REVIEW ARTICLE

Recent Advancements in Cough Management: Emerging Strategies and Therapies

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Abstract

The management of cough, a prevalent symptom impacting the quality of life, has undergone transformative developments propelled by recent research. Cough syrups, longstanding components in cough management, have witnessed substantial progress aimed at refining efficacy, safety, and targeted delivery. Modern formulations exhibit innovations in drug delivery systems, heightening bioavailability and allowing targeted drug release. Extended-release preparations and mucoadhesive syrups offer prolonged cough suppression or augmented expectorant effects. The incorporation of innovative compounds introduces diverse treatment options; transient receptor potential (TRP) channel antagonists, targeting cough receptors, prove effective in inhibiting cough reflex hypersensitivity, while anti-inflammatory agents address underlying airway inflammation. Natural remedies like ivy leaf extract, thyme, or licorice gain prominence for their antitussive and expectorant properties. Advancements in understanding cough pathophysiology enable tailored therapies for specific cough types or underlying causes. Specialized cough syrup formulations now address neuropathic cough, chronic cough associated with respiratory diseases, or cough triggered by gastroesophageal reflux, targeting the root causes of cough. This comprehensive review underscores the evolving landscape of cough management, encompassing enhanced formulations, novel compounds, and a nuanced understanding of cough pathophysiology. These advancements signify a paradigm shift in optimizing symptomatic relief and fostering an accelerated recovery process, marking a notable stride towards improving the overall well-being of individuals affected by cough.

Keywords: Cough, Expectorant, Antitussive, Transient receptor potential.

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Introduction

Coughing is a frequent symptom that can have a negative influence on a patient's quality of life. It is a natural reflex response that helps to protect the respiratory system. It is a frequent symptom experienced by people of all ages and can be caused by several circumstances. Understanding cough, its origins, and appropriate management options is critical for both healthcare providers and patients. Understanding cough, its origins, and appropriate management options is critical for both healthcare providers and patients. [1]

Coughing is frequent in the general population. According to epidemiologic research, 2 to 23% of non-smoking people have a persistent cough. Many people consider cough as a normal part of life and never complain about it. Seek medical assistance. Others seek medical attention because of the frequency of their cough, its correlation with unpleasant respiratory feelings, or apprehension about the underlying reason. It is believed that coughing accounts for up to 50% of all office visits throughout the winter. [2]

Cough is a common symptom experienced by individuals of all ages and can arise from various underlying causes. It serves as a protective reflex to clear the respiratory tract of irritants, foreign substances, or excessive secretions. However, cough can also be a bothersome symptom that significantly impacts an individual's quality of life. However, when a cough becomes persistent, disruptive, or debilitating, it warrants attention and appropriate management. [3] Acute cough, which typically follows an upper respiratory tract infection, can be bothersome at first, but it is usually self-limiting and requires no medical attention. Chronic cough is frequently the only symptom of many serious chronic respiratory disorders, but it can also be the only presenting sign of a variety of extrapulmonary ailments, including upper airway and gastrointestinal disease. [4]

Understanding the diverse causes and mechanisms of cough is crucial for effective treatment strategies. Cough can arise from respiratory infections, allergic reactions, chronic respiratory diseases, gastroesophageal reflux disease (GERD), medications, environmental factors, and other underlying pathologies. Each underlying cause may involve specific mechanisms that trigger and sustain the cough reflex. [3] The management of cough involves a multidimensional approach that encompasses both non-pharmacological

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and pharmacological strategies. Non-pharmacological interventions focus on lifestyle modifications, environmental control, and breathing techniques, while pharmacotherapy aims to alleviate symptoms, target the underlying cause, and improve the patient's quality of life. [5]

Cough syrups have long been a mainstay in the management of cough, offering symptomatic relief and aiding in the recovery process. As our understanding of cough and its treatment strategies continues to evolve, recent advancements in cough syrup formulations have provided new insights into their efficacy and mechanisms of action.[6] Cough syrups are oral liquid formulations that contain active ingredients targeting different aspects of the cough reflex. They are designed to alleviate cough symptoms by suppressing the urge to cough, promoting the expectoration of mucus, or addressing the underlying cause of cough. [7] Recent research has focused on optimizing cough syrup formulations to enhance their effectiveness and safety profiles. Advances in drug delivery systems have allowed for improved bioavailability and targeted drug release, leading to more efficient and rapid relief of cough symptoms. Novel formulations, such as extended-release preparations or mucoadhesive syrups, have been developed to provide prolonged cough suppression or enhance the expectorant effects. [8]

