© Copyright 2024 Oregon State University. All Rights Reserved

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Cough and Cold

Date of Review: August 2026

Literature Search: 1/1/2016 – 8/7/2026
Date of Last Review: May 2016

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- This literature scan looks at evidence published since the last review in 2016 for the safety and effectiveness of medicines used to treat symptoms of cough and the common cold.
- The common cold is caused by viruses, and symptoms include sore throat, nasal stuffiness and discharge, sneezing, and cough. The common cold usually resolves by itself within 1 to 2 weeks.
- As there is no cure for the common cold, only symptomatic treatment is available. Several treatments are needed to relieve the variety of symptoms, and different products are often combined into one pill: antihistamines against sneezing, cough, and nasal discharge; decongestants against nasal stuffiness; and pain relievers for sore throat.
- The Oregon Health Plan (OHP) pays for medicines to relieve cough including codeine with guaifenesin in adults aged 18 years and older; and guaifenesin and dextromethorphan with guaifenesin in children and adults. The OHP also pays for the decongestant, pseudoephedrine. For all other cough and cold medicines, the Oregon Health Authority requires providers to submit documentation before they pay for these medicines. This process is called prior authorization (PA).

Conclusions:

- There is limited high-quality evidence to evaluate the efficacy of cough and cold products. Since the last Pharmacy and Therapeutics (P & T) Committee review in 2016, 5 systematic reviews have been published to evaluate safety and effectiveness of cough and cold medications. No high-quality clinical guidelines have been published in the past 10 years.
- The objective of a 2025 systematic review was to examine the relationship between the misuse of antihistamines, cough medicines, and decongestants with the onset of psychotic symptoms.[1] Key findings indicate that antihistamines, dextromethorphan, and other over-the-counter (OTC) drugs can induce psychotic symptoms, such as paranoia, hallucinations, and thought disorders when abused.[1] Dextromethorphan is particularly associated with a chronic tendency towards psychosis, whereas other substances more commonly result in acute substance-induced psychosis.[1]
- A 2023 systematic review evaluated available literature to evaluate the safety and effectiveness of benzonatate.[2] This review reveals substantial limitations within existing evidence pertaining to the safety and clinical effectiveness of benzonatate and thus, a need for large observational studies or randomized trials to better characterize its role and value in modern medical practice.[2]

Author: Deanna Moretz, PharmD, BCPS

- A 2021 systematic review described the course of severe poisoning and deaths from benzonatate supplemented with the National Poison Data System (NPDS) fatalities module.[3] Calls to poison centers about benzonatate exposures have risen drastically (doubling since the 2012 Food and Drug Administration [FDA] warning) with a concomitant increase in the number of severe poisonings from approximately 120 in 2012 to 240 in 2019.[3] Overdose ingestions of benzonatate can cause significant toxicity with a rapid onset.[3] Duration of directly toxic effects is short, but dramatic with neurologic devastation and resuscitated patients often still have a poor outcome.[3]
- A 2022 Cochrane review evaluated the safety and effectiveness of oral antihistamine-decongestant-analgesic combinations for the common cold.[4] There was sparse data on the effectiveness of antihistamine-analgesic-decongestant combinations for the common cold.[4] Based on limited data, the effect on individual symptoms is probably too small to be clinically relevant.[4] The current evidence suggests that antihistamine-analgesic-decongestant combinations have some general benefit in adults and older children however, these benefits must be weighed against the risk of adverse effects.[4] There is no evidence of effectiveness of these medications in young children.[4]
- A 2017 systematic review on the management of acute cough associated with the common cold was conducted to update the recommendations and suggestions of the CHEST 2006 guideline on this topic.[5] Many of the published studies are small and have significant limitations and potential biases.[5] Data pooling was generally not possible, making it difficult to provide definitive recommendations.[5] The available currently marketed products in the United States (US) do not include the combination of ingredients that may be effective for cough associated with the common cold in adults; therefore, no specific recommendations could be made for the use of antihistamine, decongestant, and analgesic combinations to treat this condition in adults.[5] In addition, there were no pediatric studies of antihistamine, decongestant, and analgesic combination products that demonstrated efficacy for cough associated with the common cold.[5] In adult and pediatric patients with the common cold, no evidence was identified to support or refute the use of OTC antitussive agents, expectorants, mucolytic agents, antihistamines, or combination products for reducing cough.[5] There has been little change in the treatment choices for cough due to the common cold since publication of the 2006 CHEST cough guidelines.[5]
- The FDA has issued several Drug Safety Communications for cough and cold preparations since the last review. The FDA communications are summarized below, and significant drug labeling changes are presented in **Table 1**.

Recommendations:

- Based on review of recently published evidence, no changes to the Preferred Drug List (PDL) are warranted.
- After reviewing drug costs in executive session, the following products were designated as preferred: guaifenesin, pseudoephedrine, and dextromethorphan either as single agents or in combination with other agents if daily reimbursement cost is less than $1.00. All other products were designated as non-preferred if they did not have a PDL status.

Summary of Prior Reviews and Current Policy

- This class of medications was last reviewed by the P & T Committee at the May 2016 meeting. After a review of evidence, the committee agreed to the following recommendations:
    - Do not prefer any expectorants and remove all guaifenesin single ingredient products from the PDL.
    - Ensure there is a minimum of 1 product with codeine and 1 with dextromethorphan preferred on the PDL for refractory cough as these have the strongest evidence of efficacy.
    - After executive session, make all benzonatate products non-preferred.
    - Expand the pediatric restriction (children 13 years of age and older) to all cough and cold products (with or without codeine).
    - Restrict codeine cough products to adults 19 years of age and older.

- In the first quarter of 2026 (January 1 to March 31), there were approximately 200 claims for cough and cold products in the fee-for-service (FFS) population. Most of the claims were for preferred products (pseudoephedrine, codeine + guaifenesin, guaifenesin, and dextromethorphan + guaifenesin). There were 2 claims for the non-preferred agent, benzonatate.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high-quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
A Systematic Review of the Misuse of Antihistamines, Cough Medicines, and Decongestants and the Risk of Developing Psychosis (2025)
Certain over-the-counter medications possess pharmacological properties that render them susceptible to misuse and abuse.[1] Misuse involves improper dosage, duration, or indication, while abuse entails non-therapeutic use to achieve psychoactive effects or other illicit purposes, potentially leading to dependence and addiction.[1] The objective of this systematic review is to examine the relationship between the misuse of antihistamines, cough medicines, and decongestants, and the onset of psychotic symptoms.[1]

Literature was searched through April 2024.[1] Forty-six relevant studies out of an initial pool of 2,677 articles were analyzed.[1] Of the total 46 articles, 27 reported the use of dextromethorphan, 4 of dimenhydrinate, 3 of diphenhydramine, 2 of promethazine, and 10 of other substances (e.g., d-norpseudoephedrine, chlorpheniramine, and dextromethorphan + triprolidine and pseudoephedrine).[1] Most studies were case reports and case series, except for 3 retrospective studies and one survey.[1] Most subjects were male, while the age ranged from a minimum of 14 years to a maximum of 69 years old.[1] Regarding psychiatric comorbidity, studies showed a wide variety, with substance use disorder being the most represented diagnosis (N=18), followed by mood disorders (N=12).[1] In most studies (N=20), polydrug use was not reported; however, in cases where it occurred, concomitant use of other OTC drugs was reported.[1] In addition, concomitant use of alcohol followed by cannabis was reported.[1] Isolated cases of polydrug abuse included opiates, cocaine, ecstasy, phencyclidine, ketamine, lysergic acid diethylamide (LSD), previous methamphetamine abuse, and one case enrolled in a methadone maintenance program.[1] Regarding affective symptoms, most studies (N=7) reported excitatory symptoms (e.g., euphoria and sense of well-being), and in 8 cases, manic states.[1] Regarding psychotic symptoms, paranoia/paranoid delusion was the most reported thought disorder (N=18), while both visual and auditory hallucinations were found, either alone or in combination (N=32).[1] Negative symptoms of schizophrenia were rarely reported, except in one case with apathy and anhedonia.[1]

