

# Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation



## Review

# The Role of Guaifenesin in the Management of Chronic Mucus Hypersecretion Associated with Stable Chronic Bronchitis: A Comprehensive Review

Jill A. Ohar, MD<sup>1</sup> James F. Donohue, MD<sup>2</sup> Selwyn Spangenthal, MD<sup>3</sup>

## Abstract

Chronic obstructive pulmonary disease is the third leading cause of death and disease burden worldwide. It includes a spectrum of diseases including chronic bronchitis which is characterized by overproduction, hypersecretion and decreased elimination of mucus. Chronic bronchitis has numerous clinical consequences, including predisposition to lower respiratory tract infections, accelerated decline in lung function, increased exacerbation rate and decreased health-related quality of life.

Although the inflammatory mechanisms responsible for mucus cell metaplasia in chronic obstructive pulmonary disease and stable chronic bronchitis are poorly understood, the main goals of therapy are to decrease mucus hypersecretion by controlling inflammation and to increase mucus clearance. Non-pharmacological measures include smoking cessation and chest physiotherapy. Pharmacological interventions include expectorants and mucolytics together with long-acting beta2-adrenergic receptor agonists, anticholinergics, glucocorticoids, phosphodiesterase-4 inhibitors, antioxidants, and antibiotics.

Guaifenesin is an expectorant that is thought to increase hydration and decrease viscosity of mucus leading to improved clearance of accumulated secretions from the upper and lower airway. Although guaifenesin has a Food and Drug Administration Over-the-Counter (OTC) Monograph indication to “help loosen phlegm (mucus) and thin bronchial secretions in patients with stable chronic bronchitis,” there is limited published evidence of either mechanism of action or clinical efficacy in this disease state. Here we review the pathophysiology and consequences of chronic mucus hypersecretion and examine the evidence for the use of guaifenesin in patients with stable chronic bronchitis.

**Abbreviations:** chronic obstructive pulmonary disease, **COPD**; chronic bronchitis, **CB**; stable chronic bronchitis, **SCB**; glycerol guaiacolate ether/guaifenesin, **GGE**; chronic mucus hypersecretion, **CMH**; Food and Drug Administration, **FDA**; over-the-counter, **OTC**

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<sup>1</sup> Section of Pulmonary, Critical Care, Allergy, and Immunological Diseases, Wake Forest University School of Medicine, Winston-Salem, North Carolina

<sup>2</sup> Division of Pulmonary Diseases and Critical Care, Department of Medicine, University of North Carolina, Chapel Hill

<sup>3</sup> Internal Medicine & Pulmonology, Charlotte Lung & Health Center, Charlotte, North Carolina

## Address correspondence to:

Jill Ohar, MD  
Email: [johar@wakehealth.edu](mailto:johar@wakehealth.edu)  
Phone: 336-406-6733

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## Introduction

Chronic obstructive pulmonary disease (COPD) is defined by the World Health Organization as “chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible.”<sup>1</sup> More commonly, COPD describes a group of chronic, progressive, airflow limiting diseases, including chronic bronchitis (CB) and emphysema. As such, the disease term CB is rarely used today, as it is included within the umbrella COPD diagnosis.<sup>2</sup> Nevertheless, there is clinical value in separating out CB as a phenotype to identify patients with a beneficial response to therapy<sup>3</sup> and stable chronic bronchitis (SCB), to better contextualize the patient population that may benefit from guaifenesin/glycerol guaiacolate ether (GGE).

The CB definition used in epidemiologic studies has been variable, but the classic definition is chronic cough and sputum production for at least 3 months per year for 2 consecutive years.<sup>3</sup> For the purpose of future, prospective clinical studies the authors suggest SCB be defined as a chronic productive cough that occurs daily for at least 3 months in 2 consecutive years, in a patient who has not had an acute exacerbation within the previous 4 weeks; where an acute exacerbation of chronic bronchitis is defined as an acute worsening of a patient's symptoms, beyond normal day-to-day variations, necessitating a change in treatment with antibiotics and/or corticosteroids.

