Tiotropium bromide

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Abstract: Therapy with bronchodilators forms the pharmacologic foundation of the treatment of patients with COPD. Bronchodilators can significantly lessen dyspnea, increase airflow, improve quality of life, and enhance exercise performance. While bronchodilators decrease airway resistance and lessen dynamic hyperinflation in patients with COPD, they have not been shown to alter the rate of decline in FEV_1 over time, or improve patient survival. Fairly recently, a long-acting, once-daily anticholinergic medication, tiotropium bromide, has been developed which may improve symptom management in COPD patients. This paper reviews anticholinergic pharmacologic therapy for patients with COPD focusing on tiotropium bromide, and discusses treatment strategies based on disease stage. It is important to recognize that while bronchodilators improve symptoms, a multimodality treatment approach including respiratory and rehabilitative therapy, nutrition services, psychosocial counseling, and surgical care, is often necessary for the best possible care of patients with COPD.

Keywords: COPD, tiotropium, anticholinergic, emphysema, pharmacology

Introduction

Chronic obstructive pulmonary disease (COPD) is an enormous health threat that currently ranks as the fourth leading cause of morbidity and mortality in the US (National Heart, Lung, and Blood Institute 1998), and is the only major disease with increasing mortality (Benson and Marano 1998; Centers for Disease Control and Prevention 1999). In the year 2000, COPD accounted for over 1.5 million visits to emergency departments in the US (Mannino et al. 2002). The prevalence of COPD is also exploding internationally. By the year 2020, the World Bank and the World Health Organization project that COPD will rank fifth as a cause of worldwide disability (Murray and Lopez 1997a, 1997b, 1997c). Given the increasing patient population, there has been a great push to develop medications that will appreciably affect the care of patients with this devastating and costly disease (Croxton et al 2003).

Anticholinergic medications are a class of drugs that have long been used to improve symptomatology of patients with COPD (Gross 1988; Dollery 1991; Bauer 1992). A new inhaled anticholinergic medication, tiotropium bromide (Boehringer Ingelheim, Ingelheim, Germany), is now being used in this patient population. This medication appears to be more effective in treating patients with COPD compared with older anticholinergics. This review will discuss the pharmacology of anticholinergic bronchodilators focusing on tiotropium bromide, and discuss treatment strategies based on disease stage.

Methods

A Cochrane Database and MEDLINE search from 1966 to October 2005, and a search of the PubMed database using the terms COPD, emphysema, tiotropium, anticholinergic, and autonomic nervous system was performed. Bibliographies of identified articles were then reviewed for further references. Non-English,

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and non-human studies were excluded. Bibliographies of review articles were examined and original research was then systematically evaluated.

Pharmacology of the autonomic nervous system

The autonomic nervous system through cholinergic nerve fibers is responsible for mediating mucus secretion and bronchial smooth muscle tone in the lung. Branches of the vagus nerve innervate muscarinic cholinergic (M) receptors in parasympathetic ganglia in the lung using acetylcholine as the primary neurotransmitter. No less than 5 muscarinic cholinergic receptor subtypes (M_1–M_5) have been identified in the lung. M_1 and M_3 mediate bronchoconstriction and mucus production. M_2 is a presynaptic postganglionic autoreceptor in small airways that inhibits the M_1 and M_3 receptors via negative feedback mechanisms (Figure 1). Stimulation of the M_2 receptor inhibits cholinergic action in the lung, so agonism of this receptor leads to inhibition of bronchoconstriction. At this time, the M_4 and M_5 receptors have poorly understood function in the lung (Mak et al 1993; Barnes 1993a, 1993b; Barnes et al. 1997; ZuWallack 2004).

Older anticholinergic medications, such as ipratropium (Figure 2), block the M_1, M_2, and M_3 receptors. Specifically, these medications decrease the bronchoconstrictive action of the M_1 and M_3 receptors, but also block the inhibitory action of the M_2 receptor. Ipratropium then dissociates fairly quickly from these receptors. Thus, ipratropium is a weak bronchodilator because of its relatively short half-life compared with newer anticholinergics, and because of its inhibitory action on the M_2 receptor. A new anticholinergic called tiotropium bromide (Figure 3) has been developed which also antagonizes M_1, M_2, and M_3 receptors. However, tiotropium quickly dissociates from the M_2 receptor, and thus its net effect is that of a selective M_1 and M_3 antagonist. Tiotropium, therefore, blocks the bronchoconstrictive action of the M_1 and M_3 muscarinic receptors while allowing M_2 inhibition of bronchoconstriction to continue. Slow dissociation of tiotropium from the M_1 and M_3 receptors accounts for its long half-life.

