The Pathophysiology and Pharmaceutical Treatment of Chronic Bronchitis

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Program Overview:

To provide nurses and pharmacists with an understanding of the prevalence and incidence of chronic bronchitis

OBJECTIVES:

After completing this program, participants will be able to:

- Understand the pathophysiology of chronic bronchitis
- Describe its primary symptoms and main risk factors
- Describe the epidemiology and etiology of chronic bronchitis
- Identify the most commonly used pharmaceuticals and their potential side effects
Pathophysiology

Bronchitis is a respiratory condition that involves inflammation of the bronchial tubes (medium-sized airways) and bronchioles (the smaller branches of the bronchi) resulting in excessive secretions of mucus and tissue swelling that reduces the diameter of the bronchial tubes, making it progressively more difficult to breath. Chronic bronchitis is clinically defined as a chronic inflammation of the bronchi and bronchioles that leads to persistent coughing and production of sputum (phlegm) and mucus on a daily basis for at least three months per year, two years in a row. Other respiratory and cardiac causes of a chronic productive cough need to be excluded before a diagnosis of chronic bronchitis can be rendered.

Chronic bronchitis is often a main component of Chronic Obstructive Pulmonary Disease, or COPD, which also includes emphysema and asthma. COPD is more of a nonspecific label that refers to a set of pulmonary conditions that develops progressively due to different, but related, disease processes. COPD is characterized by airflow limitation and manifested through chronic coughing, dyspnea, expectoration, and wheezing. COPD is considered only partially reversible, and the label is most commonly used in reference to patients with chronic bronchitis and emphysema, as well as for a subset of patients with asthma.

The inflammatory mechanisms of chronic bronchitis have been extensively reviewed. The disease is caused by an interaction between noxious inhaled agents and host factors, such as genetic predisposition or respiratory infections which cause injury or irritation to the respiratory epithelium of the walls and lumen of the bronchi and bronchioles. Chronic inflammation, edema, temporary bronchospasm, and increased production of mucus by goblet cells are the result. As a consequence, airflow into and out of the lungs is reduced, sometimes to a dramatic degree. Most cases of chronic bronchitis are caused by smoking cigarettes or other tobacco products, although other examples of noxious agents include fumes from cleaning products and solvents, dust from occupational exposure, and air pollution. Ammonia, sulfur dioxide, chlorine, bromine, and hydrogen sulfide are especially harmful pollutants which are linked to respiratory diseases. Chronic bronchitis must be distinguished from common allergies which also cause mucus hypersecretion and coughing fits. When chronic bronchitis progresses to include the pathologic changes of emphysema, it is often referred to as COPD.
Studies of both smokers and those exposed to secondhand cigarette smoke have revealed increases in the number of neutrophils and macrophages within the walls and lumen of both the bronchi and bronchioles, which play an important role in perpetuating the inflammatory process of chronic bronchitis. Bronchial biopsies from former smokers show inflammatory changes that are similar to those in active smokers, suggesting that inflammation often persists in the airways once established. Increased quantities of pro-inflammatory cytokines such as interleukin-8 and tumor necrosis factor-α, as well as anti-inflammatory cytokines such as interleukin-10 have been found in the sputum of smokers with chronic bronchitis. Other structural changes in the airways of smokers include mucus gland hyperplasia, smooth muscle hypertrophy, and bronchiolar edema and fibrosis, which combine to narrow the diameter of the airways.

In non-smokers without chronic bronchitis, the normal amount of sputum produced daily is about 500 mL, which is eliminated by the action of mucociliary clearance to the hypopharynx where it is swallowed and rarely noticed. However, smokers with chronic bronchitis produce larger amounts of sputum each day, as much as 20 percent more, which does cause problems with swallowing and often leads to chronic coughing. The excess mucus-like sputum occurs as a result of an increase in the size and number of the submucosal glands and goblet cells on the surface epithelium of the bronchi. As such, mucus gland enlargement and hyperplasia of the goblet cells are the pathologic hallmarks of chronic bronchitis. Further, goblet cells are normally absent in the bronchioles, but their presence in chronic bronchitis is important in the development of the disease and progression towards COPD.