After excluding studies involving comorbidities with psychotic disorders (schizophrenia spectrum disorders or bipolar disorder), studies were categorized into 2 groups based on outcome: substance-induced psychosis and psychotic onset with a tendency toward chronicity.[1] According to the results of the review, the only substance that led to cases of psychotic onset with a tendency to chronicity was dextromethorphan, with 5 cases while 16 cases were substance-induced psychosis.[1] As for the other substances, dimenhydrinate, diphenhydramine, and promethazine only resulted in substance-induced psychosis.[1]

In summary, key findings indicate that antihistamines, dextromethorphan, and other OTC drugs can induce psychotic symptoms, such as paranoia, hallucinations, and thought disorders when abused.[1] Dextromethorphan is particularly associated with a chronic tendency towards psychosis, whereas other substances more commonly result in acute substance-induced psychosis.[1]

Benzonatate Safety and Effectiveness (2023)

Benzonatate remains one of the most commonly used medications in the US.[2] Rising safety concerns have brought scrutiny upon the prescription of benzonatate whose approval is founded upon evidence that would not stand up to current regulatory review standards.[2] Use of benzonatate in various clinical settings continues to rise as do reports of its toxicities and misuse.[2] These toxicities include cardiac arrhythmias, seizures, and death due to cardiac arrest, which may be attributed to sodium channel blockade.[2] This systematic review evaluated available literature to evaluate the safety and effectiveness of benzonatate.[2] Literature was searched through August 2022 for studies that evaluated the effectiveness, tolerability, or safety profile of benzonatate.[2]

The selection process resulted in 37 articles consisting of 21 cohort studies, 5 experimental studies, and 11 case studies and series.[2] Initial clinical studies exploring potential therapeutic benefits collected data from very small populations and limited clinical settings.[2] Few comparative studies directly assessing the clinical effectiveness of benzonatate to other modern antitussives were identified.[2] The existing studies assessing the use and effectiveness of benzonatate were primarily single-arm observational studies conducted in the mid-20th century and do not meet the current standards for evidence-based medicine.[2] Prospective and retrospective cohort studies assessing the effectiveness of benzonatate in larger populations with more complete medical and demographic information are not presently available.[2] The available smaller cohort studies that use comparators often draw comparisons between different formulations of benzonatate or placebo rather than head-to-head comparisons to other antitussives.[2]

Benzonatate safety is primarily assessed in terms of toxicity due to overdose or inappropriate use.[2] The more recent cohort studies are retrospective analyses that describe and characterize the toxicity of benzonatate and describe the morbidity and mortality related to overdose.[2] These cohorts were derived from the Food and Drug Administration (FDA) Adverse Event Reporting System, the National Poison Data System and other data vendors to describe and characterize drug toxicities from intentional and unintentional ingestion of benzonatate.[2] Case reports and case series primarily describe instances of benzonatate overdose by accidental or intentional ingestion and their subsequent clinical course in an emergency department and hospital setting.[2] Death due to cardiac arrhythmias or severe clinical sequela of cardiac arrhythmias, cardiac arrest, and seizure in the setting of overdose are described in detail across multiple case series and case reports.[2]

In summary, quality assessment of published evidence raised concerns for high degrees of biases primarily related to the limited sample size, data collection, generalizability, and study design.[2] This review reveals substantial limitations within existing evidence pertaining to the safety and clinical effectiveness of benzonatate and thus, a need for large observational studies or randomized trials to better characterize its role and value in modern medical practice.[2]

Severe Benzonatate Poisonings Reported in the Literature (2021)

This was a systematic review to describe the course of severe poisoning and deaths from benzonatate supplemented with the National Poison Data System (NPDS) fatalities module.[3] Benzonatate is a commonly prescribed cough suppressant with over 3 million prescriptions per year in the US in 2016.[3] Calls to poison centers about benzonatate exposures have risen drastically (doubling since the 2012 FDA warning) with a concomitant increase in the number of severe poisonings from approximately 120 in 2012 to 240 in 2019.[3] Sporadic cases of severe benzonatate poisoning are reported in the literature.[3]

The NPDS was queried from 2000 to 2018 for benzonatate fatalities.[3] PubMed, Cochrane, Embase, and Google Scholar were searched for combinations of benzonatate and "poisoning," "overdose," and "toxicity."[3] Seventeen cases from NPDS and 19 published reports met the inclusion criteria resulting in 36 cases, mostly (28/36) self-harm ingestions.[3] Most patients were young (median age 17 years [IQR 11-29]) and female).[3] Onset of toxicity was rapid at less than 5 minutes.[3] Most common symptoms included cardiac arrest (29), seizures (24), and dysrhythmias (24).[3] Treatments included intubation (26), cardiopulmonary resuscitation (28), vasopressors (20) and others.[3] Return of spontaneous circulation was achieved in 23/28 patients, but most had significant neurologic deficits or other end organ damage and 5 survived with a good neurologic outcome.[3]

In conclusion, overdose ingestions of benzonatate can cause significant toxicity with a rapid onset.[3] Interventions performed were generally supportive in nature.[3] Duration of directly toxic effects is short, but dramatic with neurologic devastation and resuscitated patients often still have a poor outcome.[3]

Cochrane: Oral Antihistamine-Decongestant-Analgesic Combinations for the Common Cold (2022)

Although combination formulas containing antihistamines, decongestants, and/or analgesics are sold as OTC products for the common cold quite often, the evidence for their effectiveness is limited.[4] This is an update of a review first published in 2012.[4] Literature was searched through June 2021 for RCTs conducted in adults and children.[4] Thirty studies (n=6304) including 31 treatment comparisons met inclusion criteria. The control intervention was placebo in 26 trials and an active substance (acetaminophen, chlorphenamine + phenylpropanolamine + belladonna, diphenhydramine) in 6 trials (2 trials had placebo as well as active treatment arms).[4] Reporting of methods was generally poor, and there were large differences in study design, participants, interventions, and outcomes.[4] Most of the included trials involved adult participants, while children were included in 9 trials.[4] Three trials included very young children (from 6 months to 5 years), and 5 trials included children aged 2 to 16 years of age.[4] The trials took place in different settings: university clinics, pediatric departments, family medicine departments, and general practice offices.[4]

Antihistamine-decongestant combinations were studied in 14 trials (n=1298 participants).[4] Eight trials reported on global effectiveness, of which 6 studies were pooled (281 participants on active treatment and 284 participants on placebo).[4] The odds ratio (OR) of treatment failure was 0.31 (95% confidence interval [CI] 0.20 to 0.48; moderate certainty evidence); number needed to treat for an additional beneficial outcome (NNTB) 3.9 (95% CI 3.03 to 5.2).[4] On the final evaluation day (follow-up: 3 to 10 days), 55% of participants in the placebo group had a favorable response compared to 70% on active treatment.[4] Of the 2 trials not pooled, one showed some global effect, while the other showed no effect.[4] The antihistamine-decongestant group experienced more adverse effects than the control group: 31% versus 13% participants suffered one or more adverse effects (OR 1.58, 95% CI 0.78 to 3.21; moderate certainty of evidence).[4]

Antihistamine-analgesic combinations were studied in 4 trials (n=1608).[4] Two trials reported on global effectiveness; data from one trial were presented (290 participants on active treatment and 292 participants on ascorbic acid).[4] The OR of treatment failure was 0.33 (95% CI 0.23 to 0.46; moderate certainty evidence); NNTB 6.67 (95% CI 4.76 to 12.5).[4] Forty-three percent of participants in the control group and 70% in the active treatment group were cured after 6 days of treatment.[4] The second trial also showed an effect in favor of the active treatment.[4] There were not significantly more adverse effects in the active treatment group compared to placebo (drowsiness, hypersomnia, sleepiness [7% versus 3%; OR 1.64 (95 % CI 0.48 to 5.59)]; low certainty evidence).[4]

Analgesic-decongestant combinations were evaluated in 7 trials (n=2575).[4] One trial reported on global effectiveness: 73% of participants in the analgesic-decongestant group reported a benefit compared with 52% in the control group (acetaminophen) (OR of treatment failure 0.28, 95% CI 0.15 to 0.52; moderate certainty evidence; NNTB 4.7).[4] The decongestant-analgesic group experienced significantly more adverse effects than the control group (18% versus 11%; OR 1.62 95% CI 1.18 to 2.23; high certainty evidence; number needed to treat for an additional harmful outcome (NNTH 17).[4]