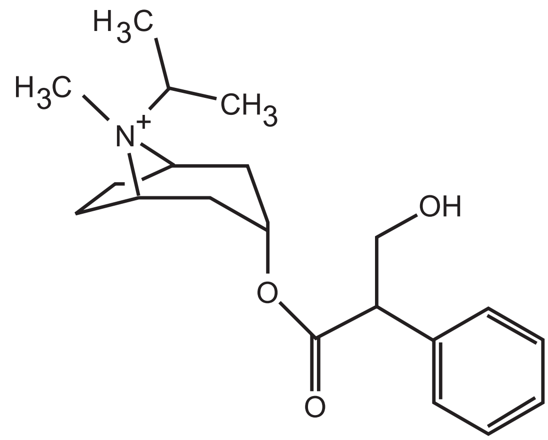

Figure 2 Chemical structure of ipratropium.

Anticholinergic medications

Ipratropium

Anticholinergic medications (Table 1) are some of the most common medications used in the treatment of COPD

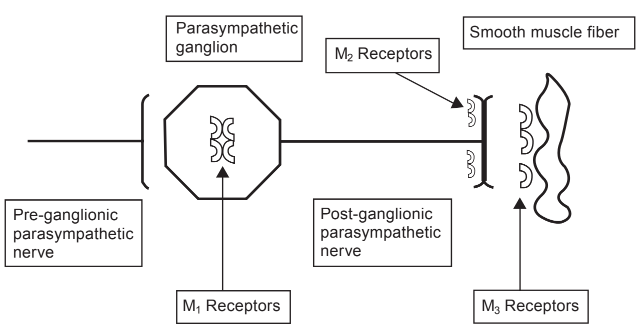

Figure 1 Pulmonary muscarinic cholinergic receptors. M_1 and M_3 receptors mediate bronchoconstriction and mucus production in the lung. M_2 receptors inhibit M_1 and M_3 receptors via negative feedback. Ipratropium inhibits all three muscarinic receptors. Tiotropium quickly dissociates from the M_2 receptor but continues to antagonize the M_1 and M_3 receptor. Thus, tiotropium blocks bronchoconstriction and allows inhibition of bronchoconstriction to continue. The slow dissociation of tiotropium from the M_1 and M_3 receptors accounts for its long half-life.

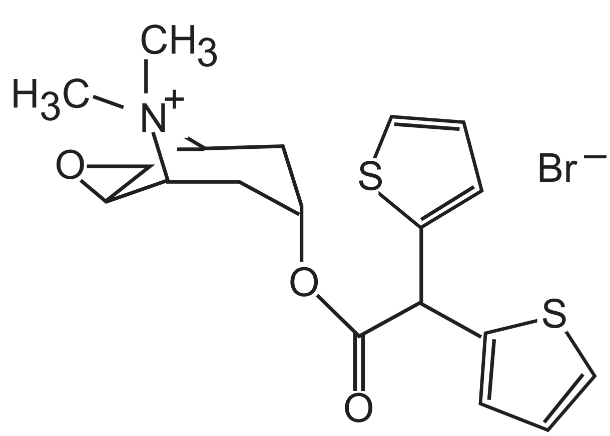

Figure 3 Tiotropium bromide. Note the similarity to ipratropium (Figure 2) and the presence of the quaternary nitrogen group, which is responsible for its efficacy.

Table 1 Anticholinergics used in the management of COPD

Drug	Metered dose inhaler (μg)	Nebulizer (mg)	Time to peak effect (hr)	Duration (hr)
ipratropium	40–80	0.25–0.5	1–2	4–6
oxitropium	200	–	1–2	6–7
albuterol–ipratropium[a]	90/18	–	1–2	6–8
tiotropium	18	–	2–3	24–36

Adapted from Dollery (1991), Bauer (1992), Gross (1988), Lipson (2004).
[a]combined β_2-agonist and anticholinergic.