Other epithelial alterations seen in chronic bronchitis include a decrease in the number and length of the cilia, and squamous cell metaplasia. Cilia are hair-like appendages that beat rapidly and function to move particles, fluid, and mucus over the surface lining of the trachea, bronchial tubes, and nasal cavities. Without proper cilia function, the result is a continuous blanket of mucus lining the airways that is difficult to mobilize and swallow. This thick mucus layer provides a substrate for bacterial growth, which can release toxins that further damage the cilia and epithelial cells. Bacterial toxins are known to stimulate mucus production, slow ciliary beating, impair immune cell function, and destroy local immunoglobulins. Eventually, ciliated cells are often replaced by goblet cells as chronic bronchitis progresses.
The constant coughing seen in patients with chronic bronchitis is multifactorial. It tends to be a combination of airway inflammation, excessive bronchial secretions, increased cough receptor sensitivity, and activation of the afferent limb of the cough reflex. When airflow obstruction is advanced, the decreased expiratory flow leads to an ineffective or unproductive cough as the mucus or phlegm is not efficiently removed. Consequently, patients with advanced chronic bronchitis / COPD display mucus retention in both the small peripheral airways and larger central airways, which increases their risks of acute viral and bacterial infections.

Respiratory infections typically cause an acute exacerbation within patients who have chronic bronchitis and are otherwise stable. During these acute attacks or exacerbations, cough and sputum production increase, the sputum may become purulent, and shortness of breath is worsened. Evidence of a viral infection is found in approximately one-third of acute, infectious episodes, and common causal agents include rhinovirus, coronavirus, influenza-B and parainfluenza. The respiratory tracts of many patients with chronic bronchitis are eventually colonized with bacteria such as *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*.

**Summary of Signs and Symptoms**

The major symptoms of chronic bronchitis are frequent coughing and excessive sputum production. The sputum may be clear, yellowish, or greenish depending on bacterial infection, and sometimes tinged with blood if small blood vessels are ruptured due to constant coughing. With acute bronchitis and the early stages of chronic bronchitis, the cough is often productive, which means that mucus is loosened and expectorated as sputum. However, as chronic bronchitis progresses and the ciliated cells become less effective and the expiratory flow decreases, coughing becomes more unproductive. So-called “smoker’s cough” is very similar and tends to be worse upon awakening and is often productive of discolored mucus in the early part of the day, but becomes less productive as the day advances.

Dyspnea, or shortness of breath, is another common symptom of chronic bronchitis and it gradually increases with the severity of the disease. Patients with chronic bronchitis often become short of breath with physical activity and begin coughing. However, dyspnea at rest usually signals that emphysema has
developed, in which case a diagnosis of COPD is often given. In addition to dyspnea, wheezing sounds often occur with chronic bronchitis, which is defined as a coarse whistling sound produced when airways are partially obstructed.

In addition to the above mentioned major symptoms, fatigue, malaise, sore throat, muscle aches, nasal congestion, headaches, and edema also commonly affect patients with chronic bronchitis. Severe coughing may cause chest pains and exacerbate high blood pressure. Cyanosis (a bluish gray skin coloration caused by lack of oxygen) may develop in patients with advanced chronic bronchitis and COPD. The presence of a fever is more common in acute bronchitis, but it occurs in chronic cases also and is usually indicative of a secondary viral or bacterial lung infection. The major complications of chronic bronchitis are severe shortness of breath to the point of cyanosis, polycythemia (an abnormally high concentration of red blood cells needed to carry oxygen), irreversible bronchospasm leading to COPD, pneumonia, cor pulmonale (enlargement and weakness of the right heart ventricle due to lung disease), total respiratory failure, and death. Currently, COPD is the fourth leading cause of death in the United States. 