Antihistamine-analgesic-decongestant combinations were included in 6 trials (n=1014).[4] Five trials reported on global effectiveness, of which 2 studies in adults could be pooled: global effect reported with active treatment (52%) and placebo (34%) was equivalent to a difference of less than one point on a four- or five-point scale; the OR of treatment failure was 0.47 (95% CI 0.33 to 0.67; low certainty evidence); NNTB 5.6 (95% CI 3.8 to 10.2).[4] One trial in children aged 2 to 12 years, and two trials in adults found no beneficial effect.[4] In one trial 2% suffered adverse effects with the active treatment versus 4% with placebo.[4] Two other trials reported no differences between treatment groups.[4]

In summary, there was sparse data on the effectiveness of antihistamine-analgesic-decongestant combinations for the common cold.[4] Based on limited data, the effect on individual symptoms is probably too small to be clinically relevant.[4] The current evidence suggests that antihistamine-analgesic-decongestant combinations have some general benefit in adults and older children.[4] These benefits must be weighed against the risk of adverse effects.[4] There is no evidence of effectiveness in young children.[4]

Pharmacologic and Nonpharmacologic Treatment for Acute Cough Associated With the Common Cold (2017)

This systematic review on the management of acute cough associated with the common cold was conducted to update the recommendations and suggestions of the CHEST 2006 guideline on this topic.[5] Literature was searched for evidence of clinically relevant treatment effects for pharmacologic or nonpharmacologic therapies in reducing the duration/severity of acute cough associated with the common cold through April 2014.[5] Studies of adults and pediatric patients with cough due to common cold symptoms were included and assessed for relevance and quality.[5] Pharmacologic interventions included acetylcysteine, antihistamine monotherapy, expectorant monotherapy, cough suppressant monotherapy, antihistamine + expectorant, antihistamine + suppressant, expectorant + suppressant, antihistamine + suppressant + expectorant, supplements (zinc, vitamin C), antihistamine + decongestants, inhaled nasal steroids, inhaled antihistamines, inhaled ipratropium bromide, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and OTC cough and cold remedies.[5] Thirty-six RCTs and 6 systematic reviews met the inclusion and exclusion criteria.[5] The systematic reviews were mostly of good quality.[5] Generally, however, the relevant study data were quite limited and of low quality.[5]

- *Decongestants and Antihistamines*

One systematic review identified 4 RCTs that evaluated the effects of antihistamine and decongestant combinations on the severity of cough.[5] The data (3 studies in adults and one pediatric study) included 672 cold episodes.[5] Data pooling was not possible due to different treatments and combinations.[5] Overall, the results were inconsistent, making it impossible to form any conclusion regarding the effectiveness of this combination of products.[5] This review also identified 2 RCTs of antihistamine and analgesic combinations.[5] Three hundred forty-one adult subjects had cough symptoms evaluated daily for 5 days. Both trials failed to show an effect from the active treatment compared with placebo or acetaminophen for cough.[5] Two RCTs with a total of 249 subjects treated with a decongestant and analgesic combination.[5] No effect on cough was observed.[5]

Three RCTs studied combinations of antihistamine, decongestant, and analgesic combinations.[5] Two studies included 555 adult subjects, and one pediatric study included 201 children.[5] Data pooling was not possible, and study results were inconsistent.[5] The two adult studies did demonstrate some treatment effect on

cough with the combination of dextromethorphan, doxylamine, paracetamol, and ephedrine.[5] The author concluded that this combination may be effective for acute cough associated with common cold in adults.[5] The pediatric study using the combination of acetaminophen, diphenhydramine, and pseudoephedrine showed no effect on cough; however, dextromethorphan was not included in the combination product administered in the pediatric study.[5]

The available currently marketed products in the US do not include the combination of ingredients that may be effective for cough associated with the common cold in adults; therefore, no specific recommendations could be made for the use of antihistamine, decongestant, and analgesic combinations to treat this condition in adults.[5] In addition, there were no pediatric studies of antihistamine, decongestant, and analgesic combination products that demonstrated efficacy for cough associated with the common cold.[5]

- *Over-the-Counter Medications*

Another systematic review, assessed to be of good quality, included 6 trials with a total of 1,526 adult patients that compared antitussive agents with placebo.[5] The antitussive agents studied included codeine, dextromethorphan, and moguisteine.[5] Moguisteine is an antitussive product that is not available in the US or the United Kingdom. Four trials of antitussive studies were identified in 327 pediatric subjects.[5] Overall, the studies had very poor quality with variable results and data pooling was not possible.[5] Three trials comparing the expectorant guaifenesin with placebo in 304 subjects were included in this systematic review.[5] Data quality was very low, and studies had conflicting results.[5] No studies were identified that reported outcomes with the use of expectorants in pediatric subjects.[5]

Four studies evaluated other product combinations against placebo in 836 adults; 3 of the studies found antihistamines to be no more effective than placebo in relieving cough symptoms.[5] Two studies evaluated other product combinations in 99 pediatric patients.[5] Overall, these studies were very small and heterogeneous, using widely varied drug preparations and dosing frequencies.[5] These limitations did not lead to any possible data pooling.[5] None of the pediatric studies showed a benefit over placebo for antitussive therapy, antihistamines, decongestants, or antitussive/bronchodilator treatment.[5]

In conclusion, for adult and pediatric patients with the common cold, no evidence was identified to support or refute the use of OTC antitussive agents, expectorants, mucolytic agents, antihistamines, or combination products for reducing cough.[5] There has been little change in the treatment choices for cough due to the common cold since publication of the 2006 CHEST cough guidelines.[5] Many of the published studies are small and have significant limitations and potential biases.[5] Data pooling was generally not possible, making it difficult to provide definitive recommendations.[5]

After review, 15 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
High-Quality Guidelines: No high-quality guidelines were identified.

New FDA Safety Alerts:
Drug Safety Communications and News Releases:

- November 2024: The FDA announced it is proposing to remove oral phenylephrine as an active ingredient that can be used in OTC drug products for the temporary relief of nasal congestion after an agency review of the available data determined that oral phenylephrine is not effective for this use. For now, companies may continue to market OTC drug products containing oral phenylephrine as a nasal decongestant. This is a proposed order. Only a final order will affect what products can be marketed. The proposed order is based on effectiveness concerns, not on safety concerns.[6]

  Currently, oral phenylephrine is widely used as a nasal decongestant active ingredient in many OTC drug products. It is important to note that some products only contain oral phenylephrine as a single, active ingredient. Others contain oral phenylephrine and another active ingredient (e.g., acetaminophen or dextromethorphan), and the presence of oral phenylephrine in these medicines does not affect how other active ingredients work to treat the symptoms for which they are intended.[6]

- March 2021: The FDA warned that the abuse and misuse of the OTC nasal decongestant propylhexedrine can lead to serious harm such as heart and mental health problems. Some of these complications, which include fast or abnormal heart rhythm, high blood pressure, and paranoia, can lead to hospitalization, disability, or death. Reports of individuals abusing and misusing propylhexedrine have increased in recent years. Propylhexedrine is safe and effective when used as directed.[7]

  Propylhexedrine is a nasal decongestant that is available OTC in an inhaler. It is used short term to temporarily relieve nasal congestion due to colds, hay fever, or other upper respiratory allergies. The recommended dose for adults and children older than 6 years is 2 inhalations in each nostril not more often than every 2 hours. Do not use it for more than 3 days at a time. Prolonged use may cause nasal congestion to recur or worsen. Currently, propylhexedrine is only marketed under the brand name Benzedrex.[7]

  The FDA requested that all manufacturers of OTC propylhexedrine nasal decongestant inhalers consider product design changes that support its safe use. For example, modifying the product to create a physical barrier that would make tampering with the device and abusing the propylhexedrine inside more difficult. In addition, decreasing the amount of medicine the device contains could also reduce the risk of serious side effects if abused or misused. The FDA continues to evaluate this safety issue and will determine if additional FDA actions are needed.[7]

- January 2018: The FDA required safety labeling changes for prescription cough and cold medicines containing codeine or hydrocodone to limit the use of these products to adults 18 years and older because the risks of these medicines outweigh their benefits in children younger than 18 years of age. This update replaced the April 2017 communication summarized below. The FDA also required the addition of safety information about the risks of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing to the Boxed Warning, the most prominent warning, of the drug labels for prescription cough and cold medicines containing codeine or hydrocodone.[8]

