

Review Article

Darwinizing cough and its modern triggers: newer management approach to cough associated with allergy, asthma, upper airway cough syndrome

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ABSTRACT

Cough is a crucial defensive reflex of the respiratory system, essential for expelling irritants and secretions. It can present as acute or chronic cough, often exacerbated by allergic conditions such as allergic rhinitis (AR) and upper airway cough syndrome (UACS). Effective management of cough focuses on addressing the underlying aetiology while simultaneously offering symptomatic relief. Fixed-dose combinations (FDCs) are becoming an increasingly effective approach to enhance patient adherence and streamline treatment. Non-sedating antihistamines, like Bilastine, have demonstrated efficacy in alleviating AR and associated cough, making them an ideal choice for cough syrup formulations. The combination of Bilastine with Dextromethorphan and Phenylephrine provides a suitable treatment option for cough related including UACS, asthma, and respiratory allergies. This formulation is particularly well-suited for pediatric patients aged six and older, offering effective relief from throat irritation without sedation, being well-tolerated, and minimizing risks of cardiovascular and hepatotoxic effects. Pulmonologist, Otolaryngologist, Physician and paediatrician opinions have been gathered to review current practices and provide insights into effective management strategies. This review delves into the pathophysiology and clinical significance of cough, particularly in relation to respiratory allergies, highlighting its complexities and the need for ongoing research to refine treatment strategies and improve patient outcomes.

Keywords: Cough, Allergic rhinitis, Pathophysiology, Management strategies, Fixed-dose combinations, Patient-reported outcomes, Bilastine

INTRODUCTION

Cough is a common symptom in both children and adults, classified as acute (lasting up to 3–4 weeks) or chronic (persisting over 4–8 weeks).¹ Acute cough is typically caused by viral upper respiratory infections, while causes

of chronic cough vary by age. In children, it is commonly associated with upper respiratory infections, asthma-like symptoms, and post-infectious cough, often influenced by allergic factors, especially in those with a family history of asthma or allergies.² In adults, risk factors for chronic cough include smoking, asthma, chronic obstructive

pulmonary disease (COPD), upper airway cough syndrome (UACS), gastroesophageal reflux disease (GERD), allergic rhinitis (AR), and obesity. Chronic cough is associated with substantial healthcare utilization, especially in older adults and those with comorbidities.^{3,4}

AR is a common trigger for cough, often characterized by symptoms like a loud, barking sound and sneezing, typically associated with hay fever. The cough is typically paroxysmal, non-productive, and may last for minutes to days. Symptoms include rhinorrhoea, nasal itching, nasal congestion, paranasal pain, postnasal drip, and sneezing, which are reversible with or without treatment. UACS, formerly postnasal drip syndrome, is a common cause of chronic cough due to hypersensitivity in the upper airways from chronic inflammation, often related to AR.^{5,6} UACS frequently overlaps with allergic conditions, with many chronic cough cases linked to UACS triggered by allergies and upper respiratory disorders, such as nasal and sinus diseases.⁷

Antihistamines and decongestants help reduce nasal secretions and congestion, while Antitussives relieve cough. These formulations often combine decongestants, antihistamines, antitussives, expectorants, and/or acetaminophen. First-generation Antihistamines can cause sedation by crossing the blood-brain barrier, potentially impairing daily activities and increasing accident risk.^{9,10} Bilastine, a non-sedating H1-antihistamine, effectively treats allergic conditions across all ages, providing rapid symptom relief for AR and Urticaria with prolonged action. Dextromethorphan Hydrobromide (DM) is a cough suppressant for unproductive cough, while Phenylephrine, a selective adrenergic receptor agonist, serves as an effective nasal decongestant by constricting nasal mucosal blood vessels, thereby relieving congestion.^{5,6}

This manuscript explores the multifactorial risk factors, allergic triggers, mechanisms, and management complexities of cough, focusing on current treatment strategies. It emphasizes the role of fixed-dose combinations (FDCs), especially containing Bilastine, in simplifying therapy and enhancing outcomes, offering insights into innovative solutions for effective cough management.