## Review of Mucus Hypersecretion in COPD

The surface liquid covering the epithelial lining of the airways is known to comprise at least 2 layers: the mucus (gel) layer and the periciliary layer surrounding the cilia which consists of a gel mesh of cell-tethered mucins and polysaccharides.<sup>4,5,6</sup> Mucus consists of a mixture of fluid and secretions from surface epithelium and submucosal glands and is predominantly comprised of water (95%) glycoproteins (2%–3%), proteoglycans (0.1%–0.5%), lipids (0.3%–0.5%), proteins, and DNA.<sup>7</sup> The glycoprotein component consists of secreted mucins, particularly the large polymeric structures MUC5AC and MUC5B, which account for the rheologic properties of mucus.<sup>8</sup>

Under normal conditions, mucus protects the airway. Hydration of mucus affects its viscous and elastic

properties, which in turn determines how effectively it is cleared by ciliary action and cough.<sup>9</sup> Effective mucus clearance is essential for lung health, whereas abnormalities in mucus production and qualitative properties such as mucus hydration are central to the pathophysiology of airway disease including CB.<sup>10</sup> Certain stress conditions including smoking, infection, pathogenic factors, and oxidative stress result in secretory cell hypertrophy and goblet cell hyperplasia in the airway, and subsequent overproduction of mucus. Pathological mucus is not easily cleared given that solids may increase up to 15% resulting in higher viscosity and elasticity.<sup>9</sup> Additionally, in CB, mucus osmotic pressure is increased, resulting in compression of the cilia, slowing of mucociliary transport and delayed mucociliary clearance.<sup>10</sup> Furthermore, in CB there is a direct correlation between forced expiratory volume in 1 second and the percentage solids of mucus, demonstrating a strong relationship between disease progression and mucus abnormalities.<sup>10</sup>

The conversion from healthy to pathologic mucus occurs by multiple mechanisms that change its hydration and biochemical constituents including abnormal secretion of sodium chloride and water, increased production of mucins, infiltration of mucus with neutrophils, macrophages, polymorphonuclear leukocytes, other pro-inflammatory cells, and heightened bronchovascular permeability. The persistent accumulation of mucus results from a combination of overproduction and decreased mucociliary clearance that can lead to inflammation and infection.<sup>11</sup> CB, SCB and COPD are conditions characterized by chronic mucus hypersecretion (CMH), ciliary dysfunction and impaired mucus clearance.<sup>11,12</sup> CMH is not only a clinical symptom but also an independent risk factor for disease progression and poor prognosis of patients with chronic inflammatory airway diseases. CMH is associated with more frequent exacerbations and hospitalizations,<sup>13</sup> lung function decline,<sup>14</sup> decreased health-related quality of life<sup>15</sup> and higher mortality in patients with COPD.<sup>16</sup>

Cigarette smoking is a major trigger of CMH and is the leading risk factor for death in patients with COPD.<sup>14</sup> Cigarette smoke induces an epidermal growth factor receptor cascade, which results in the production of mucins and goblet cell hyperplasia.<sup>17</sup>

CMH becomes increasingly common with age. Allinson et al<sup>18</sup> concluded that the severity of CMH-associated symptoms in middle age among active

smokers is predictive of the risk of airflow limitation in later life and that the longer CMH is present the greater the decline in lung function.

CMH and mucus accumulation in COPD reflects the failure of cough—the major rescue mucus clearance pathway. Button et al<sup>19</sup> demonstrated how abnormal mucus and its interactions with the cell surface produce a failure of cough clearance. The authors identified mucus concentration-dependent cohesive and adhesive properties governed by mucus viscous energy dissipation as rate-limiting for the efficacy of cough clearance and demonstrated how returning mucus concentrations to normal ranges can restore cough efficacy. There are 2 objectives in the treatment of CMH, namely, short-term relief of symptoms through improved mucus clearance and long-term benefit by altering or reversing the hypersecretory phenotype.<sup>20</sup> The use of mucoactive drugs to inhibit CMH and improve mucociliary clearance is therefore important in the treatment of SCB and the chronic bronchitic phenotype of COPD.