  These products will no longer be indicated for use in children, and their use in this age group is not recommended. Health care professionals should reassure parents that cough due to a cold or upper respiratory infection is self-limited and generally does not need to be treated. For those children in whom cough treatment is necessary, alternative medicines are available. These include OTC products such as dextromethorphan, as well as prescription benzonatate products.[8]

- April 2017: The FDA restricted the use of codeine and tramadol medicines in children. These medicines carry serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years, and should not be used in these children. These medicines should also be limited in some older children. Single-ingredient codeine and all tramadol-containing products are FDA-approved only for use in adults. The FDA is also recommending against the use of codeine and tramadol medicines in breastfeeding mothers due to possible harm to their infants.[9]

Table 1. Description of New FDA Safety Alerts[10]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Homatropine + hydrocodone Guaifenesin + Hydrocodone Promethazine + Codeine	HYCODAN FLOWTUSS TUSSIONEX PHENERGAN W/CODEINE	6/18	Boxed Warning and Contraindications	**Boxed Warning:** WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; MEDICATION ERRORS; CYTOCHROME P450 3A4 INTERACTION; CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; INTERACTION WITH ALCOHOL; NEONATAL OPIOID WITHDRAWAL SYNDROME Addiction, Abuse, and Misuse Hydrocodone or codeine exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Reserve hydrocodone or codeine for use in adult patients for whom the benefits of cough suppression are expected to outweigh the risks, and in whom an adequate assessment of the etiology of the cough has been made. Assess each patient's risk prior to prescribing hydrocodone or codeine and prescribe for the shortest duration that is consistent with individual patient treatment goals, monitor all patients regularly for the development of addiction or abuse, and refill only after reevaluation of the need for continued treatment. Life-Threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of hydrocodone or codeine. Monitor for respiratory depression, especially during initiation of hydrocodone therapy or when used in patients at higher risk.

				Accidental Ingestion Accidental ingestion of even one dose of hydrocodone or codeine, especially by children, can result in a fatal overdose of hydrocodone. Risk of Medication Errors Ensure accuracy when prescribing, dispensing, and administering hydrocodone or codeine. Dosing errors can result in accidental overdose and death. Always use an accurate milliliter measuring device when measuring and administering hydrocodone. Cytochrome P450 3A4 Interaction The concomitant use of hydrocodone or codeine with all cytochrome P450 3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Avoid the use of hydrocodone and codeine in patients taking a CYP3A4 inhibitor or inducer. **Contraindications:** Hydrocodone is contraindicated for all children younger than 6 years of age. Codeine is contraindicated for all children younger than 12 years of age.
Oxymetazoline	UPNEEQ	5/2021	Warnings and Precautions	**Ptosis as Presenting Sign of Serious Neurologic Disease** Ptosis may be associated with neurologic or orbital diseases such as stroke and/or cerebral aneurysm, Horner syndrome, myasthenia gravis, external ophthalmoplegia, orbital infection and orbital masses. Consideration should be given

				to these conditions in the presence of ptosis with decreased levator muscle function and/or other neurologic signs.

References:

1. Mosca A, Chiappini S, Mancusi G, et al. Over-the-counter Psychosis: A Systematic Review of the Misuse of Antihistamines, Cough Medicines, and Decongestants and the Risk of Developing Psychosis. *Current Neuropharmacology*. 23(8):956-973. doi:https://dx.doi.org/10.2174/011570159X344365250114064248
2. Costantino RC, Leonard J, Gorman EF, Ventura D, Baltz A, Gressler LE. Benzonatate Safety and Effectiveness: A Systematic Review of the Literature. *Ann Pharmacother*. 57(10):1221-1236. doi:https://dx.doi.org/10.1177/10600280221135750
3. Minhaj FS, Leonard JB. A description of the clinical course of severe benzonatate poisonings reported in the literature and to NPDS: A systematic review supplemented with NPDS cases. *Human & Experimental Toxicology*. 40(12_suppl):S39-S48. doi:https://dx.doi.org/10.1177/09603271211030560
4. De Sutter AI, Eriksson L, van Driel ML. Oral antihistamine-decongestant-analgesic combinations for the common cold. *Cochrane Database of Systematic Reviews*. 1:CD004976. doi:https://dx.doi.org/10.1002/14651858.CD004976.pub4
5. Malesker MA, Callahan-Lyon P, Ireland B, Irwin RS. Pharmacologic and Nonpharmacologic Treatment for Acute Cough Associated With the Common Cold: CHEST Expert Panel Report. *Chest*. 152(5):1021-1037. doi:https://dx.doi.org/10.1016/j.chest.2017.08.009
6. FDA New Release. FDA Proposes Ending Use of Oral Phenylephrine as OTC Active Ingredient. https://www.fda.gov/news-events/press-announcements/fda-proposes-ending-use-oral-phenylephrine-otc-monograph-nasal-decongestant-active-ingredient-after 11/7/2024. Accessed 8/11/206.
7. FDA Drug Safety Communication. Abuse and Misuse of the Nasal Decongestant Propylhexedrine Causes Serious Harm. https://www.fda.gov/media/146936/download?attachment 3/25/2021. Accessed 8/11/2026.
8. FDA Drug Safety Communication. Labeling changes for prescription opioid cough and cold medicines. https://www.fda.gov/media/110565/download 1/11/2018. Accessed 8/11/206.
9. FDA Drug Safety Communication. Restricted Use of Prescription Codeine Pain and Cough Medicines in Children and Breastfeeding Women. https://web.archive.org/web/20260207093936/https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-restricts-use-prescription-codeine-pain-and-cough-medicines-and 4/20/2017. Accessed 8/11/2026.
10. Food and Drug Administration. Drug Safety Labeling Changes. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/. Accessed 8/11/2026.

Appendix 1: Current Preferred Drug List

Generic	Brand	FormDesc	PDL
codeine phosphate/guaifenesin	CODEINE-GUAIFENESIN	LIQUID	Y
codeine phosphate/guaifenesin	DURAGANIDIN NR	LIQUID	Y
codeine phosphate/guaifenesin	GUAIFEN-C	LIQUID	Y
codeine phosphate/guaifenesin	GUAIFENESIN-CODEINE	LIQUID	Y
codeine phosphate/guaifenesin	IOPHEN C-NR	LIQUID	Y
codeine phosphate/guaifenesin	MAR-COF CG	LIQUID	Y
codeine phosphate/guaifenesin	CHERATUSSIN AC	SYRUP	Y
codeine phosphate/guaifenesin	GUAIFENESIN-CODEINE	TABLET	Y
guaifenesin	GUAIFENESIN	SYRUP	Y
guaifenesin	TUSSIN	SYRUP	Y
guaifenesin	GUAIFENESIN	TAB ER 12H	Y
guaifenesin	GUAIFENESIN ER	TAB ER 12H	Y
guaifenesin	MUCINEX	TAB ER 12H	Y
guaifenesin	MUCUS ER	TAB ER 12H	Y
guaifenesin	MUCUS RELIEF ER	TAB ER 12H	Y
guaifenesin	MUCUS-ER MAX	TAB ER 12H	Y
guaifenesin	CHEST CONGESTION RELIEF	TABLET	Y
guaifenesin	GUAIFENESIN	TABLET	Y
guaifenesin	MUCOSA	TABLET	Y
guaifenesin	MUCUS RELIEF	TABLET	Y
guaifenesin	AQUAMIST	TABLET ER	Y
guaifenesin	GUAIBID LA	TABLET ER	Y
guaifenesin	GUAIFENESIN	TABLET ER	Y
guaifenesin	MONAFED	TABLET ER	Y
guaifenesin/dextromethorphan	CHILDREN'S COUGH RELIEF	LIQUID	Y
guaifenesin/dextromethorphan	DEXTROMETHORPHAN-GUAIFENESIN	LIQUID	Y
guaifenesin/dextromethorphan	GUAIFENESIN-DEXTROMETHORPHAN	LIQUID	Y
guaifenesin/dextromethorphan	GUAIFENESIN-DM	LIQUID	Y
guaifenesin/dextromethorphan	IOPHEN DM-NR	LIQUID	Y
guaifenesin/dextromethorphan	MUCOLYTE-DM	LIQUID	Y
guaifenesin/dextromethorphan	MUCUS RELIEF DM MAX	LIQUID	Y
guaifenesin/dextromethorphan	MUCUS RELIEF MAX	LIQUID	Y
guaifenesin/dextromethorphan	ROBAFEN DM	LIQUID	Y
guaifenesin/dextromethorphan	TUSNEL DIABETIC	LIQUID	Y
guaifenesin/dextromethorphan	TUSSIN DM	LIQUID	Y
guaifenesin/dextromethorphan	TUSSIN DM MAX	LIQUID	Y
guaifenesin/dextromethorphan	CHEST CONGESTION RELIEF DM	SYRUP	Y