EPIDEMIOLOGY OF COUGH

Cough impacts 9.6% of the global population, with a prevalence of 5-10% in India.¹² Second most common reason for primary care visits in India, making up 30% of cough is a prevalent global health issue, affecting approximately 9.6% of the population, with a 5-10% prevalence in India. Acute cough impacts about 9–64% of individuals, while chronic cough varies regionally, affecting 3% in rural India and 24% in the U.S., with a global impact on 11.8% of adults.¹³⁻¹⁵

A survey of 5,115 participants revealed that 57% experienced dry cough with minimal sputum, 24% had a

productive cough with thick mucus, 16% had productive cough without significant difficulty, and 3% presented with bronchospastic cough.¹⁶ In Figure 1. A study of 7,400 primary care physicians and 204,912 patients found respiratory symptoms in over half of the cases, with cough being the second most common symptom after fever. Diagnoses for cough included upper respiratory tract infections (12.2%), lower respiratory tract infections (8.1%), asthma (7.4%), COPD (4%), tuberculosis (2.5%), and congestive heart failure (0.5%) (Figure 1).¹⁷

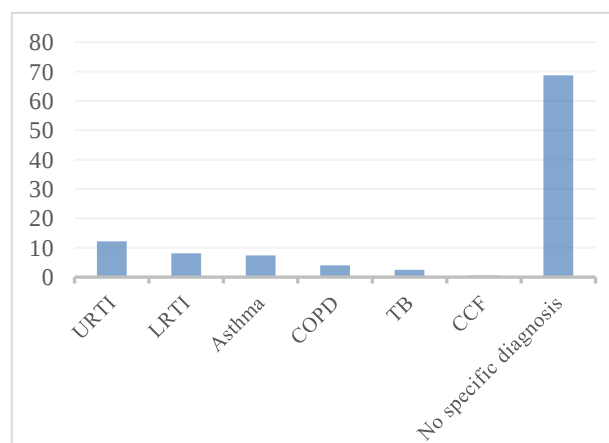


Figure 1: Distribution of conclusive diagnoses among patients presenting with cough in primary care setting in India.¹⁷

URT I Upper respiratory tract infection, LRT I: Lower respiratory tract infection, COPD: Chronic obstructive pulmonary disease, TB: Tuberculosis, CCF: Congestive cardiac failure.

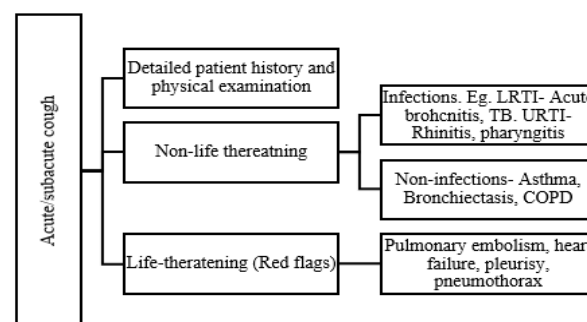


Figure 2: Approach of cough management at the primary care level.¹⁶

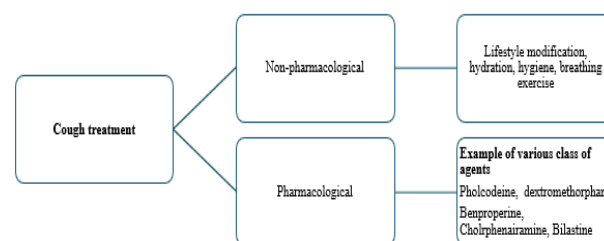


Figure 3: Approach for cough management: Non-pharmacological and pharmacological treatment.³⁶

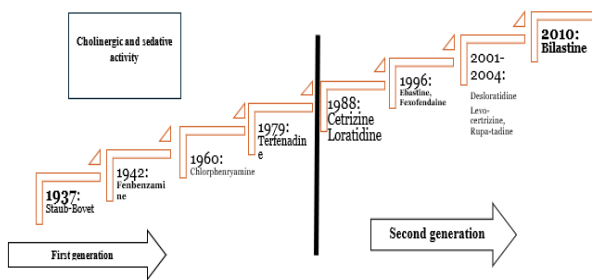


Figure 4: Evolution of antihistamines.³⁹

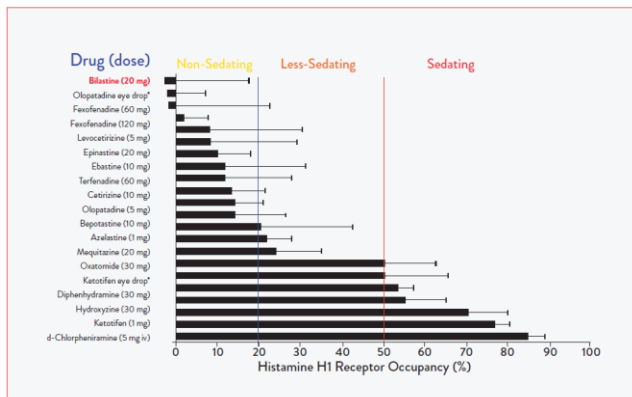


Figure 5: Brain histamine H1 receptor occupancy levels of different antihistamines and their classification based on sedative effects.⁴³