In addition to traditional ingredients, newer cough syrups now incorporate innovative compounds that target specific aspects of cough pathophysiology. For example, some formulations may include agents that modulate cough receptors, such as transient receptor potential (TRP) channel antagonists, to inhibit cough reflex hypersensitivity. [9] Others may contain substances with anti-inflammatory properties to address underlying airway inflammation associated with cough. [10] Recent studies have also explored the potential of natural compounds and herbal extracts in cough syrup formulations. Certain herbal ingredients, such as ivy leaf extract or thyme, have shown promising efficacy in reducing cough frequency and intensity. These natural remedies provide an alternative option for individuals seeking more holistic or plant-based cough management strategies. [4]

Moreover, advancements in understanding the mechanisms of cough have led to the development of targeted therapies for specific cough types. Cough syrups can now be tailored to address neuropathic cough, chronic cough associated with specific respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease), or cough triggered by gastroesophageal reflux. These specialized formulations aim to address the underlying cause of cough and provide more targeted relief. [11,12] This review article provides an in-depth overview of cough and its management, focusing on recent advances in our understanding of the underlying mechanisms and the evolving therapeutic strategies. In this section, the definition and classification of cough, distinguishing between acute and chronic cough as well as productive and non-productive cough is focused. Furthermore, the goals of cough management and the multidimensional approach required for effective treatment is discussed.

Treatment Approaches for Cough

Non-pharmacological Treatment option

Non-pharmacological techniques to treat coughs, however, offer worthwhile alternatives to pharmacological procedures in today's world when drug side effects are affecting us. When patients are active, non-pharmacological treatments (e.g., exercise) are the most effective. [13]

Warm broths, as well as non-caffeinated drinks, are all good for keeping hydrated and easing cough symptoms. Following are some of the ways to manage cough without drugs.

- Humidification: Dry air can aggravate coughing by irritating the airways. In dry locations or during the winter months, adding moisture to the air with a humidifier or vaporizer might ease cough symptoms. It helps to relieve coughing, soothe the throat, and calm the respiratory system. By placing a cool mist vaporizer in the children room also help keep nasal passage moist. But one should keep in mind to change its water on daily basis and keep the vaporizer clean to avoid any bacterial or fungal growth.
- Steam Inhalation: Steam inhalation is a famous and successful cough treatment method. Warm, humid air is inhaled to assist release of mucus and relieve congestion. Including essential oils that calm the airways and lessen the sensitivity of the cough response, like eucalyptus or peppermint, can have extra positive effects.
- Salt water gargle: Salt water is healing and disinfecting, and also the simplest and most inexpensive remedy. You just need to gargle with a glass of warm water that has been mixed with a teaspoon of salt. For it to work, just make sure you repeat this multiple times daily.
- Saline nasal irrigation: Nasal congestion can cause postnasal drip, which causes a lingering cough. In order to clear congestion and lessen coughing, saline nasal irrigation involves flushing the nasal passages with a saltwater solution. Using neti pots or nasal sprays, you can utilize this approach to efficiently open your nasal passages. As it results in dryness, it is followed by nasya – the application of herbal oils to lubricate and moisturize the nasal cavities.
- Ginger: It not only helps in fighting cough and cold symptoms but also in fighting infections and reducing inflammation
- Honey: Honey has long been known to have medicinal benefits for treating coughs. It has antibacterial and antioxidant qualities and works as a natural cough suppressant. A spoonful of honey can be consumed or added to warm herbal tea to temporarily relieve cough symptoms. In some studies, it was also reported that honey is more effective than dextromethorphan or

diphenhydramine. [14]