guaifenesin/dextromethorphan	GUAIFENESIN-DEXTROMETHORPHAN	SYRUP	Y
guaifenesin/dextromethorphan	GUAIFENESIN-DM	SYRUP	Y
guaifenesin/dextromethorphan	MINTAB DM	SYRUP	Y
guaifenesin/dextromethorphan	TUSSIN DM	SYRUP	Y
guaifenesin/dextromethorphan	DEX GG	TAB ER 12H	Y
guaifenesin/dextromethorphan	GUAIBID DM	TAB ER 12H	Y
guaifenesin/dextromethorphan	MONAFED DM	TAB ER 12H	Y
guaifenesin/dextromethorphan	MUCUS DM ER	TAB ER 12H	Y
guaifenesin/dextromethorphan	MUCUS DM MAX ER	TAB ER 12H	Y
guaifenesin/dextromethorphan	MUCUS RELIEF DM ER	TAB ER 12H	Y
guaifenesin/dextromethorphan	MUCUS RELIEF DM MAX ER	TAB ER 12H	Y
guaifenesin/dextromethorphan	CHEST CONGESTION RELIEF DM	TABLET	Y
guaifenesin/dextromethorphan	CHEST CONGESTION-COUGH RELIEF	TABLET	Y
guaifenesin/dextromethorphan	GUAIFENESIN-DEXTROMETHORPHAN	TABLET	Y
guaifenesin/dextromethorphan	MUCOSA DM	TABLET	Y
guaifenesin/dextromethorphan	MUCUS RELIEF DM	TABLET	Y
guaifenesin/dextromethorphan	MUCUS RELIEF DM COUGH	TABLET	Y
pseudoephedrine HCl	NASAL DECONGESTANT	TABLET	Y
pseudoephedrine HCl	PSEUDOEPHEDRINE HCL	TABLET	Y
pseudoephedrine HCl	Q-FED	TABLET	Y
pseudoephedrine HCl	SUDOGEST	TABLET	Y
acetaminophen/guaifenesin	CHEST CONGESTION	TABLET	N
benzonatate	BENZONATATE	CAPSULE	N
bromphenir mal/dextrometh HBr	CHILDRENS COLD AND COUGH	LIQUID	N
bromphenir mal/dextrometh HBr	CHILDREN'S COLD AND COUGH	LIQUID	N
bromphenir mal/dextrometh HBr	CHILDREN'S COLD-COUGH RLF DM	LIQUID	N
brompheniram/phenylephrine/DM	LOHIST-DM	LIQUID	N
brompheniram/phenylephrine/DM	CHILDREN'S COLD-COUGH	SOLUTION	N
brompheniram/phenylephrine/DM	COLD-COUGH	SOLUTION	N
brompheniram/phenylephrine/DM	DIMAPHEN DM	SOLUTION	N
brompheniram/phenylephrine/DM	ENDACOF-DM	SOLUTION	N
brompheniram/phenylephrine/DM	RYNEX DM	SOLUTION	N
brompheniramin/pseudoephedrine	RYNEX PSE	LIQUID	N
brompheniramin/pseudoephedrine	BROFED	SYRUP	N
brompheniramine/phenylephrine	CHILDREN'S COLD-ALLERGY	SOLUTION	N
brompheniramine/phenylephrine	CHILD'S DIBROMM COLD-ALLERGY	SOLUTION	N
brompheniramine/phenylephrine	RYNEX PE	SOLUTION	N
brompheniramine/pseudoephed/DM	BROMPHENIRAMINE-PSEUDOEPHED-DM	SYRUP	N
camphor/eucalyptus/menthol	VAPOR STEAM	LIQUID	N

carbinoxamine-pseudoephedrine	COLDEC DS	SYRUP	N
carbinoxamine-pseudoephedrine	COLDEC D	TABLET ER	N
Car-Pen/Car-Pen Tan/PE Tan/PE	CARBATUSS-12	ORAL SUSP	N
cetirizine HCl/pseudoephedrine	ALL DAY ALLERGY-D	TAB ER 12H	N
cetirizine HCl/pseudoephedrine	ALLERGY RELIEF NASAL DECONGEST	TAB ER 12H	N
cetirizine HCl/pseudoephedrine	ALLERGY RELIEF-D	TAB ER 12H	N
cetirizine HCl/pseudoephedrine	CETIRIZINE-PSEUDOEPHEDRINE ER	TAB ER 12H	N
Chlor-Mal/Phenyleph/Methscop	NOREL SD	LIQUID	N
chlorpheniramine/codeine phos	TUXARIN ER	TAB ER 12H	N
chlorpheniramine/dextromethorp	COUGH & RUNNY NOSE	LIQUID	N
chlorpheniramine/dextromethorp	COUGH FORMULA	LIQUID	N
chlorpheniramine/dextromethorp	EXTRA STRENGTH COUGH FORMULA	LIQUID	N
chlorpheniramine/dextromethorp	COUGH-COLD	TABLET	N
chlorpheniramine/dextromethorp	COUGH-COLD HBP	TABLET	N
chlorpheniramine/PE/codeine	CAPCOF	LIQUID	N
chlorpheniramine/phenyleph/DM	CEROSE-DM	LIQUID	N
chlorpheniramine/phenyleph/DM	ED-A-HIST DM	LIQUID	N
chlorpheniramine/phenyleph/DM	NOHIST-DM	LIQUID	N
chlorpheniramine/phenyleph/DM	ED A-HIST DM	TABLET	N
chlorpheniramine/phenylephrine	PREHIST	CAPSULE ER	N
chlorpheniramine/phenylephrine	CENTERGY	DROPS	N
chlorpheniramine/phenylephrine	ED A-HIST	LIQUID	N
chlorpheniramine/phenylephrine	NOHIST-LQ	LIQUID	N
chlorpheniramine/phenylephrine	COLD-ALLERGY PE	TABLET	N
chlorpheniramine/phenylephrine	ED A-HIST	TABLET	N
chlorpheniramine/phenylephrine	SINUS-ALLERGY PE	TABLET	N
chlorpheniramine/pseudoephed	PSEUDO-CHLOR	CAP ER 12H	N
chlorpheniramine/pseudoephed	LOHIST-D	LIQUID	N
chlorpheniramine/pseudoephed	TRIACTING COLD AND ALLERGY	SYRUP	N
chlorpheniramine/pseudoephed	SUDOGEST COLD AND ALLERGY	TABLET	N
desloratadine/pseudoephedrine	CLARINEX-D 12 HOUR	TBMP 12HR	N
dexbromphen/pseudoeph/chlophed	CHLO TUSS	LIQUID	N
dexbromphen/pseudoephedrine/DM	DURATUSS DM	LIQUID	N
dexbromphen/pseudoephedrine/DM	M-END DMX	LIQUID	N
dexbrompheniramin/phenylephrin	ALAHIST PE	TABLET	N
dexbrompheniramine/codeine ph	DURATUSS AC	LIQUID	N
dexbrompheniramine/pseudoephed	CONEX	SOLUTION	N
dexbrompheniramine/pseudoephed	CONEX PEDIATRIC	SOLUTION	N
dexbrompheniramine/pseudoephed	CONEX	TABLET	N