CLASSIFICATION AND COMMON CAUSES OF COUGH IN ADULTS AND PAEDIATRIC POPULATIONS

Cough is classified as acute, subacute, and chronic, each with specific causes. Acute cough primarily results from viral infections; subacute cough often follows post-infection inflammation. Chronic cough is commonly associated with Asthma, GERD, and Upper Airway Cough syndrome. In children, acute cough is usually due to infections, while chronic cough is linked to asthma and environmental factors

In adults, cough is classified by duration: acute (<3 weeks), subacute (3–8 weeks), and chronic (>8 weeks), each with specific causes. Acute cough usually results from viral infections like colds or influenza I but can arise from asthma, COPD exacerbations, or bacterial infections such as pneumonia. Subacute cough often follows viral illness, due to post-infectious inflammation, asthma, COPD, or UACS, with post-infectious cough common in Asia. Chronic cough typically involves UACS, asthma, GERD, or non-asthmatic eosinophilic bronchitis, often with multiple underlying causes (Table 1).¹⁸

Table 2 outlines common cough causes by age group and duration. In toddlers and children, acute cough is primarily due to infections, while recurrent and chronic cases often involve asthma, GERD, and environmental factors like

passive smoke. For adolescents, asthma and GERD are common causes across all durations, with chronic cases additionally linked to smoking and, rarely, tumours.¹⁹

RISK FACTORS AND CLINICO-AETIOLOGICAL PROFILE OF COUGH PATIENTS: ALLERGIES, HYPERSENSITIVITY, AND ENVIRONMENTAL TRIGGERS.

In India, allergies are responsible for 43% of dry cough cases. UACS, asthma, and GERD account for 85% to 100% of chronic cough cases. Allergic rhinitis is the most common comorbidity among cough patients. Occupational exposure to irritants contributes to high recurrence rates of cough. Cough patients often have multiple risk factors, comorbidities, overlapping allergies asthma and infections. Cough is influenced by respiratory allergies, hypersensitivity and high IgE levels.²¹ Cough triggers include chemical, thermal, and mechanical stimuli, notably in chronic cough patients. Cough hypersensitivity syndrome (CHS) involves heightened sensitivity to low-intensity stimuli through central and peripheral neural pathways.²¹⁻²³

In India, allergy causes 43% of dry cough cases, while UACS, asthma, and GERD account for 85–100% of chronic cough. Beyond asthma, allergic cough includes eosinophilic bronchitis, rhinitis, and adenoid hypertrophy. A survey by Rege et al, found AR as the main comorbidity in cough patients, followed by chronic bronchitis, with high recurrence in those exposed to occupational irritants or infections, highlighting the need for targeted UACS and rhinitis management.²⁴⁻²⁸

BEYOND THE SNEEZE: UNCOVERING THE HIDDEN LINK BETWEEN AR, UACS, AND CHRONIC COUGH.

UACS is influenced not only by nasal diseases but also by chronic inflammation in the pharynx or larynx, such as allergic pharyngitis and chronic tonsillitis. These inflammations may result from prolonged exposure to nasal or sinus secretions. Rhinosinus diseases, or external factors like allergens and irritants, can irritate and inflame the nasal airway, leading to postnasal drip that aggravates pharyngeal hypersensitivity. This hypersensitivity exacerbates cough, either as a direct consequence of UACS or due to coexisting conditions like AR, asthma, or asthmatic bronchitis.⁷ UACS-related cough, therefore, can originate from both AR and non-allergic rhinitis (NAR).