**Diagnosing Chronic Bronchitis**

Physicians diagnose chronic bronchitis by using a combination of medical history, physical exam, and diagnostic tests. A history of a daily cough that lasts at least three months, especially if has occurred two years in a row, fits the criteria for a clinical diagnosis of chronic bronchitis. A history of smoking and/or working with noxious chemicals is also very relevant. The physical examination usually includes listening for wheezing, determining if there is a prolongation of exhalation, and looking for evidence of cyanosis, which are all signs of airflow obstruction. A sputum sample showing neutrophil granulocytes (inflammatory white blood cells) and a positive culture for pathogenic microorganisms such as Streptococcal species are also indications that the patient might have chronic bronchitis. However, for expectorated sputum samples to be considered valid, conventional wisdom is that there should be fewer than 10 squamous cells and more than 25 white blood cells per high-power microscopic field.
A chest X-ray is often taken if bronchitis is suspected to help rule out other lung conditions such as pneumonia, tuberculosis, or bronchial obstructions. Chest X-rays can also reveal hyperinflation of the lungs, or diaphragmatic flattening, which is suggestive of chronic bronchitis, or lung collapse and consolidation which would support a diagnosis of pneumonia. Additional tests such as a complete blood count, arterial blood gas measurements, and CT scan of the chest are often done to characterize the function of the lungs and to help exclude other serious conditions such as lung cancer. A raised white blood count (especially neutrophils) and elevated C-reactive protein indicates inflammation and possible infection. Polycythemia, as noted above, is an indication of chronic bronchitis or COPD. If bronchitis is suspected, a pulmonologist with specialized training in the management of lung diseases will often perform a pulmonary function test (PFT) on the patient.

Documentation of airflow obstruction by PFT is critical for the diagnosis of chronic bronchitis and provides valuable therapeutic information about the patient’s responsiveness to inhaled bronchodilator therapy. A measured forced expiratory volume in one second (FEV1) of less than 70 percent of the total forced vital capacity (FVC) defines obstructive airway disease; an FEV1/FVC ratio of less than 50 percent indicates end-stage obstructive airway disease. Bronchitis may show a decreased FEV1 and FEV1/FVC ratio, but rarely causes a high residual volume. This is because the air flow obstruction with chronic bronchitis is due to increased resistance, which does not cause the airways to collapse prematurely and trap air in the lungs. In most elderly adults, age-related physiological changes in lung elasticity cause a 30 mL per year decline in the FEV1, so that progressive rates of decline that exceed this amount represent true disease progression. The median survival for patients with an FEV1 of less than 1 L is only four years. In short, measured airflow obstruction coupled with chronic sputum production confirms the clinical diagnosis of chronic bronchitis.

**Epidemiology and Etiology**

In the United States, estimates from interviews taken by the National Center for Health Statistics in the mid-1990s concluded that at least 16 million people were afflicted with COPD, about 14 million of which were thought to have had chronic bronchitis. However, it has since been suggested that these statistics underestimate the prevalence of COPD by as much as 50 percent, because many patients underreport their symptoms and their conditions remain undiagnosed. More recent estimates claim that between 5-6 percent
of American adults experience chronic bronchitis (which is similar to the National Center for Health Statistics data from the 1990s), and it is two times more common in women than in men. Although people of any age can develop chronic bronchitis, the majority of people diagnosed with the disease are 45 years of age or older. However, structural changes of the airways suggestive of chronic bronchitis have been described in otherwise healthy smokers as young as 20 years old.

It is currently not clear if the rates of chronic bronchitis in the United States or around the world are increasing, decreasing, or static compared to past decades. Many regions of the U.S. and other industrialized countries are banning cigarette smoking in public areas, which would certainly reduce the primary causal factor of chronic bronchitis, but urban pollution and the use of noxious chemicals may be increasing in many regions. Regardless, education on the negative health effects related to smoking cigarettes and other tobacco products remains very important. Cigarette smoke is composed of a complex mixture of more than 400 components and the specific etiologic role of these components has not been established, although collectively it is widely recognized that they greatly contribute to respiratory injury.

A 2001 survey found that 17 percent of smokers, 12 percent of former smokers, and 6 percent of non-smokers met the criteria for chronic bronchitis. Statistics from the U.S. Centers for Disease Control and Prevention suggest that about 49 percent of long-term smokers eventually develop chronic bronchitis and 24 percent further develop emphysema / COPD. Some researchers suggest that between 85-90 percent of cases of chronic bronchitis and COPD in developed countries are directly or indirectly caused by exposure to tobacco smoke. The overall 10-year mortality rate following the diagnosis of chronic bronchitis is 50 percent, with respiratory failure following an acute exacerbation being the most frequent cause of death. As such, cigarette smoking is the most important risk factor for the development of chronic bronchitis.