dexbrompheniramine/pseudoephed	DURAHIST	TABLET	N
dexbrompheniramn/chlophedianol	CHLO HIST	SOLUTION	N
dexchlorphen/phenylephrine/DM	WESTUSSIN DM	SYRUP	N
dexchlorphenir/pse/chlophedian	VANACOF	LIQUID	N
dexchlorpheniram/chlophedianol	VANACOF-2	LIQUID	N
dexchlorpheniram/phenylephrine	RYMED	TABLET	N
dexchlorpheniramine/DM	POLY-HIST DM	LIQUID	N
dextromethorphan HBr	DEXTROMETHORPHAN HBR	CAPSULE	N
dextromethorphan HBr	LONG-ACTING COUGH	CAPSULE	N
dextromethorphan HBr	COUGH RELIEF	LIQUID	N
dextromethorphan HBr	TUSSIN LONG-ACTING	LIQUID	N
dextromethorphan HBr	DIABE-TUSS DM	SYRUP	N
dextromethorphan HBr	TUSSIN MAXIMUM STRENGTH	SYRUP	N
dextromethorphan HBr	TUSSIN PEDIATRIC	SYRUP	N
dextromethorphan polistirex	12-HOUR COUGH RELIEF	SUS ER 12H	N
dextromethorphan polistirex	CHILDREN'S COUGH DM ER	SUS ER 12H	N
dextromethorphan polistirex	COUGH DM ER	SUS ER 12H	N
dextromethorphan polistirex	DEXTROMETHORPHAN POLISTIREX	SUS ER 12H	N
dextromethorphan/pseudoephed	COUGH FORMULA D	ELIXIR	N
dextromethorphan/triprolidine	ENDAL	SOLUTION	N
dextromethorphn/acetaminoph/cp	FLU HBP	TABLET	N
diphenhyd/phenyleph/acetaminop	NIGHTTIME SEVERE COUGH-COLD	POWD PACK	N
DM/acetaminophen/doxylamine	NIGHTTIME COLD-FLU	CAPSULE	N
DM/acetaminophen/doxylamine	NIGHTTIME COLD-FLU	CAPSULE	N
DM/acetaminophen/doxylamine	NIGHTTIME COLD-FLU RELIEF	CAPSULE	N
DM/acetaminophen/doxylamine	ALL-NITE COLD-FLU RELIEF	LIQUID	N
DM/acetaminophen/doxylamine	NIGHTTIME COLD-FLU	LIQUID	N
DM/acetaminophen/doxylamine	NIGHTTIME COLD-FLU	LIQUID	N
DM/acetaminophen/doxylamine	NIGHTTIME COLD-FLU RELIEF	LIQUID	N
DM/acetaminophen/doxylamine	NITE TIME COLD-FLU	LIQUID	N
DM/pe/acetaminophen/chlorphenr	TUSSIN COUGH-COLD-FLU	LIQUID	N
DM/pe/acetaminophen/chlorphenr	COLD MULTI-SYMPTOM	TABLET	N
DM/pe/acetaminophen/chlorphenr	COLD MAX DAY-NIGHT	TABLET SEQ	N
DM/PE/acetaminophen/doxylamine	DAYTIME-NIGHTTIME COLD-FLU	CAP SEQ	N
DM/PE/acetaminophen/doxylamine	NIGHTTIME MAX COLD-FLU	CAPSULE	N
DM/PE/acetaminophen/doxylamine	NIGHTTIME SEVERE COLD-FLU	LIQUID	N
DM/PE/acetaminophen/doxylamine	SEVERE COLD-FLU NIGHTTIME	LIQUID	N
DM/p-ephed/acetaminoph/doxylam	NIGHTTIME COLD	CAPSULE	N
DM/p-ephed/acetaminoph/doxylam	NITE TIME COLD-FLU	CAPSULE	N

DM/p-ephed/acetaminoph/doxylam	NITE TIME	LIQUID	N
DM/pseudoephed/acetaminoph/cpm	FLU/COLD/COUGH NIGHTTIME	PACKET	N
DM/pseudoephed/acetaminoph/cpm	FLU/COUGH/COLD	POWD PACK	N
DM/pseudoephed/acetaminoph/cpm	MULTI-SYMPTOM COLD-COUGH	TABLET	N
DM/pseudoephed/acetaminophen	PSEUDOEPHEDRINE SEVERE COLD	TABLET	N
d-methorphan/PE/acetaminophen	DAY TIME COLD-FLU	CAPSULE	N
d-methorphan/PE/acetaminophen	DAYTIME COLD-FLU RELIEF	CAPSULE	N
d-methorphan/PE/acetaminophen	DAY TIME COLD-FLU	LIQUID	N
d-methorphan/PE/acetaminophen	DAYTIME COLD-FLU	LIQUID	N
d-methorphan/PE/acetaminophen	DAYTIME COLD-FLU RELIEF	LIQUID	N
d-methorphan/PE/acetaminophen	DAY MULTI-SYMP FLU-SEVERE COLD	POWD PACK	N
d-methorphan/PE/acetaminophen	COLD MAX DAYTIME	TABLET	N
d-methorphan/PE/acetaminophen	MAPAP COLD FORMULA	TABLET	N
d-methorphan/pe/dexbromphenir	BRANTUSSIN DM	LIQUID	N
d-methorphan/pe/dexbromphenir	WESTUSSIN DM NF	LIQUID	N
d-methorphan/pe/dexbromphenir	ALAHIST CF	TABLET	N
doxylamine/phenylephrine HCl	POLY HIST FORTE	TABLET	N
eucalyptus oil/menthol	COUGH DROPS	LOZENGE	N
fexofenadine/pseudoephedrine	ALLERGY-CONGESTION-D ER	TAB ER 12H	N
fexofenadine/pseudoephedrine	FEXOFENADINE-PSE ER	TAB ER 12H	N
fexofenadine/pseudoephedrine	FEXOFENADINE-PSE ER	TAB ER 24H	N
guaifen/dextromethorphan/PE	TUSNEL-DM PEDIATRIC	DROPS	N
guaifen/dextromethorphan/PE	ADULT TUSSIN CF	LIQUID	N
guaifen/dextromethorphan/PE	CHILDREN'S MULTI-SYMPTOM COLD	LIQUID	N
guaifen/dextromethorphan/PE	CHILD'S MUCUS RELIEF M-S COLD	LIQUID	N
guaifen/dextromethorphan/PE	DEXTROMETHORPH-GUAIF-PHENYLEPH	LIQUID	N
guaifen/dextromethorphan/PE	MUCUS RELIEF CONGEST-COUGH	LIQUID	N
guaifen/dextromethorphan/PE	ROBAFEN CF	LIQUID	N
guaifen/dextromethorphan/PE	TUSNEL DM	LIQUID	N
guaifen/dextromethorphan/PE	TUSNEL DM PEDIATRIC	LIQUID	N
guaifen/dextromethorphan/PE	TUSSIN CF	LIQUID	N
guaifen/dextromethorphan/PE	VANACOF DM	LIQUID	N
guaifen/dextromethorphan/PE	VANACOF DMX	LIQUID	N
guaifen/dextromethorphan/PE	AQUANAZ	TABLET	N
guaifen/dextromethorphan/PE	DECONEX DMX	TABLET	N
guaifen/dextromethorphan/PE	VANATAB DM	TABLET	N
guaifen/phenyleph/acetaminophn	COLD HEAD CONGEST SEVERE	TABLET	N
guaifen/phenyleph/acetaminophn	HEAD CONGESTION-MUCUS	TABLET	N
guaifen/phenyleph/acetaminophn	HEAD CONGESTION-MUCUS PE	TABLET	N