A multinational study reported that 47% of AR patients experienced frequent cough, though only 11% sought medical attention. Persistent AR heightens cough severity and sensitivity year-round. AR-related cough is driven by mechanisms such as the rhino-bronchial reflex and UACS, with nasal inflammation amplifying the cough reflex even outside allergy seasons.²⁹ NAR, on the other hand, is more prevalent than AR in UACS-related cough, present in 59% of cases compared to 41% for AR. While both conditions

share symptoms like postnasal drip and congestion, AR is more commonly linked to asthma, whereas NAR frequently involves sinus abnormalities.³¹⁻³⁴

In summary, AR contributes to chronic cough primarily through mechanisms such as UACS and the rhino-bronchial reflex. While NAR is more common in UACS-related cough, AR has stronger associations with asthma, whereas NAR often manifests with sinus-related issues. Further research is needed to clarify the shared and distinct neurogenic mechanisms of AR and NAR

ROLE OF HISTAMINE IN PATHOGENESIS OF UACS AND AR INDUCED COUGH

Histamine, a key inflammatory mediator, stimulates sensory neurons and increases cough sensitivity. It activates nasal sensory nerves, enhancing cough reflexes. Studies show nasal histamine inhalation raises cough sensitivity in both healthy individuals and those with AR, even without triggering a cough. Nasal inflammation, often linked to histamine, correlates with cough in UACS patients. Histamine stimulates the Naso-ciliary nerve, activating brain regions responsible for the cough reflex. Cough sensitivity increases in AR patients during allergy seasons, indicating histamine exacerbates symptoms. Understanding histamine's role is key to targeted therapies.³⁵

TARGETED STRATEGIES FOR EFFECTIVE MANAGEMENT IN PRIMARY CARE

In primary care, a focused examination of cough's underlying causes is crucial for effective targeted treatment (Figure 2). The assessment algorithm begins by classifying patients into productive versus nonproductive and acute versus chronic cough categories, which aids in guiding therapeutic decisions (Figure 3).¹⁶ A variety of strategies can be employed to manage cough symptoms effectively, necessitating a thorough understanding of the underlying causes.³⁶

Indian experts recommend the use of antihistamines, decongestants, antitussives, and expectorants-either individually or in combination-to relieve cough and rhinitis symptoms associated with the common cold and allergies.¹⁶ According to the Indian Environmental Medical Association (EMA), antihistamines are integral to the management of cough resulting from the common cold, UACS, or post-infectious cough, particularly when used alongside other symptomatic treatments.³⁷

ROLE OF ANTIHISTAMINE IN COUGH SUPPRESSION

Antihistamines inhibit cough via peripheral and central mechanisms. First-generation antihistamines have actions on multiple receptors, leading to more side effects, including sedation. Second-generation antihistamines are selective, causing fewer CNS side effects and improving

safety. Guidelines support the use of antihistamines for chronic cough, especially in allergic patients.

In evaluating the role of antihistamines in managing cough, it is important to understand the potential mechanisms by which these agents may exert their effects. Table 3 summarizes the various pathways through which antihistamines could inhibit cough.

Centrally penetrant H1 antihistamines reduce cough by interacting with non-histaminergic receptors, regulating cough reflex sensitivity and mucus production. Sedating antihistamines are effective for managing UACS-related cough.¹² The evolution of antihistamines is depicted in Figure 4.

First-generation antihistamines non-selectively block H1, muscarinic, adrenergic, and dopaminergic receptors, causing adverse effects like cardiovascular, urinary, and gastrointestinal issues. Their high lipophilicity enables CNS side effects, including drowsiness, reduced concentration, and impaired learning and memory.

Second-generation antihistamines selectively target H1 receptors with lower lipophilicity, reducing CNS effects. They effectively manage cough from histamine allergies without sedative side effects, offering improved safety. Their minimal CNS penetration and lack of interaction with adrenergic, muscarinic, and dopaminergic receptors reduce adverse effects compared to first-generation antihistamines.³⁹

ROLE & SCOPE OF BILASTINE COMBINATION IN COUGH MANAGEMENT

Bilastine is a non-sedating H1-antihistamine. It has a rapid onset, long duration of action, and a favorable safety profile with minimal sedation, even in people who require precision and complex activities. Well-tolerated in children aged 2 to <12 years, showing safety comparable to placebo. Significantly improves symptom scores and quality of life, outperforming some antihistamines like fexofenadine. Minimal drug-drug interactions allow safe co-administration with other medications. Taking Bilastine with food does not significantly impact its efficacy. Promising in managing chronic cough associated with upper airway conditions.