There are 4 main classes of mucoactive drugs: expectorants (which induce discharge or expulsion of mucus from the respiratory tract by coughing or sneezing), mucolytics (that decrease mucus viscosity), mucokinetics (that increase ciliary beat frequency) and mucoregulators (that regulate mucus secretion).<sup>21</sup> Although some mucoactive drugs exhibit overlapping effects, only mucolytics and expectorants have a direct action on mucus properties.<sup>21</sup> One such expectorant is guaifenesin (3-[2-methoxyphenoxy]-1,2-propanediol; [glycerol guaiacolate ether] [GGE]), an orally administered, OTC medication that is thought to help loosen and thin bronchial secretions and make cough more productive. The exact mechanism of action is unclear and studies to assess the effect of GGE on mucociliary and cough clearance have yielded conflicting results.<sup>22-35</sup> (Table 1).

GGE is thought to exert its principal pharmacological action by stimulating receptors in the gastric mucosa, via the so-called neurogenic theory or gastro-pulmonary reflex.<sup>30-35</sup> Animal studies have shown that GGE acts as an irritant<sup>27,33</sup> to stimulate gastric vagal receptors which then trigger cholinergic parasympathetic reflexes resulting in vagal stimulation of respiratory tract fluid secretion.<sup>27</sup> The result is an increase in volume and decrease in viscosity of bronchial secretions. Increased gastric vagal stimulation and subsequent vagal activity in

the airways may enhance mucociliary clearance.<sup>31,32</sup> GGE may also directly stimulate vagal nerve endings in bronchial secretory glands and certain centers in the brain, which in turn enhance respiratory secretion flow.<sup>22</sup>

Studies in patients with CB have demonstrated that guaifenesin reduces sputum surface tension<sup>23</sup> and viscosity<sup>24</sup> and increases mucociliary clearance.<sup>24,25</sup> GGE has also been shown to inhibit cough reflex sensitivity,<sup>26</sup> suppress mucin production, increase mucociliary transport and decrease viscosity and elasticity of secretions.<sup>28,29</sup>

### Clinical Experience with Guaifenesin in SCB

GGE is currently the only U.S. Food and Drug Administration (FDA)-approved expectorant in the United States.<sup>22</sup> It is available in tablet form for both immediate and extended release, as a single active ingredient in branded and generic cough medicines and as an ingredient in multi-symptom cough and cold products. The extended-release form is only available in tablet format (single ingredient and combinations) but the majority of marketed immediate-release products (single ingredient or combinations) are liquids (syrups).

GGE is included in the FDA's OTC Monograph for "Cold, Cough, Allergy, Bronchodilator and Anti-Asthmatic Drug Products for Over-the-Counter Human Use" as an expectorant<sup>36</sup> and also has a professional indication for SCB, although it is specifically excluded for use during acute exacerbations of CB. The monograph indication for SCB was seemingly granted on the basis of 4 heterogeneous, non-regulatory studies in patients with bronchopulmonary disease<sup>20,23,37-39</sup> one of which appears to be available only as an abstract.<sup>23</sup>

Hayes et al studied 21 patients with SCB and chronic productive cough.<sup>37</sup> Patients self-administered a cough syrup containing 100 mg GGE & 1 mg desoxyephedrine HCl versus placebo every 2-3 hours as needed and served as their own control during a placebo cross-over phase. No treatment-related differences were observed in pre-and post-intervention chest X-rays, blood counts, urinalysis, erythrocyte sedimentation rate or bacteriological examination of sputum. Subjective results included a significant