**Prevention**

Smoking cessation is the single most effective way to reduce the risk of future morbidity from chronic bronchitis, although smoking tobacco products causes irreversible changes to the respiratory system. Studies have demonstrated physiological evidence of active airway inflammation in bronchial biopsy
specimens from symptomatic ex-smokers, even after they had been smoke-free for up to 13 years.\textsuperscript{20} As such, total avoidance of tobacco smoke is the ideal preventative strategy, although completely avoiding second-hand smoke often proves difficult, especially in regions or countries that don’t regulate smoking in the workplace or public areas. Deterring children from smoking through proper and consistent education remains a logical and economically viable solution that could dramatically reduce the incidence of chronic bronchitis. Further, enacting and enforcing laws against childhood smoking as well as restricting advertising from tobacco companies would also be beneficial.

Once a smoker decides to quit smoking, use of various smoking cessation tools such as nicotine replacement systems, behavior modification training, and support groups can be helpful. Such tools are most effective when a supportive physician sees the patient regularly throughout the smoking cessation period. If successful, smoking cessation can have a dramatic effect on coughing. Several studies have shown that coughing disappears or markedly decreases in over 90 percent of patients after smoking cessation, and in about half of cases this occurred within one month.\textsuperscript{21,22} However, in patients with more severe degrees of airflow obstruction, chronic coughing is more likely to persist despite the avoidance of cigarettes or other respiratory irritants.

In addition to avoiding cigarette smoke, reduction or elimination of exposure to environmental inhaled irritants such as aerosolized hair and deodorant products at home, organic dusts or noxious fumes at work, and air pollution with high sulfur dioxide levels is also a prudent strategy to reduce the risk of developing chronic bronchitis. In addition, cold environments and dry air are known to aggravate coughing and dyspnea, so avoidance or use of facial masks and humidifiers are often helpful to control the symptoms of chronic bronchitis.

**Natural Remedies**

Pulmonary rehabilitation is a natural treatment method for chronic bronchitis that combines education and graded physical exercise. The education portion often includes smoking cessation techniques and information about the relationship between tobacco use and chronic bronchitis. Breathing techniques can be helpful in overcoming the anxiety of acute bronchial exacerbations. This involves breathing in through
the nose so that the air is moistened, cleansed and warmed by the sinuses, and then breathing out through the mouth with pursed lips to help optimize the lung's function. When chronic bronchitis is severe, airflow and blood flow may not move appropriately through the lungs; thus, breathing techniques can help match airflow and blood flow precisely.\textsuperscript{18} When airflow is severely restricted, supplemental oxygen therapy may be required during activity and/or sleeping. However, oxygen supplementation can result in decreased respiratory drive, leading to increased blood levels of carbon dioxide and subsequent respiratory acidosis.

Some studies have indicated that supplementing with N-acetylcysteine (NAC) can help relieve symptoms of COPD and reduce the number of attacks of severe bronchitis by acting as an antioxidant to reduce oxidative stress on the lungs.\textsuperscript{23} NAC is a modified dietary amino acid that displays strong antioxidant properties. The dosages in studies have ranged from 400-1,200 mg per day. Other powerful antioxidants include vitamins A and C, which are able to scavenge free-radicals that cause inflammatory reactions. Further, vitamin A is required for the formation and maintenance of moist mucus membranes, including those that line the bronchi and lungs.

Natural expectorants and decongestants used for acute and chronic bronchitis include essential oils (eucalyptus, citrus, pine, cedar wood, bergamot, myrrh, sweet fennel, jasmine, lavender, tea tree, marjoram) and herbal remedies such as lobelia (\textit{Lobelia inlata}), mullein (\textit{Verbascum densiflorum}), and peppermint. Studies have found that essential oils called monoterpenes are more effective than placebo for acute bronchitis and just as effective as antibiotics.\textsuperscript{24} Aromatherapy is an especially effective method of delivery for essential oils for those with chronic bronchitis and involves running a humidifier (day and/or night) infused with the oils.\textsuperscript{25}

\textbf{The Pharmaceutical Treatment of Chronic Bronchitis}

Chronic bronchitis is treated symptomatically as the disease causes physiological changes in the respiratory system that cannot be fully reversed. The two major classes of medications used to treat chronic bronchitis are bronchodilators and corticosteroids. Wheezing and shortness of breath are treated by reducing bronchospasms (the reversible narrowing of bronchi and bronchioles due to smooth muscle
constriction) with bronchodilators such as inhaled anticholinergics, inhaled beta-adrenergic agonists, and methylated xanthine derivatives. Inflammation and edema of the respiratory epithelium may be reduced with inhaled corticosteroids and PDE4 inhibitors. Over-the-counter (OTC) drugs can be helpful for expectoration and suppressing the cough reflex. Antibiotics are reserved for acute bronchitis caused by bacterial infection or acute exacerbations of chronic bronchitis.