Bilastine is a non-sedating H1-antihistamine effective for AR and Urticaria across all ages. It offers rapid relief with long-lasting effects, requires no dosage adjustments, and has minimal drug interactions. Approved in Europe since 2010, it is used in 120 countries. Clinical trials show its efficacy, excellent tolerability, and significant quality of life improvements for patients with AR or chronic urticaria.⁴¹

Bilastine (20 mg) has a favourable safety profile with minimal sedation and CNS side effects, due to low brain H1-receptor occupancy, comparable to placebo and significantly lower than hydroxyzine (25 mg). Its limited

ability to cross the blood-brain barrier reduces CNS-related adverse effects, making it a preferred choice for allergic conditions. The dose equivalence of bilastine 3.3 mg/5 ml can be correlated as follows: in adults, 10 ml administered three times daily (6.6 mg×3, equivalent to 20 mg/day) aligns with the recommended adult dose, and in

children over 6 years, 5 ml administered three times daily (3.3 mg×3, equivalent to 10 mg/day) aligns with the approved paediatric dose. This flexibility in dosing supports effective symptom control while maintaining a favourable safety profile across age groups.

Table 1: Most common causes of cough in adults.¹⁸

Acute cough	Subacute cough	Chronic cough
Respiratory infections (Viral cause -most likely)	Postinfectious cough	UACS
Exacerbation of underlying disease like Asthma and COPD	Exacerbation of underlying disease such as asthma and COPD	Asthma, GERD
Pneumonia	UACS	Non-asthmatic eosinophilic bronchitis

Table 2: Causes of cough in children and adolescents.¹⁹

	Acute	Recurrent	Chronic
Toddlers	Infections, foreign matter	Asthma, GERD, Aspiration, Second-hand smoke,	Asthma, GERD, Aspiration, pertussis, passive smoke, post infection
Children	Infection, foreign matter	Asthma, GERD, second-hand smoke	Asthma, GERD, pertussis, mycoplasma, passive smoke, obstructive sleep apnoea
Adolescent	Infections	Asthma, GERD, aspiration	Asthma, GERD, smoking, pertussis, aspiration, tumour

Table 3: Mechanisms of antihistamines in suppressing cough from UACS.³⁸

Mechanisms of antihistamines	
Peripheral direct	Histamine receptors on sensory afferent nerves may stimulate cough production.
Peripheral indirect	Histamine-induced nasal mucus secretion can stimulate pharyngeal or laryngeal mechanoreceptors, triggering a cough response, possibly influenced by cholinergic mechanisms as well.
Central Direct	CNS H1 receptors may promote cough, requiring H1 antihistamines that penetrate the brain and target nonhistaminergic receptors to effectively reduce cough excitability.
Central Indirect	CNS H1 receptors regulate nasal mucus secretion, requiring centrally penetrant antihistamines that bind to these receptors, induce sedation, and reduce cough excitability.

Table 4: Comparison of first-generation vs second generation antihistamines.⁴⁰

Characteristic	Bilastine	Cetirizine	Ebastine	Fexofenadine	Levocetirizine	Loratidine
H1receptor selectivity	+++	+	++	+	++	+
Indicated for AR	Yes	Yes	Yes	Yes	Yes	Yes
Paediatric indication	No	Children aged 6-12 yrs	Children aged ≥ 2 years	Children aged ≥ 3 years	Children aged ≥ 2 years	Children aged ≥ 2 years
Dosage adjustment in renal impairment	No	Yes	Caution	No	Yes	No
Dosage adjustment in hepatic impairment	No	Yes	Caution	No	Yes	Yes

Continued.

Characteristic	Bilastine	Cetirizine	Ebastine	Fexofenadine	Levocetirizine	Loratidine
Dosage adjustment in elderly	No	No	No	No	Yes	No
Contraindications	No	Severe renal impairment	Severe hepatic impairment	No	Severe renal impairment	No
Number of ARIA-recommended antihistamine properties	10	6	6.5	9.5	6.5	6.5

Non sedative properties of bilastine

Among non-sedating antihistamines, Bilastine and Fexofenadine are categorized as "non-brain-penetrating" due to their minimal H₁-receptor occupancy, which is close to zero. Figure 5 demonstrates the brain histamine H₁-receptor occupancy of first- and second-generation antihistamine following oral administration.⁴² Bilastine can be the suitable option for pilots and for individuals performing complex tasks, including driving. Approved by the Japanese Ministry of Land, Infrastructure, Transport, and Tourism, it shows no significant impact on sleepiness, vigilance, or task performance, even at higher doses. In simulated altitude studies, Bilastine performed similarly to non-sedating antihistamines like fexofenadine and desloratadine, while sedating agents like hydroxyzine impaired cognitive function and task performance.⁴⁶ Reményi Á et al, conducted a randomized, double-blind study comparing Bilastine 20 mg, cetirizine 10 mg, and placebo in 33 individuals at ground level and 4,000 m altitude.