guaifen/phenyleph/acetaminophn	MUCUS RELIEF SINUS CONG PAIN	TABLET	N
guaifen/phenyleph/acetaminophn	SINUS CONGESTION-PAIN SEVERE	TABLET	N
guaifen/phenyleph/acetaminophn	SINUS SEVERE	TABLET	N
guaifenesin	ADULT TUSSIN	LIQUID	N
guaifenesin	CHEST CONGESTION RELIEF	LIQUID	N
guaifenesin	GUAIFENESIN	LIQUID	N
guaifenesin	IOPHEN-NR	LIQUID	N
guaifenesin	MUCOLYTE	LIQUID	N
guaifenesin	MUCUS-CHEST CONGESTION	LIQUID	N
guaifenesin	TUSNEL-EX	LIQUID	N
guaifenesin	TUSSIN	LIQUID	N
guaifenesin	TUSSIN MUCUS-CHEST CONGESTION	LIQUID	N
guaifenesin	GUAIFENESIN	TABLET	N
guaifenesin/dextromethorphan	VANACOF XP	LIQUID	N
guaifenesin/DM/acetaminophen	TUSSIN CF SEVERE MULTI-SYMPTOM	LIQUID	N
guaifenesin/DM/pseudoephedrine	DECONGESTANT D	LIQUID	N
guaifenesin/DM/pseudoephedrine	ROLATUSS	LIQUID	N
guaifenesin/DM/pseudoephedrine	TUSNEL PEDIATRIC	LIQUID	N
guaifenesin/DM/pseudoephedrine	TUSNEL	SOLUTION	N
guaifenesin/DM/pseudoephedrine	COLDMIST DM	SYRUP	N
guaifenesin/DM/pseudoephedrine	CAPMIST DM	TABLET	N
guaifenesin/DM/pseudoephedrine	POLY-VENT DM	TABLET	N
guaifenesin/DM/pseudoephedrine	TUSNEL	TABLET	N
guaifenesin/phenylephrine HCl	TUSNEL PEDIATRIC	DROPS	N
guaifenesin/phenylephrine HCl	ED BRON GP	LIQUID	N
guaifenesin/phenylephrine HCl	CHEST CONGESTION RELIEF PE	TABLET	N
guaifenesin/phenylephrine HCl	DECONEX IR	TABLET	N
guaifenesin/phenylephrine HCl	DURAVENT PE	TABLET	N
guaifenesin/phenylephrine HCl	MUCUS RELIEF PE	TABLET	N
guaifenesin/phenylephrine HCl	PHENYLEPHRINE GG	TABLET ER	N
guaifenesin/pseudoephedrne HCl	TUSSIN SEVERE CONGESTION	CAPSULE	N
guaifenesin/pseudoephedrne HCl	GUAIFENESIN W/PSEUDOEPHEDRINE	CAPSULE ER	N
guaifenesin/pseudoephedrne HCl	COLDMIST S	SYRUP	N
guaifenesin/pseudoephedrne HCl	COLDMIST LA	TAB ER 12H	N
guaifenesin/pseudoephedrne HCl	GUAIFEN PSE	TAB ER 12H	N
guaifenesin/pseudoephedrne HCl	GUAIFENESIN W/PSEUDOEPHEDRINE	TAB ER 12H	N
guaifenesin/pseudoephedrne HCl	GUAIFENESIN-PSEUDOEPHEDRINE ER	TAB ER 12H	N
guaifenesin/pseudoephedrne HCl	GUAIFEN-PSE	TAB ER 12H	N
guaifenesin/pseudoephedrne HCl	MUCUS D	TAB ER 12H	N

guaifenesin/pseudoephedrne HCl	MUCUS RELIEF D	TAB ER 12H	N
guaifenesin/pseudoephedrne HCl	MUCUS RELIEF D ER	TAB ER 12H	N
guaifenesin/pseudoephedrne HCl	PSE 120	TAB ER 12H	N
guaifenesin/pseudoephedrne HCl	PSE 60	TAB ER 12H	N
guaifenesin/pseudoephedrne HCl	PSEUDO GG TR	TAB ER 12H	N
guaifenesin/pseudoephedrne HCl	POLY-VENT IR	TABLET	N
hydrocodone bit/homatrop me-br	HYCODAN	SOLUTION	N
hydrocodone bit/homatrop me-br	HYDROCODONE-HOMATROPINE MBR	SOLUTION	N
hydrocodone bit/homatrop me-br	HYDROMET	SOLUTION	N
hydrocodone bit/homatrop me-br	HYCODAN	TABLET	N
hydrocodone bit/homatrop me-br	HYDROCODONE-HOMATROPINE MBR	TABLET	N
hydrocodone/chlorphen p-stirex	HYDROCODONE-CHLORPHENIRAMNE ER	SUS ER 12H	N
hydrocodone/cpm/pseudoephed	KG-TUSSIN	SYRUP	N
hydrocodone/cpm/pseudoephed	Q-V TUSSIN	SYRUP	N
hydrocodone/guaifenesin	HYDROCODONE W/GUAIFENESIN	SYRUP	N
hydrocodone/guaifenesin	MEDCODIN	SYRUP	N
hydrocodone/guaifenesin	VI-Q-TUSS	SYRUP	N
hydrocodone/pseudoephed/guaif	DRITUSS HD	ELIXIR	N
hydrocodone/pseudoephed/guaif	MEDTUSS HD	ELIXIR	N
hydrocodone/pseudoephed/guaif	KG-TUSS HD	SOLUTION	N
ibuprofen/pseudoephedrine HCl	COLD-SINUS RELIEF	CAPSULE	N
ibuprofen/pseudoephedrine HCl	IBUPROFEN COLD	ORAL SUSP	N
ibuprofen/pseudoephedrine HCl	IBUPROFEN COLD-SINUS	TABLET	N
loratadine/pseudoephedrine	ALLERGY D-12 HOUR	TAB ER 12H	N
loratadine/pseudoephedrine	ALLERGY RELIEF D-12	TAB ER 12H	N
loratadine/pseudoephedrine	ALLERGY-CONGESTION RELIEF 12HR	TAB ER 12H	N
loratadine/pseudoephedrine	CLARITIN-D 12 HOUR	TAB ER 12H	N
loratadine/pseudoephedrine	LORATADINE-D	TAB ER 12H	N
loratadine/pseudoephedrine	ALLERGY D-24 HOUR	TAB ER 24H	N
loratadine/pseudoephedrine	ALLERGY RELIEF D-24HR	TAB ER 24H	N
loratadine/pseudoephedrine	ALLERGY RELIEF-NASAL DECONGEST	TAB ER 24H	N
loratadine/pseudoephedrine	ALLERGY-CONGESTION RELIEF	TAB ER 24H	N
loratadine/pseudoephedrine	LORATA-DINE D	TAB ER 24H	N
loratadine/pseudoephedrine	LORATADINE-D	TAB ER 24H	N
menthol	COUGH DROPS	LOZENGE	N
naproxen sodium/pseudoephedrin	ALL DAY SINUS AND COLD-D	TAB ER 12H	N
oxymetazoline HCl	NEO-SYNEPHRINE 12 HOUR	DROPS	N
oxymetazoline HCl	NASAL DECONGESTANT	MIST	N
oxymetazoline HCl	NASAL MIST	MIST	N

oxymetazoline HCl	NASAL SPRAY	MIST	N
oxymetazoline HCl	NASAL DECONGESTANT	SPRAY	N
oxymetazoline HCl	NASAL SPRAY	SPRAY	N
oxymetazoline HCl	NASAL SPRAY ORIGINAL	SPRAY	N
oxymetazoline HCl	NO DRIP	SPRAY	N
oxymetazoline HCl	OXYMETAZOLINE HCL	SPRAY	N
PE/PE & Pyrilamine Tannate/CPM	PHENA-S 12	ORAL SUSP	N
pheniramine/phenylephrine/DM	ALAHIST DM	LIQUID	N
phenyleph/hydrocodon/pyrilamin	CODITUSS DH	SYRUP	N
phenylephrine HCl	ALCONEFRIN 12	DROPS	N
phenylephrine HCl	ALCONEFRIN 25	DROPS	N
phenylephrine HCl	ALCONEFRIN 50	DROPS	N
phenylephrine HCl	NEO-SYNEPHRINE	JELLY (G)	N
phenylephrine HCl	NASAL FOUR	SPRAY	N
phenylephrine HCl	NASAL SPRAY	SPRAY	N
phenylephrine HCl	NEO-SYNEPHRINE	SPRAY	N
phenylephrine HCl	SINUS RELIEF	SPRAY	N
phenylephrine HCl	NEO-SYNEPHRINE	SPRAY/PUMP	N
phenylephrine HCl	NASAL DECONGESTANT PE	TABLET	N
phenylephrine HCl	SINUS CONGESTION PE	TABLET	N
phenylephrine HCl/acetaminophn	SINUS CONGESTION-PAIN	TABLET	N
phenylephrine HCl/acetaminophn	SINUS MAXIMUM STRENGTH	TABLET	N
phenylephrine HCl/acetaminophn	SINUS PRESSURE-PAIN	TABLET	N
phenylephrine HCl/acetaminophn	SINUS-HEADACHE	TABLET	N
phenylephrine HCl/pheniramine	ALAHIST D	TABLET	N
phenylephrine HCl/prometh HCl	PROMETHAZINE-PHENYLEPHRINE HCL	SYRUP	N
phenylephrine/acetaminophn/cpm	ALLERGY MULTI-SYMPTOM	TABLET	N
phenylephrine/acetaminophn/cpm	NOREL AD	TABLET	N
phenylephrine/DM/acetaminop/GG	DAYTIME MAX COLD-FLU	CAPSULE	N
phenylephrine/DM/acetaminop/GG	COLD MULTI-SYMPTOM DAYTIME	LIQUID	N
phenylephrine/DM/acetaminop/GG	DAYTIME SEVERE COLD-FLU	LIQUID	N
phenylephrine/DM/acetaminop/GG	SEVERE DAYTIME COLD-FLU	LIQUID	N
phenylephrine/DM/acetaminop/GG	TUSSIN CF MAX SEVERE M-S COLD	LIQUID	N
phenylephrine/DM/acetaminop/GG	COLD-FLU SEVERE	TABLET	N
phenylephrine/DM/acetaminop/GG	DAYTIME SEVERE COLD-FLU RELIEF	TABLET	N
phenylephrine/DM/acetaminop/GG	MUCUS RELIEF COLD-FLU	TABLET	N
phenylephrine/DM/acetaminop/GG	MUCUS RELIEF SINUS PAIN COUGH	TABLET	N
phenylephrine/DM/acetaminop/GG	MUCUS RLF COLD-FLU-SORE THROAT	TABLET	N
phenylephrine/DM/acetaminop/GG	SEVERE COLD-FLU	TABLET	N