1) Bronchodilators

Bronchodilators are usually inhaled and work by relaxing the smooth muscles that encircle the bronchi, which allows the inner airways to expand and be able to intake and exhale more air. Bronchodilators are usually delivered by means of a metered-dose inhaler (MDI) with a spacer, which is sometimes called a “puffer.” The use of an MDI with a spacing device held between the patient's lips reduces the need to tightly coordinate inhalation and activation of the inhaler. Proper education and consistent use of the spacing device greatly increases drug effectiveness and reduces the amount of wasted medication. Examples of inhaled anticholinergics include ipratropium bromide (Atrovent, Apovent, Aerovent) and tiotropium (Spiriva). Examples of beta-adrenergic agonists are more numerous and include albuterol (Ventolin, Proventil, AccuNeb, Vospire, ProAir), metaproterenol (Alupent), formoterol (Foradil), and salmeterol (Serevent).

Inhaled ipratropium bromide and sympathomimetic agents (beta₂-agonists) are the mainstays of therapy to provide relief of bronchospasm, and they are considered first-line treatments for patients with chronic bronchitis. The anticholinergic agent ipratropium produces greater bronchodilation, and the effects last longer compared to sympathomimetic agents, but it has a slower onset of action. Beta₂-agonists such as albuterol provide more rapid bronchodilation but have a shorter duration of action than ipratropium, except for the long-acting agent salmeterol. However, salmeterol should only be used as maintenance therapy, not as a rescue bronchodilator. Oral sympathomimetic agents are rarely tolerated in the dosages required for sustained, adequate relief of bronchospasm, and these agents can worsen concomitant cardiovascular disease.
The effects of therapy with short-acting inhaled beta$_2$-agonists in patients with chronic bronchitis have been shown to improve pulmonary function, breathlessness, and exercise tolerance; there is some evidence that chronic cough improves with regular use, but there is no significant reduction in sputum production with this therapy. In comparison, the long-term effects of ipratropium therapy have been shown to improve pulmonary function and breathlessness, reduce the incidence and severity of coughing, and significantly reduce the volume of sputum. Inhalation of the anticholinergic tiotropium has shown significant bronchodilation and relief of dyspnea in COPD patients, but it has virtually no effect on coughing.

Administration of ipratropium delivered through an MDI (three to six puffs every six hours) is often enough to achieve an optimal outcome in patients with chronic bronchitis and COPD. Ipratropium works by blocking the muscarinic acetylcholine receptors in the smooth muscles of the bronchi in the lungs, which dilates them, but it does not decrease mucociliary clearance. Inhaled ipratropium produces few side effects; the most common are dry mouth, tiredness, skin flushing, nausea, and headache.

If the outcome of using ipratropium is suboptimal, then beta$_2$-agonists should be administered or combined with ipratropium. The combination of ipratropium and a beta$_2$-agonist (initially administered by an MDI, two puffs of each agent every six hours) often allows adequate, sustained relief of bronchospasms while minimizing the adrenergic side effects associated with higher doses of the beta$_2$-agonists alone. Ipratropium is combined with albuterol under the trade names Combivent (an MDI) and Duoneb (a nebulizer) for the management of chronic bronchitis, COPD, and asthma. Ipratropium is combined with fenoterol under the trade names Duvovent and Berodual-N for the management of asthma and with fenoterol under the trade names Duvovent and Berodual-N for the management of asthma.