Bilastine showed no cognitive impairment at either altitude, while cetirizine increased errors and worsened attention at altitude. The study concluded that Bilastine is the preferred antihistamine for tasks requiring sustained attention in hypobaric conditions. On-road driving tests and high-speed formula-1 simulator studies showed Bilastine (20 mg and 40 mg) had no impact on driving performance, including lateral position or reaction times, compared to placebo, even under challenging conditions. Bilastine's minimal blood-brain barrier penetration reduces sedation and psychomotor impairment, making it suitable for higher doses. However, patients should assess their response before engaging in attention-demanding tasks, as rare drowsiness may occur.⁴⁶

Clinical efficacy and safety of Bilastine

A systematic review found Bilastine superior to placebo in improving total symptom scores, nasal and non-nasal symptoms, and QoL in AR patients. In a comparative study, bilastine demonstrated greater effectiveness than fexofenadine in reducing Total Nasal Symptom Scores (TNSS) in AR patients.⁴⁵

Two randomized crossover studies showed Bilastine 20 mg had a rapid onset and long duration in AR patients. In European grass pollen exposure, Bilastine matched Cetirizine 10 mg and outlasted Fexofenadine 120 mg. In Japanese cedar pollen exposure, Bilastine had a faster onset than Fexofenadine 60 mg. Four clinical trials evaluated once daily Bilastine 20 mg over 2 to 4 weeks in adults and adolescents with seasonal allergic rhinitis (SAR) and persistent allergic rhinitis (PAR). These studies demonstrated that Bilastine significantly reduced total symptom scores (TSS) compared to placebo, and was as effective as desloratadine 5 mg, cetirizine 10 mg, or fexofenadine 60 mg in managing symptoms.⁴⁷⁻⁵⁰ Pooled analyses further confirmed Bilastine's efficacy in alleviating nasal obstruction and ocular symptoms associated with allergic rhino-conjunctivitis.^{51,52}

Bilastine 20 mg daily improved QoL more than placebo, similar to loratadine 10 mg and desloratadine 5 mg, as measured by the rhino-conjunctivitis QoL Questionnaire. A 52-week study showed Bilastine maintained its effectiveness and improved QoL year-round.⁴⁶ Bilastine's adverse event rate was similar to placebo, with common events including headache, somnolence, and fatigue. It caused less somnolence (1.8% vs 7.5%) and fatigue (0.4% vs 4.8%) compared to cetirizine. Long-term studies confirm Bilastine's tolerability and suitability for ongoing antihistamine therapy.⁴⁶

In a phase 3, multicentre, double-blind study, Novak Z et al, assessed the safety and tolerability of Bilastine 10 mg in children aged 2 to <12 years with allergic Rhino-conjunctivitis and chronic Urticaria over 12 weeks. No significant differences were found between Bilastine and placebo, concluding that Bilastine 10 mg has a safety and tolerability profile comparable to placebo in this paediatric population.⁵³ Another study by Rodriguez M et al, reported pharmacokinetic and safety data in children aged 6-11 years which supports the suitability of the paediatric dose of Bilastine 10 mg and confirms its safety profile similar to that of placebo.⁵⁴

Bilastine-drug and food interactions

Bilastine has a favourable pharmacokinetic profile with minimal drug-drug interactions (DDIs), as it undergoes

negligible metabolism and is excreted renally. It does not affect CYP enzymes, does not interact with anticoagulants, corticosteroids, and oral contraceptives. While a P-glycoprotein (P-gp) substrate, its interaction with P-gp substrates like digoxin is minimal. Caution is advised with potent P-gp inhibitors in patients with renal impairment.⁴² Taking Bilastine with food does not significantly affect its efficacy. Bilastine, a non-sedating H1-antihistamine, is effective for managing chronic cough, especially with upper airway conditions like UACS. Its strong efficacy in AR, minimal drug interactions, and low sedation risk make it a promising option. Clinical trials confirm its safety, with minimal impact on cognition or daily activities, even when taken with food or other medications.