phenylephrine/hydrocodone/cpm	DURADAL HD	SYRUP	N
phenylephrine/hydrocodone/cpm	DURADAL HD PLUS	SYRUP	N
phenylephrine/hydrocodone/cpm	H-C TUSSIVE	SYRUP	N
phenylephrine/hydrocodone/cpm	KG-DAL HD	SYRUP	N
phenylephrine/hydrocodone/cpm	KG-DAL HD PLUS	SYRUP	N
phenylephrine/Pyril Tan/cpm	TRIOTANN	ORAL SUSP	N
phenylephrine/Pyril Tan/cpm	TRIOTANN-S	ORAL SUSP	N
Phenylephrine/Pyrilamine Tan	R-TANNA 12	ORAL SUSP	N
promethazine HCl/codeine	PROMETHAZINE-CODEINE	SYRUP	N
promethazine/dextromethorphan	PROMETHAZINE-DM	SOLUTION	N
pseudoeph/DM/guaifen/acetamin	MULTI-SYMPTOM	LIQUID	N
pseudoeph/DM/guaifen/acetamin	DURAFLU	TABLET	N
pseudoephed/acetaminophen/cpm	CODIMAL	CAPSULE	N
pseudoephed/cod/chlorphenir	PHENYLHISTINE DH	LIQUID	N
pseudoephed/codeine/guaifen	CODAFED	SYRUP	N
pseudoephed/codeine/guaifen	KG-FED	SYRUP	N
pseudoephed/codeine/guaifen	KG-FED PEDIATRIC	SYRUP	N
pseudoephed/codeine/guaifen	PHENYLHISTINE	SYRUP	N
pseudoephed/codeine/guaifen	RYNA-CX	SYRUP	N
pseudoephed/hydrocodone	H-C TUSSIVE-D	SOLUTION	N
pseudoephedrine HCl	12 HOUR NASAL DECONGESTANT	TABLET ER	N
pseudoephedrine HCl	NASAL DECONGESTANT	TABLET ER	N
pseudoephedrine HCl	PSEUDOEPHEDRINE ER	TABLET ER	N
pseudoephedrine HCl	SINUS 12 HOUR	TABLET ER	N
pseudoephedrine HCl	SUDOGEST	TABLET ER	N
pseudoephedrine HCl	SUPHEDRINE 12 HOUR	TABLET ER	N
pseudoephedrine/acetaminophen	MAXIMUM SINUS II	TABLET	N
pseudoephedrine/azatadine	TRINALIN	TABLET ER	N
pyrilamine/chlophedianol	NINJACOF	LIQUID	N
pyrilamine/chlophedianol	VANACOF CP	LIQUID	N
pyrilamine/dextromethorphan hb	CAPRON DM	LIQUID	N
pyrilamine/dextromethorphan hb	CAPRON MAX	LIQUID	N
pyrilamine/dextromethorphan hb	PYRILAMINE-DEXTROMETHORPHAN	LIQUID	N
pyrilamine/dextromethorphan hb	CAPRON DMT	TABLET	N
pyrilamine/phenylephrine/DM	CODIMAL DM	LIQUID	N
pyrilamine/phenylephrine/DM	POLYTUSSIN DM	LIQUID	N
pyrilamine/pseudoeph/chlophed	NINJACOF-D	LIQUID	N
thonzylamine/phenylephrine	NASOPEN PE	LIQUID	N
thonzylamine/phenylephrine/DM	POLY-HIST DM	LIQUID	N

triprolidine/phenylephrine/DM	HISTEX-DM	LIQUID	N
triprolidine/phenylephrine/DM	TRIPONEL	LIQUID	N
triprolidine/pseudoephedrin/DM	HISTEX-DM	LIQUID	N
triprolidine/pseudoephedrin/DM	TRIPONEL	LIQUID	N
triprolidine/pseudoephedrine	APHEDRID	TABLET	N
triprolidine/pseudoephedrine	APRODINE	TABLET	N
triprolidine/pseudoephedrine	COLD, ALLERGY & SINUS	TABLET	N
cpm/PE/DM/acetaminophen/guaifn	COLD-FLU SEVERE DAY-NIGHT	TABLET SEQ	
guaifenesin/dextromethorphan	COUGH DM	SYRUP	
menthol	COUGH DROPS	LOZENGE	
pectin	THROAT DROPS	LOZENGE	
phenylephrine HCl	BIORPHEN	AMPUL	
phenylephrine HCl	PHENYLEPHRINE HCL	AMPUL	
phenylephrine HCl	BIORPHEN	VIAL	
phenylephrine HCl	IMMPHENTIV	VIAL	
pyrilamine mal/pseudoephedrine	HISTANAZ	TABLET	

Appendix 2: New Comparative Clinical Trials

A total of 57 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Appendix 3: Medline Search Strategy
Ovid MEDLINE(R) ALL <1946 to August 07, 2026>

1	Codeine/tu [Therapeutic Use]	1130
2	Dextromethorphan/tu [Therapeutic Use]	421
3	Pseudoephedrine/tu [Therapeutic Use]	57
4	benzonatate.mp. or Antitussive Agents/	3155
5	Common Cold/th [Therapy]	387
6	guiafenesin.mp.	3
7	Brompheniramine/tu [Therapeutic Use]	91
8	Dextroamphetamine/tu [Therapeutic Use]	956
9	Phenylephrine/tu [Therapeutic Use]	861
10	Ephedrine/ or carbinoxamine.mp. or Histamine Antagonists/ or Nasal Decongestants/	13611
11	Chlorpheniramine/tu [Therapeutic Use]	451
12	Cetirizine/tu [Therapeutic Use]	622
13	dexbrompheniramine.mp.	46

14	Doxylamine/tu [Therapeutic Use]	101
15	Loratadine/ or desloratadine.mp.	1661
16	fexofenadine.mp. or Histamine H1 Antagonists/ or Histamine H1 Antagonists, Non-Sedating/	17451
17	Hydrocodone/tu [Therapeutic Use]	275
18	homatropine.mp.	321
19	Oxymetazoline/tu [Therapeutic Use]	126
20	Pheniramine/tu [Therapeutic Use]	44
21	Promethazine/tu [Therapeutic Use]	665
22	Pyrilamine/tu [Therapeutic Use]	61
23	thonzylamine.mp.	27
24	Triprolidine/tu [Therapeutic Use]	66
25	Antitussive Agents/tu [Therapeutic Use]	1085
26	Expectorants/tu [Therapeutic Use]	1487
27	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	39743
28	Cough/th [Therapy]	1354
29	Common Cold/th [Therapy]	387
30	28 or 29	1727
31	27 and 30	603
32	limit 31 to (english language and humans and yr="2016 -Current")	57

Appendix 4: Key Inclusion Criteria

Population	Adults and Children
Intervention	Medications presented in Appendix 1
Comparator	Medications presented in Appendix 1
Outcomes	Resolve cough and cold symptoms, adverse effects
Timing	1 week to 24 weeks
Setting	Outpatient