In contrast to anticholinergics, beta$_2$-agonists act upon the beta receptors and stimulate adenylyl cyclase activity which closes calcium channels and relaxes the smooth muscle that lines the bronchi. High doses of beta$_2$-agonists can cause a variety of side effects, the most common being hand tremor, anxiety, headache, muscle cramps, dry mouth and palpitation. Other more serious symptoms, albeit less common, include tachycardia, arrhythmia, paradoxical bronchospasm, hypotension, hypokalemia, urticaria, myocardial ischemia, insomnia, and behavioral disturbances.
Theophylline, also known as dimethylxanthine, is a methylated xanthine derivative drug used in therapy for respiratory diseases such as chronic bronchitis, COPD, and asthma. Theophylline has long been a mainstay of therapy for chronic bronchitis, although narrow therapeutic range, numerous side effects and common drug interactions limit its use nowadays. Theophylline is administered intravenously and orally, not through an MDI. In regard to respiratory diseases, its actions include relaxing bronchial smooth muscle, improving collateral ventilation and mucociliary clearance, increasing heart rate and blood pressure, and mildly reducing inflammation. Therapy with oral theophylline does improve cough in stable patients with chronic bronchitis. Theophylline therapy is usually only considered if administration of ipratropium and/or beta₂-agonists proves to be suboptimal. However, a long-acting theophylline preparation taken in the evening can be useful in patients whose symptoms worsen at night and in whom more frequent inhaler use would further disrupt sleep.

2) Corticosteroids

Corticosteroids mimic the effects of hormones naturally produced in the adrenal glands sitting atop the kidneys. When prescribed in doses that exceed the body's usual levels, corticosteroids suppress inflammatory reactions. As such, corticosteroids are able to decrease bronchial swelling and mucus secretion, which reduces airway obstruction and allows for better airflow. They can be delivered by inhalation using an MDI (commonly used in chronic bronchitis and asthma management) or by systemic therapy with oral or parenteral preparations. Inhaled steroids often cause fewer side effects than systemic (oral) steroids. Examples of steroids include prednisone, methylprednisolone (Medrol, Depo-Medrol), budesonide (Pulmicort), fluticasone (Flovent), beclomethasone (Qvar) and mometasone (Asmanex). Combination therapy with both steroids and bronchodilators can also be utilized, such as fluticasone with salmeterol (Advair).

There is limited evidence to justify the use of inhaled corticosteroids to control cough in patients with stable chronic bronchitis, although combined therapy with long-acting beta₂-agonists have been shown to reduce the exacerbation rate and to reduce cough in long-term trials in patients with COPD. Therapy with inhaled corticosteroids is usually only recommended when airflow obstruction is severe or very severe (FEV1 less than 50 percent) and when there is a history of frequent acute exacerbations of chronic
bronchitis. As such, the use of corticosteroids has generally been discouraged because there is little or no evidence of benefit in stable patients with chronic bronchitis, and the well-known side effects precludes any long-term trials in the future. A maximum of a two-week trial is recommended for use in patients who exhibit an acute exacerbation of chronic bronchitis in order to reduce the likelihood of side effects. Potential risks of corticosteroid therapy include steroid myopathy which can reduce ventilatory muscle strength, immune system suppression, edema, weight gain, and steroid-induced osteoporotic vertebral compression fractures.

3) PDE4 Inhibitors

Phosphodiesterase type-4 (PDE4) inhibitors are a newer class of anti-inflammatory drug that can be used for acute exacerbations of chronic bronchitis and COPD. PDE4 hydrolyzes cyclic adenosine monophosphate (cAMP) to inactive adenosine monophosphate (AMP). Thus, inhibition of PDE4 blocks hydrolysis of cAMP, thereby increasing levels of cAMP within cells, which suppresses the release of cytokines and other inflammatory signals and inhibits the production of reactive oxygen species. As such, PDE4 inhibitors display anti-inflammatory properties and may have antidepressive and antipsychotic effects. PDE4 inhibitors such as roflumilast (Daliresp, Daxas) are used primarily for acute exacerbations that involve excessive bronchitis and mucus production, although they are not intended to replace first-line treatments such as ipratropium and beta₂-agonists. Roflumilast is taken orally as a pill, not inhaled.

4) Over-the-Counter Drugs

Over-the-counter (OTC) cough suppressants such as dextromethorphan (Pertussin, Vicks 44, Benylin), guaifenesin (Robitussin, Mucinex) and codeine (OTC in Canada) are recommended only for short-term symptomatic relief of coughing and may make patients feel more comfortable; however, there is no scientific evidence that they cause bronchodilation or help mucus to become less viscous. Studies have shown that codeine and dextromethorphan (but not pipazethate) suppress coughing frequency by 40-60 percent, although only small patient populations have been investigated.