ROLE OF DEXTROMETHORPHAN (DM) AND PHENYLEPHRINE

DM, suppresses cough by raising the cough threshold, with effects starting in 15–30 minutes and lasting 5–6 hours. DM is metabolized to Dextrophan, which also has antitussive properties.⁸ DM is the only antitussive proven to reduce acute cough through objective cough counting, the gold standard for the FDA. In a study with 451 patients, a 30 mg dose of DM significantly reduced cough counts compared to placebo. Subsequent studies confirmed its rapid action and efficacy, even in syrup form. DM has shown efficacy in cough challenge models, with peak effects around two hours and lasting up to 24 hours due to slow blood-brain barrier penetration. In acute cough cases, DM's 30 mg dose is estimated to be 17% more effective than placebo.⁵⁵ Phenylephrine is a selective adrenergic agonist that acts as an effective nasal decongestant by causing vasoconstriction in nasal mucosa, reducing blood vessel diameter and alleviating congestion.

The maximum recommended dose of dextromethorphan hydrobromide is 120 mg/day for adults and adolescents aged 12 years and older, 60 mg/day for children aged 6–12 years. For phenylephrine hydrochloride, the maximum recommended dose for adults and children aged 12 years and older is 60 mg/day (10 mg every 4 hours). For children aged 6 to under 12 years, the maximum dose is 30 mg/day (5 mg every 4 hours).⁵⁷ Thus, in adults, a dosage of 10 ml administered three times daily delivers 60 mg/day of dextromethorphan and 30 mg/day of phenylephrine, aligning with the recommended upper limits for adult dosing. For children above 6 years, a dosage of 5 ml administered three times daily provides 30 mg/day of dextromethorphan and 15 mg/day of phenylephrine, remaining within the acceptable paediatric dosing range.

FIXED DOSE COMBINATIONS-BILASTINE, DEXTROMETHORPHAN, PHENYLEPHRINE

A phase 3 study in multiple centres in India evaluated the oral syrup combination of Bilastine 3.3 mg, Dextromethorphan hydrobromide 10 mg, and Phenylephrine hydrochloride 5 mg per 5 ml. After detailed

deliberation by the pulmonary approval committee of the central drugs standard control (CDSCO) of India recommended the combination to manufacture and market in India for relief of coughs and upper respiratory symptoms, including nasal congestion, associated with allergy or the common cold.^{58,59} Guidelines for cough management in India 2024 from Indian chest society recommends FDC of bilastine (3.3 mg/5 ml) +dextromethorphan hydrobromide (10 mg/5 ml)+phenylephrine hydrochloride (5mg/5ml) for dry cough.³⁶

SUMMARY

Cough is a reflex that helps clear irritants from the respiratory system and is key in diagnosing underlying conditions. It can be acute or chronic, often triggered by infections, allergies, or irritants. AR increases cough sensitivity, worsening symptoms. Tailored management, including fixed-dose combinations (FDCs), enhances adherence. Second-generation antihistamines like Bilastine provide non-sedative, non-cardiotoxic, and non-hepatotoxic relief, making them suitable for patients with comorbidities. Dextromethorphan and phenylephrine are also effective in treating cough and related symptoms, including nasal congestion, especially in those over six years. Although fexofenadine is considered a first-line choice for AR, studies have shown that it is not as efficacious for treating cough associated with AR. Bilastine has been demonstrated to be more effective than cetirizine and levocetirizine in cough formulations, providing better relief from allergic symptoms without significant sedation.^{40,47-50} Food may impact the bioavailability of Bilastine, reducing it in varying degrees. However, studies have confirmed that this reduction does not hinder its antihistamine efficacy in managing cough symptoms.⁶⁰

Understanding the link between cough and allergic triggers is key for effective treatment. The introduction of FDCs with Bilastine, Dextromethorphan, and Phenylephrine offers added advantage of reducing pill burden and enhancing convenience for patients, especially in managing dry allergic cough. While symptomatic treatment provides quick relief, it is essential to prioritize diagnosing and addressing the underlying etiology for long-term benefit. The panel recommends using this preparation exclusively for dry allergic cough to ensure targeted symptomatic relief. Ongoing research into cough pathophysiology and allergic responses will further refine treatment strategies for better management of cough and its causes.

Experts' opinion- pulmonologist perspective on cough & its evolution

The increasing prevalence of cough due to evolving environmental triggers, rapid industrialization, and globalization underscores the need for innovative management strategies. Allergic cough, emerging as a

significant trend globally, affects individuals across all age groups, including those otherwise healthy or with comorbidities. In allergic respiratory diseases, repeated exposure to airborne allergens induces airway and systemic inflammation through the binding and cross-linking of IgE antibodies on mast cells or basophils. This chronic condition predisposes patients to new sensitizations, with AR and asthma frequently coexisting.