**Table 1. Guaifenesin: Mechanism of Action and Effects on Mucus**

Ref #	First Author (Year)	Study Design	Observed Mechanism of Action
23	Chodosh S (1964)	Double-blind. 100 mg guaifenesin daily for 14 days versus placebo. In vivo	Decreased sputum surface tension
24	Chodosh S (1973)	Double-blind, crossover. 800 or 2400 mg/day guaifenesin for 4 weeks versus placebo. In vivo	Reduced surface tension and adhesiveness of mucus; Improved mucociliary clearance
25	Thomson ML (1973)	Double-blind, crossover study. 600 mg guaifenesin versus placebo. In vivo.	Increased mucociliary clearance
26	Dicpinigaitis PV (2003)	Randomized, single-blind study. Single dose of 400 mg guaifenesin versus placebo. In vivo.	Inhibition of cough reflex sensitivity through (1) a central antitussive effect (2) a peripheral effect whereby increased sputum volume shields cough receptors in the respiratory epithelium from tussive stimuli
27	Kagan L (2009)	Rat model PK study	Expectorant effect is mediated by stimulation of the gastrointestinal tract and not by systemic exposure
28	Seagrave J (2011)	In vitro	Suppressed mucin production; Increased mucociliary transport; Decreased mucus viscoelasticity
29	Seagrave J (2012)	In vitro	Inhibition of mucin [MUC5AC] production; Reduced viscosity and elasticity of mucus; Increased mucociliary transport rates

reduction in the severity of cough, reduced frequency of cough and decreased sputum viscosity, however no statistical analysis was included in the publication.

Chodosh et al studied 26 patients with SCB in a double-blind, placebo-controlled, cross-over study. Patients received 100mg GGE daily for 7 days during the active treatment phase.<sup>23</sup> Initially, and after 7 days on each regimen, clinical assessment, ventilatory tests and sputum cytology, physical characteristics and chemical determinations were performed. The single page study report states that all of the data were statistically analyzed, but no statistical results are provided. Nevertheless, the author concluded that compared to placebo, the guaifenesin-treated patients experienced significant general clinical improvement, decreased sputum surface tension and decreased sputum viscosity.

Wójcicki et al studied 23 patients with SCB and chronic cough in a double-blind, cross-over study. Patients were treated for a total of 4 weeks, divided into 4 x 7-day treatment periods when they received either (1) Duopect (GGE 120 mg/narcotine 17 mg), (2) narcotine 17 mg, (3) GGE 120 mg, (4) placebo.<sup>38</sup> Of patients treated with the GGE/narcotine combination,

54% experienced a subjective marked reduction in cough frequency and severity. A total of 79% of patients on GGE and 75% on combination therapy experienced subjective improvement in tenaciousness of sputum versus 34% treated with narcotine and 21.8% with placebo.

Finiguerra et al conducted a double-blind placebo-controlled study of GGE in 40 patients with both acute and chronic bronchitis. Patients were treated for 15 days with either GGE 190 mg or placebo syrup.<sup>39</sup> Efficacy of treatment was assessed on modifications in the characteristics of the expectorate (volume and appearance), difficulty expectorating and cough. Volume and appearance were expressed on a quantitative and semi-quantitative scale. In the group treated with GGE, results showed a reduction in the volume and viscosity of sputum, accompanied by improved ease of expectoration, reduced cough intensity and reduced dyspnea. However, due to the paucity of objective measurements versus subjective measurements and the failure to stratify those patients with acute and those with CB, no meaningful conclusions can be drawn.

Although these early studies suggest some degree

of clinical benefit from GGE, they were performed in small cohorts, lack objective measurements and statistical analyses are missing or limited in value. Additionally, they all utilized doses significantly less than the currently accepted and FDA-approved daily dosing range of 1200-2400 mg and none of the patients were treated for longer than 15 days, leaving many clinical questions unanswered.