5) Antibiotics
Therapy with antibiotics is currently not recommended for patients with stable chronic bronchitis because of concerns about antibiotic resistance and the potential side effects of the drugs. However, the use of antibiotics for treatment of an exacerbation of chronic bronchitis is recommended as it has been shown to shorten the course of the episode. The use of antibiotics is most effective in patients with purulent sputum, severely obstructed airflow and in those with a greater severity of the three main symptoms of chronic bronchitis: coughing, excessive sputum production, and dyspnea. A meta-analysis of studies of antibiotic therapy for chronic bronchitis conducted during the past 40 years identified only six controlled trials in which any documented improvement in peak expiratory respiratory flow occurred with antibiotic use. However, while the mean airflow improvement was generally modest, patients with more severe symptoms seemed to benefit the most. It should be noted that antibiotic therapy does not significantly affect cough frequency or clearance when compared to a placebo.

In instances of acute exacerbations, antibiotic therapy should be directed against Streptococcal and Haemophilus species, as well as Moraxella catarrhalis. Ampicillin and other first-line antibiotics such as tetracyclines (doxycycline), trimethoprim-sulfamethoxazole (Bactrim), fluoroquinolones (levofloxacin) and the second-generation macrolides (clarithromycin, azithromycin) generally have good activity against these lower respiratory pathogens and penetrate well into bronchial tissues. Acute exacerbations can also be caused by viruses, in which case antibiotics are strongly contraindicated. Sputum culture is important for distinguishing a bacterial from a viral exacerbation.

Relatively common side effects of antibiotic use include acquired resistance to antibiotic therapy, serious allergic reactions (including anaphylaxis), nausea, diarrhea, disruption of the intestinal flora and fauna, systemic overgrowth of pathogenic bacteria (such as Clostridium difficile) and yeast species (such as Candida albicans), and numerous potential interactions with other drugs.

A role for antibiotic prophylaxis in patients having four or more acute exacerbations per year has been suggested, although the effectiveness of this approach in preventing hospitalizations or morbidity has not been documented. A more defined role exists for yearly influenza immunizations, since post-influenza bacterial infections are a significant cause of exacerbations of chronic bronchitis.
Summary of Recommendations

1) For patients with chronic cough who have constant exposure to respiratory irritants such as personal tobacco use, passive smoke exposure, and workplace hazards, avoidance should always be recommended. It is the most effective means to improve or eliminate the cough of chronic bronchitis. Approximately 90 percent of patients will have resolution of their cough after smoking cessation.

2) For stable patients with chronic bronchitis, there is no role for long-term prophylactic therapy with antibiotics.

3) For patients with acute exacerbations of chronic bronchitis, the use of broad-spectrum antibiotics is recommended along with short-acting beta₂-agonists or anticholinergic bronchodilators (those with more severe airflow obstruction at baseline are the most likely to benefit); theophylline should not be used for treatment of severe exacerbations.

4) For patients with chronic bronchitis, central cough suppressants such as codeine and dextromethorphan are recommended only for short-term symptomatic relief of coughing.

5) For stable patients with chronic bronchitis, ipratropium bromide therapy should be offered to improve cough and be considered a first-line drug.

6) For stable patients with chronic bronchitis, therapy with short-acting beta₂-agonists can be used to control bronchospasm and relieve dyspnea; in some patients, it may also reduce chronic cough.
7) For stable patients with chronic bronchitis, treatment with theophylline should be considered to control chronic cough if ipratropium and/or beta_2-agonists are ineffective; however, careful monitoring for complications is necessary.

8) For stable patients with chronic bronchitis, treatment with a long-acting beta_2-agonist when coupled with short-term use of an inhaled corticosteroid can be offered to control chronic cough.

9) For stable patients with chronic bronchitis and an FEV1 of less than 50 percent or those with frequent acute exacerbations, inhaled corticosteroid therapy should be considered for short-term use.

10) For stable patients with chronic bronchitis, long-term maintenance therapy with oral corticosteroids such as prednisone should not be used; there is no evidence that it improves cough and sputum production and the risks of serious side effects are high.
References:

30) PDR Medical Staff. PDR Guide to Drug Interactions, Side Effects and Indications; 2009 edition.