- Lemon: It has multiple benefits. In cough and cold fresh lemons can help to reduce mucus. Also, its anti-inflammatory and anti-bacterial properties helps in reducing runny nose and coughing problems.
- Postural Drainage and Chest Percussion: People with productive coughs, especially those with respiratory diseases like chronic bronchitis or cystic fibrosis, might benefit from posture drainage and chest percussion methods. These methods entail arranging the body to allow mucus to drain from particular lung segments and vibrating or clapping rhythmically on the chest wall to loosen mucus and enable coughing up. Topical rubs including menthol and eucalyptus can help in opening up nasal passages.
- Breathing Techniques: Using breathing techniques to control cough symptoms, such as diaphragmatic breathing or pursed-lip breathing, can be beneficial. It can improve breathing functions in patients with primary or secondary respiratory diseases[15]. Deep, calm breaths that use the diaphragm promote relaxation and lessen the sensitivity of the cough reflex by engaging the diaphragm. Pursedlip breathing, which involves taking breaths in through the nose and out via pursed lips, can assist in regulating breathing and lessen coughing fits.
- Avoid Irritants: Avoiding smoking or exposure to passive smoke, limiting consumption of substances known to dry out the larynx, such as alcohol, caffeine, and medicated cough lozenges, increasing systemic and surface hydration through steam inhalation, and increasing the amount and frequency of water intake are just a few of the issues specific to vocal hygiene[16]. Airway inflammation and coughing frequency can be decreased by limiting exposure to these triggers.

Pharmacological Treatment Options

Expectorants and mucolytics

Expectorants are medications that help facilitate the removal of mucus from the respiratory tract by increasing the volume or reducing the viscosity of mucus. They promote productive cough, aiding in the clearance of excess mucus and irritants. The key mechanism of expectorants is to stimulate the secretion of fluid in the respiratory tract, which helps to liquefy and thin the mucus, making it easier to expel. The main expectorant agent used in cough syrups is guaifenesin. The drugs used as expectorants are Theophylline A, Guaifenesin, etc. There are various herbal drugs that are used as an expectorant: Grapes, Licorice root, Adhatoda vasica, *Pinus sylvestris* L, etc. The scientist has discussed the rationale behind combining expectorant drugs, emphasizing that each drug may have a different mode of action, potentially leading to synergistic effects and improved expectorant properties. The author highlights the importance of individual patient response and the consideration of each expectorant's specific characteristics. The article concludes that while combining multiple expectorants in a cough syrup may seem logical, there is insufficient evidence to support the clinical superiority of such combinations over using a single expectorant. Guaifenesin is an expectorant commonly used in cough syrups and is known to increase the output of respiratory tract fluids, thereby thinning and loosening mucus. its ability to promote productive cough and enhance mucus clearance, which can alleviate symptoms and improve respiratory function in chronic bronchitis patients. [17] Patients with coughs regularly present to doctors in both primary and secondary care.1,2 Acute cough, which frequently follows an upper respiratory tract infection, can be annoying at first, but it is typically self-limiting and seldom requires considerable medical intervention. Chronic cough is frequently the only symptom of many significant chronic respiratory disorders, but it can also be the only presenting characteristic of a variety of extrapulmonary ailments, including upper airway and gastrointestinal disease. Furthermore, triterpene saponin herbal medicines have numerous benefits in cough treatment. Because they are derived from natural sources, they may be safer and more acceptable than manufactured drugs. [18] The study was conducted to assess the effectiveness of over-the-counter (OTC) cough treatments in treating acute cough in adults by analyzing randomized controlled trials (RCTs). It was observed that limited evidence to support the efficacy of OTC cough medicines in alleviating acute cough in adults was provided. [19]

Mucolytics are medications that directly target the structure of mucus, altering its physical properties to facilitate expectoration. They work by breaking down the chemical bonds within mucus, reducing its viscosity and making it easier to cough up. Mucolytics are particularly beneficial in conditions where there is excessive, thick, or tenacious mucus production. The most commonly used mucolytic agent is acetylcysteine. A study was conducted to analyze the effectiveness of acetylcysteine. The purpose of the research was to evaluate the effectiveness and safety of Ivy leaf (*Hedera helix*) cough syrup to acetylcysteine in adults and children with acute bronchitis. Both ivy leaf cough syrup and acetylcysteine improved cough symptoms and overall respiratory health, according to the findings. There were no statistically significant variations in effectiveness between the two therapies. Furthermore, as compared to acetylcysteine, ivy leaf cough syrup was shown to have a higher safety profile, with fewer reported ill effects. The results indicate that ivy leaf cough syrup may be a viable alternative to acetylcysteine in the treatment of acute bronchitis, with comparable efficacy and enhanced safety. [20]