Although efficacy data is lacking for GGE, post-marketing surveillance safety reports covering more than 50 years in the United States and around the world support a favorable safety profile.<sup>40</sup> GGE was not associated with any *potentially related* fatalities during a 17-year surveillance period or a subsequent 6-year detection period. The few published reports of serious adverse events have been in the context of chronic overdose and when it has been used in combination with other cough and cold medications where causality could not be established. Common side-effects include headache, dizziness and gastrointestinal disturbance at high doses.<sup>22,40</sup>

Four recently published, patient case studies<sup>41-44</sup> in patients with COPD and CB have suggested that high dose GGE (1200-2400 mg/day), administered daily for 3 years or longer, might result in fewer infectious complications, reduced antibiotic use and improved quality of life, but these are all retrospective and single patient case reports.

## Discussion

CB is part of the umbrella term COPD and is characterized by overproduction, hypersecretion and decreased elimination of mucus. Patients with SCB can be defined as those with chronic productive cough for at least 3 months in 2 consecutive years, and no acute exacerbations in the previous 4 weeks.<sup>45</sup>

The CMH seen in this condition is associated with increased morbidity and mortality. Treating this symptom may provide relief, prevent complications and slow disease progression. One potential, frequently overlooked, therapeutic option is the expectorant GGE. More commonly perceived as an OTC cough and cold product, the authors were surprised to learn recently that it has had a professional prescribing indication for SCB since 1989.<sup>36</sup>

Targeting CMH with the expectorant GGE is theoretically appealing. Mechanism of action data,

although limited, suggest that GGE suppresses mucin production, acts as an irritant to gastric vagal receptors and recruits efferent parasympathetic reflexes that cause glandular exocytosis in the respiratory mucosa and reduces the viscosity of mucus secretion by reducing adhesiveness and surface tension as well as increasing hydration which helps to facilitate removal of accumulated mucus secretions from the upper and lower airway and increases mucociliary clearance.<sup>23-35</sup>

Airway pathophysiology studies utilizing new biological models of cough and technologies that can measure reduction of mucus adhesive and cohesive strength could help to more accurately elucidate the mechanism of action of GGE.<sup>19</sup>

Additionally, a better understanding of the role that central nervous system pathways play in regulating airway functions in both normal and disease states could provide novel therapeutic approaches for the treatment of CMH and other diseases whose clinical, biochemical, and pharmacological features indicate a pathophysiological link with the central nervous system.<sup>18</sup>

The clinical evidence supporting the use of GGE in CB is weak. The 4 studies that formed the basis of the approval were all published prior to 1983,<sup>23,37-39</sup> involved small numbers of patients and do not meet today's scientific, methodological, statistical or regulatory evidence-based medicine standards.

This paucity of Level I evidence may be the reason why GGE is not included in any of the current U.S. or European COPD guidelines. It also suggests a clear need for further investigation of GGE in patients with SCB, specifically multicenter randomized, double blind, controlled studies using relevant, validated endpoints, standardized dosing and rigorous statistical analysis. We recommend that such studies should be carefully designed to investigate what, if any, role guaifenesin plays in the reduction of CMH symptoms and its impact on quality of life and health care resource utilization, as well as its possible effects on exacerbation frequency. The importance of symptoms is acknowledged by the current Global Initiative for Chronic Obstructive Lung Disease document,<sup>45</sup> which recommends evaluating symptom burden and exacerbation history separately. There is also an increasing evidence base demonstrating that symptoms (including cough and sputum production) drive the burden of disease in COPD and have a substantial detrimental impact on health status, quality of life, and daily activities, and

also contribute to increased anxiety and depression levels, increased risk of exacerbations, and worsened disease prognosis.<sup>46-53</sup>

In addition, given that antibiotic resistance and antibiotic-associated *Clostridium difficile* colitis are among the biggest public health challenges of our time,<sup>54,55</sup> reduction of antibiotic use should be included as a secondary end point in all future COPD studies, as should health care utilization.

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