Studies indicate that approximately 60% of asthma patients also have AR, while many with AR are at risk of developing asthma.⁶¹ Effective management of allergic cough includes trigger identification and mitigation, as seasonal allergens often exacerbate symptoms like postnasal drip, throat irritation, and persistent dry cough. A newer generation of non-sedative, well-tolerated antihistamine combinations offer a promising approach to managing cough associated with allergies, AR, UACS, and asthma. The combination of Dextromethorphan, Phenylephrine, and Bilastine is particularly suitable for adults and children above six years with active lifestyles, offering effective relief without causing daytime drowsiness. Within the recommended doses, this combination is well-tolerated, including in patients with comorbid conditions, making it a valuable option for improving outcomes in allergic cough management.

Expert opinion-ENT perspective on cough due to allergic rhinitis & upper airway cough syndrome

Chronic cough often presents alongside upper airway symptoms such as abnormal throat sensations and a postnasal drip sensation. In patients with cough attributed to UACS, the symptoms may stem from sensory neuropathy rather than the rate or volume of nasal discharge. This distinction highlights the need for a nuanced approach to diagnosis and management. Empiric therapy combining a second-generation or newer-generation antihistamine with a decongestant is both diagnostic and therapeutic. Nonpharmacologic strategies, including trigger avoidance, also play a crucial role in the treatment pathway. UACS may result from rhinosinusitis or non-rhinosinus-related conditions, with overlapping aetiologies being common.⁶² Cough in these cases arises not only from postnasal drip but also from irritation or inflammation of upper airway structures, which can directly stimulate cough receptors independently or in conjunction with postnasal drip. For patients with cough associated with AR, UACS, allergies, or other upper airway diseases, a combination of Bilastine, Dextromethorphan, and Phenylephrine offers an effective and well-tolerated option, addressing multiple underlying mechanisms to provide symptomatic relief.

Pediatrician's perspective on non-sedative cough syrup

Cough patterns in children evolve as the respiratory system anatomy, control physiology, and associated reflexes mature with age. Approximately 70% of children experience cough associated with allergies, making it a

common symptom across paediatric age groups. Effective management requires addressing the underlying cause, as most cough-related illnesses in children only require symptomatic and supportive care. Cough management in children lacks global standardization, with international experts relying on diverse guidelines and differing approaches to diagnosis and treatment. Cough suppression should be considered only for dry cough to enhance quality of life, while expectorants aim to increase mucus volume for airway clearance. However, young children seldom expectorate effectively, even with excessive secretions. Regular follow-up after prescribing cough syrups should be emphasized to ensure optimal management and outcomes. Non-sedative cough syrups are particularly beneficial in addressing the unique needs of paediatric patients, offering symptom relief without affecting their daily activities.

For children experiencing cough due to allergies, AR, or UACS, an ideal treatment includes a non-sedating antihistamine for 24-hour symptom control without affecting daytime alertness, a cough suppressant for dry cough relief during the day and night, and a nasal decongestant to improve breathing. In school-aged children, maintaining alertness and activity levels is crucial for their growth, health, and overall well-being. A non-sedating antihistamine, such as Bilastine, is the preferred choice for managing allergy-related cough in this age group. When combined with Dextromethorphan and phenylephrine, this formulation effectively addresses the primary aetiology and provides trigger management, making it suitable for children aged six years and older.

Physician's perspective on the fixed-dose combination of bilastine, dextromethorphan, and phenylephrine

For managing cough associated with allergies, UACS, and AR, Bilastine stands out as the preferred choice among newer non-sedative antihistamines, supported by clinical studies and expert consensus. According to ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines, Bilastine ranks highest in antihistamine properties, offering superior outcomes compared to alternatives like Fexofenadine, which is commonly used but less favourable for cough management in these conditions. Bilastine's flexibility in administration—with or without food—adds to its convenience, although food may reduce its bioavailability to some extent. Importantly, clinical studies confirm that this reduction does not compromise its antihistamine efficacy, making Bilastine a reliable choice in the fixed-dose combination with Dextromethorphan and Phenylephrine for enhanced therapeutic outcomes.

CONCLUSION

This review delves into the pathophysiology and clinical significance of cough, particularly in relation to respiratory allergies, highlighting its complexities and the need for ongoing research to refine treatment strategies and improve patient outcomes.

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