Antitussives

Antitussives are medications used to suppress or relieve coughing. This article provides an overview of antitussives, their mechanisms of action, and their role in the management of cough. Antitussives work by acting on the cough reflex in the central nervous system, either by directly suppressing the cough centre or by reducing the sensitivity of cough

receptors in the respiratory tract (Llor *et al*., 2023). The most used antitussive agents include opioids, such as codeine and dextromethorphan (DXM), as well as non-opioid medications like pholcodine and benzonatate. These medications can be effective in reducing cough frequency and intensity, particularly in cases of dry or non-productive cough. However, it is important to use antitussives judiciously, as they may mask underlying conditions and hinder the clearance of mucus in productive coughs. [20]

DXM is a frequent constituent in OTC cough syrups and is commonly used as an antitussive drug. However, there have been cases of DXM overuse and abuse, which have resulted in neurotoxic consequences such as changed mental state. The case series examines four incidents in which children had changed states of awareness after ingesting DXM-containing cough syrups. The youngsters who were afflicted had symptoms such as bewilderment, disorientation, and somnolence. They needed medical attention, which included hospitalization and supporting care. The essay emphasizes the need of healthcare professionals and carers to be aware of the possible hazards of DXM usage, especially in youngsters. It emphasizes the significance of correct dosage, following suggested parameters, and closely monitoring children who are given DXM-containing cough syrups [21]. Another study examined the effectiveness of compound pholcodine syrup and compound codeine phosphate oral solution in the treatment of cough caused by lung cancer. A randomized controlled study including individuals with lung cancer and a troublesome cough was carried out. The participants were separated into two groups, one getting compound pholcodine syrup and the other compound codeine phosphate oral solution. Cough frequency and severity were measured before and after therapy using standardized measurement methods. Both compound pholcodine syrup and compound codeine phosphate oral solution considerably decreased cough frequency and intensity in lung cancer patients, according to the findings. However, no significant difference in efficacy was seen between the two drugs. The study indicated that compound pholcodine syrup and compound codeine phosphate oral solution is both beneficial in treating cough caused by lung cancer. [21] The study focuses on the development and assessment of cough syrups made with natural components that may have antitussive qualities. The study comprised the development of numerous cough syrups utilizing herbal extracts such as honey, ginger, and tulsi (holy basil), all of which are traditionally used to treat coughs. Several formulations have been developed using various ratios and combinations of the botanical components. The researchers assessed the produced syrups' physicochemical qualities, sensory features, and antitussive effectiveness. [22]

Beta-2 Agonists and Bronchodilators

Beta-2 agonists are a class of medications that act on the beta-2 adrenergic receptors in the airways, leading to smooth muscle relaxation and bronchodilation. They are commonly used in the treatment of respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD), where cough is a prominent symptom. Beta-2 agonists provide rapid relief by relaxing the bronchial smooth muscles and improving airflow, which can alleviate coughing episodes. Additionally, bronchodilators, which include beta-2 agonists as well as other classes of medications such as anticholinergics, is used in terms of their effectiveness in cough management. The article highlights the importance of proper inhalation techniques and adherence to prescribed treatment regimens for optimal cough control. [23]

Bronchodilators are a class of medications that work by relaxing and widening the airways, improving airflow and alleviating respiratory symptoms. While primarily used in the treatment of asthma and COPD, bronchodilators have also shown efficacy in cough management, particularly in cough associated with airway hyperresponsiveness or bronchospasm. bronchodilators can help relieve cough by targeting the underlying respiratory conditions that contribute to cough. By relaxing the smooth muscles of the airways, bronchodilators reduce bronchial constriction and facilitate easier breathing. This, in turn, can reduce cough frequency and severity. [24]

Combining bronchodilators with cough syrup can provide comprehensive relief by addressing both airway constriction and excessive mucus production. The use of bronchodilators and cough syrup should be based on individual patient characteristics, underlying causes of cough, and healthcare professional recommendations. Proper dosing, adherence to treatment regimens, and awareness of potential side effects are crucial for optimal management.

