4.5 mg	Tablet and syrup formulations
methscopolamine	12.5 mg	Safe and effective use has not been established in children	Tablet, chewable tablet, and syrup formulations
scopolamine	2.4 mg	Safe and effective use has not been established in children	Tablet and solution formulations
<b>Antihistamines</b>			
brompheniramine	48 mg	Ages: six to 11 years: 24 mg two to five years: 12 mg one to two years: 6 mg six to 12 months: 3 mg three to six months: 2 mg one to three months: 1 mg	Tablet, capsule, solution, syrup and suspension formulations
carbinoxamine	32 mg	Ages: over six years: 24 mg three to six years: 16 mg two to three years: 8 mg	Solution, suspension, syrup formulations
chlorpheniramine	24 mg	Ages: over six years: 12 mg two to five years: 4 mg	Suspensions, solutions, extended-release tablets, chewable tablets Extended release formulations are not recommended for children under age six years
clemastine	2 mg	Ages: 12 years and older: 2 mg less than 12 years: safe and effective use has not been established.	Tablet and caplet formulations
cyproheptadine	32 mg	Ages: seven to 14 years: 16 mg two to six years: 12 mg	Syrup and tablet formulations
dexbrompheniramine	12 mg	Ages: twelve years and older: 12 mg less than 12 years: safe and effective use has not been established	Tablets, extended-release tablets, and syrup formulations

**Dosages (continued)**

Drug (Products containing drug)	Maximum Recommended Daily Dose		Availability
	Adult	Child	
<b>Antihistamines (continued)</b>			
dexchlorpheniramine	No maximum dosing information available	Available for use in patients ages two and older	Extended release tablet and oral solution formulations Extended release tablets are not recommended for use in children three to five years of age
diphenhydramine	300 mg	Ages: six years and older: 300 mg	Tablet and suspension formulations
doxylamine	25 mg	Ages: 12 years and older: 25 mg	Suspension and chewable tablet formulations
hydroxyzine	400 mg	Ages: six years and older: 100 mg less than six years: 50 mg infants: safety and efficacy have not been established	– Tablet, capsules, and solution formulations
promethazine	100 mg	Ages: Adolescents: 100 mg two years and older: lesser of 25 mg/dose or 0.5 mg/pound/dose	Tablets and syrup formulations
pyrilamine	No maximum dosing information available	Available for use in patients ages two years and older	Tablet, syrup, suspension, and chewable tablet formulations
triprolidine	10 mg	Ages: six to eleven years: 5 mg four to five years: 3.75 mg two to three years: 2.5 mg four months to one year: 1.25 mg	Tablet, solution, and suspension formulations

**Dosages (continued)**

Drug (Products containing drug)	Maximum Recommended Daily Dose		Availability
	Adult	Child	
<b>Antitussives (opiate)</b>			
codeine	360 mg	Ages: Adolescents: 360 mg less than three years: Safe and effective use has not been established	Tablet, capsule, syrup, and solution formulations
dihydrocodeine	90 mg	Ages: six to twelve years: 45 mg two to five years: 22.5 mg	Syrup and solution formulations
hydrocodone	30 mg (as an antitussive)	Ages: two years and older: 0.6 mg/kg (as an antitussive)	Capsule and syrup formulations
<b>Antitussives (non-opiate)</b>			
carbetapentane	240 mg	Ages: six to twelve years: 120 mg four to five years: 30 mg two to three years: 15 mg	Tablets, capsules, extended- release capsules, and suspension formulations
chlorphedianol	100 mg	Ages: two to twelve years: 50 mg	Solution formulations
dextromethorphan	120 mg	Ages: six to eleven years: 60 mg two to five years: 30 mg	Tablet, chewable tablet, suspension, and solution formulations

**Dosages (continued)**

Drug (Products containing drug)	Maximum Recommended Daily Dose		Availability
	Adult	Child	
<b>Decongestants</b>			
phenylephrine	60 mg	Ages: six to twelve years: 30 mg two to five years: 15 mg	Tablet, chewable tablet, solution, and syrup formulations
pseudoephedrine	240 mg	Ages: six to eleven years: 120 mg two to five years: 60 mg	Chewable tablet, capsule, solution, suspension, and syrup formulations
<b>Expectorants</b>			
guaifenesin	2,400 mg	Ages: six to eleven years: 1,200 mg two to five years: 600 mg < two years: 300 mg	Extended-release capsule, tablet, solution, suspension, and syrup formulations
potassium guaiacolsulfonate	1,800 mg	Ages: three to twelve years: 0.6 mg/kg/day	Syrup formulation

**CLINICAL TRIALS****Search Strategy**

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

This class contains a vast number of combination cough and cold products whose constituent ingredients are available both as prescription and over-the-counter medications. All of the products contained in this monograph have supporting evidence related to the safety and efficacy of their constituent ingredients. There are numerous placebo-controlled studies available, but none that are comparative to other agents within this class.

## META-ANALYSIS

A 2005 Cochrane Review suggested caution in determining clinically significant benefits of any of the non-antibiotic treatments of the common cold other than first-dose decongestants and antihistamine-decongestant combinations.<sup>17</sup> The review included comparison of several products including Echinacea, heated humidifier air, dextromethorphan, guaifenesin, vitamin C, zinc lozenges, and two combination antihistamine-decongestant products. Dexbrompheniramine 6 mg in combination with pseudoephedrine 120 mg was administered twice daily for one week in one study. Another study evaluated loratadine 5 mg in combination with pseudoephedrine 120 mg twice daily for four days. The authors concluded that most non-antibiotic treatments for the common cold are probably not effective; however, dextromethorphan, guaifenesin, combination antihistamine-decongestants, first-dose decongestants, and possibly zinc lozenges show promise.

A 2012 Cochrane Review on the efficacy of over-the counter (OTC) medications to treat an acute cough included 26 trials with of antitussives, expectorants, mucolytics, antihistamines, antihistamine-decongestant combinations, and other combinations with placebo with variable results.<sup>18</sup> The review could not confirm clear evidence of efficacy of OTC medications to treat an acute cough.

A 2007 meta-analysis was done to assess the efficacy of oral phenylephrine 10 mg as a nasal decongestant in the symptomatic relief from the common cold.<sup>19</sup> To be included in the analysis, studies had to have a single-dose, randomized, placebo-controlled design; involve an orally administered product in which phenylephrine 10 mg was the sole active ingredient; enroll patients with acute nasal congestion due to the common cold; evaluate nasal airway resistance as the efficacy endpoint; and have sufficient data points to allow re-analysis and/or meta-analysis of phenylephrine 10 mg and placebo. Eight studies met the inclusion criteria, involving seven cross-over studies of 113 subjects. Significant differences in favor of phenylephrine were seen in four of the eight studies ( $p \leq 0.05$ ). Phenylephrine was significantly more effective than placebo at the primary time points (45, 90, 120, and 180 minutes). This meta-analysis and re-analysis support the effectiveness of a single oral dose of phenylephrine 10 mg as a decongestant in adults with acute nasal congestion associated with the common cold.

## SUMMARY

The common cold induces acute cough by directly irritating the upper airway structures. Viral infections of the airway can produce the common cold syndrome including rhinosinusitis. Active treatment of the symptoms associated with cough and cold may include combination products containing anticholinergics, first-generation antihistamines, opiate and non-opiate antitussives, decongestants, and expectorants. The available data do not result in any differentiation among the drugs in their particular class. These products are available in various combinations and individually as both prescription and OTC products. Awareness of the active ingredients is critical in ensuring proper dosing, patient safety, and effective use of these products.

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