Corticosteroids

Corticosteroids, a class of anti-inflammatory medications, have shown significant efficacy in managing and treating cough. Corticosteroid drugs for pulmonary inhalation and/or nasal delivery include beclomethasone dipropionate, budesonide, ciclesonide, fluticasone furoate, fluticasone propionate, mometasone furoate, and triamcinolone acetonide. [25]

Synthetic medications called corticosteroids imitate the effects of the hormone cortisol, which is naturally generated by the adrenal glands. They are frequently utilised in the treatment of a variety of inflammatory disorders because they have strong anti-inflammatory and immunosuppressive characteristics. When used to treat cough, corticosteroids work by decreasing airway inflammation and stifling the cough reflex. [26]

A persistent cough is a common symptom of respiratory tract diseases, such as acute bronchitis and pneumonia. In certain situations, corticosteroids have been researched as an additional therapy. Numerous clinical studies have shown that short courses of oral corticosteroids can help patients with acute respiratory tract infections feel better faster and lower the severity and duration of their coughing fits. [27]

A study published in the New England Journal of Medicine in 2015 examined the efficacy of prednisolone, a

corticosteroid, in patients with post-infectious cough. The researchers found that prednisolone treatment significantly reduced cough frequency and improved symptoms compared to a placebo group. [27]

Frequently, a chronic cough is related to allergy and asthmatic disorders. The cornerstone of therapy for asthma is inhaled corticosteroids (ICS), which have shown effectiveness in lowering airway inflammation and regulating cough symptoms. Intranasal corticosteroids are helpful in treating cough in individuals with allergic rhinitis or postnasal drip-induced cough by lowering nasal inflammation and postnasal drip infections. [16]

Corticosteroids are essential for managing COPD exacerbations. Oral corticosteroids are frequently administered for a brief period during acute exacerbations to decrease airway inflammation and improve lung function, including cough symptoms. However, long-term use of systemic corticosteroids in stable COPD is generally avoided due to potential side effect. However, due to possible adverse effects, longterm use of systemic corticosteroids in stable COPD is often avoided. [28]

Antihistamines:

Antihistamines are frequently used to treat allergies and symptoms like sneezing, itching, and runny nose that are brought on by histamine release. They function by counteracting the effects of histamine, a substance produced by the body in response to allergic responses. Antihistamines reduce the allergic reaction by primarily targeting histamine receptors. [29]

Cough syrups are medications formulated to alleviate coughing.

It's important to consider the specific active ingredients present in each medication. Combination cough syrups that already contain antihistamines should not be combined with additional antihistamine medications. In this way we can avoid exceeding the recommended dosage and potentially experiencing adverse effects.

If you wish to combine an antihistamine with a cough syrup that does not contain antihistamines, it is generally safe to do so, provided you follow the recommended dosages of both medications.

Decongestant Cough Syrups: Decongestant cough syrups typically contain active ingredients that provide relief by targeting nasal congestion, reducing swelling in the nasal passages, and promoting easier breathing. The primary active ingredient found in most decongestant cough syrups is pseudoephedrine or phenylephrine. These compounds work by constricting the blood vessels in the nasal passages, which helps to relieve congestion. [30]

- A study published in the journal Chest in 2009 examined the effectiveness of the antihistamine levocetirizine in treating cough due to upper respiratory tract infections. The researchers found that levocetirizine significantly reduced cough frequency and severity compared to a placebo group. [31]
- Another study published in the American Journal of Respiratory and Critical Care Medicine in 2013 investigated the use of the antihistamine cetirizine for chronic persistent cough not related to respiratory infections. The researchers observed a modest improvement in cough symptoms with cetirizine treatment compared to a placebo, suggesting its potential as an adjunctive therapy for chronic cough. [16]

Immunomodulators

Immunomodulators and their Mechanisms of Action: Immunomodulators are substances that can modify the immune response, either by enhancing or suppressing it. In the context of cough syrups, immunomodulators are included to modulate the immune system's response to respiratory infections, reduce inflammation, and potentially alleviate cough symptoms. Some common immunomodulators found in cough syrups include herbal extracts, vitamins, minerals, and certain synthetic compounds. [32]

Conclusion and Future Prospective

Recent advancement in cough syrup formulations has significantly improved the management of cough, offering tailored treatment options and enhanced efficacy. The optimization of formulation, incorporation of innovative compounds, and targeted therapies have provided a more comprehensive approach to cough management. However, further research and clinical studies are needed to validate the safety and efficacy of these recent advancements and translate them into clinical practice for the benefit of patients with cough.

The future of cough syrup management holds exciting prospects with the development of targeted therapies, personalized medicine approaches, and emerging treatment modalities. Advancements in understanding the molecular mechanisms of cough, immunomodulation, neurology, and the integration of technology are paving the way for more effective and individualized treatments.

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