and have been used safely for decades (Anthonisen et al 1994). They are available for delivery by both metered dose inhaler and nebulizer. Their duration of action varies between 4 and 36 hours. Most anticholinergics, such as ipratropium, are quaternary ammonium derivatives that have difficulty crossing the blood–brain barrier and are poorly absorbed in the body (Ferguson 2000). The quaternary ammonium structure likely enhances their efficacy and minimizes the side-effects that beleaguer β-agonists. These medications have been shown to diminish the sense of dyspnea, and mucus hypersecretion via their inhibition of the cholinergic system (Ghafouri et al 1984). Anticholinergics have also been shown to improve oxyhemoglobin saturation with sleep (Martin et al 1999; McNicholas et al 2004), and provide similar, or greater, bronchodilation compared with β_2-agonists (Karpel 1991; COMBIVENT Inhalation Aerosol Study Group 1994; Rennard et al 1996). Data suggest that in some patients who have COPD, ipratropium may be effective when β_2-agonists are not effective (Braun and Levy 1991). Anticholinergics have a reasonable safety profile, and are not prone to receptor downregulation or tachyphylaxis (Rennard et al 1996). However, these medications may be associated with an increased number of adverse cardiovascular events in patients with COPD (Anthonisen et al 2002).

Combining ipratropium with long-acting β_2-agonists may also have additive benefits for patients. Van Noord et al (2000) studied salmeterol compared with salmeterol plus ipratropium. The study found that both salmeterol alone or in combination with ipratropium improved bronchodilation compared with placebo, but the combination of the medications appeared to elicit a greater bronchodilator response and improvement in FEV_1 than salmeterol alone. Dorinsky et al (1999) found that the combination of ipratropium and albuterol was superior to either medication alone in identifying patients with reversibility on spirometric testing of pulmonary function.

Tiotropium

Tiotropium, with its extremely long duration of action, avoids one of the main limitations of first-generation anticholinergic medications – the necessity of frequent dosing. Casaburi et al (2002) showed that once-daily tiotropium, compared with placebo, improved bronchodilation, dyspnea scores, health status scores, and decreased COPD exacerbations and hospitalizations. The primary adverse side-effect observed in the study was dry mouth. In a fairly short 12-week study in patients with COPD, tiotropium was shown to provide a higher post-dose FEV_1, and higher peak and FVC, compared with salmeterol (Briggs et al 2005). In a 6-month study of tiotropium compared with salmeterol, tiotropium produced a greater degree of bronchodilation, reduction in dyspnea scores, and improvement in health-related quality of life (Donohue 2002). In a longer 1-year study, Vincken et al (2002) demonstrated diminished salbutamol use and improvement in peak expiratory flow rates. Compared with ipratropium, tiotropium appeared to reduce the number of exacerbations, increase the time to a first exacerbation, and increase the time to first hospitalization in patients with COPD. Quality of life scores were also improved. More recently, a randomized, placebo-controlled study of tiotropium in mostly male veterans with COPD showed a decrease in exacerbation rate compared with placebo. While the effect was small, it was statistically significant (Niewoehner et al 2005). At this time, it is not known whether this effect would also be seen in women.

Anticholinergics and exercise tolerance

Numerous studies have demonstrated improvements in exercise tolerance in patients with COPD with the use of anticholinergic medications (Spence et al 1993). Hay et al (1992) studied the use of oxitropium in patients with COPD. The study showed significant improvements in breathlessness and walking distance, and an increased FEV_1 with its use. Improvements in walking distances and symptoms were unrelated to changes in either FEV_1 or FVC, which may suggest that routine reversibility testing is not a good predictor of symptomatic benefit in patients with COPD.

Tsukino et al (1998) investigated the combined effect of theophylline with ipratropium. The study found that both ipratropium and theophylline improved exercise tolerance but combination therapy with the two medications produced greater improvements in pulmonary function and exercise capacity than either drug alone. In this study the average serum theophylline levels were around 18.3μg/mL, which increases the risk of adverse side-effects.

Casaburi et al (2005) showed that the combination of tiotropium in combination with pulmonary rehabilitation improved treadmill endurance and reduced dyspnea scores compared with rehabilitation alone. These effects seemed to be sustained for at least 3 months after the rehabilitation course was completed. Maltais et al (2005) demonstrated that tiotropium improved symptom-limited exercise tolerance compared with placebo in COPD patients up to 8 hours following dosing.

Tiotropium also appears to reduce lung hyperinflation at rest and during exertion (Celli et al 2003; Maltais et al 2005). This may be an important effect as dynamic hyperinflation likely contributes to the sense of dyspnea that often limits exercise in COPD patients (O'Donnell et al 1998; Taube et al 2000). Following 4 weeks of therapy, tiotropium clearly improves lung volumes compared with placebo (Figure 4) (Celli et al 2003).

Recently, combination therapies using tiotropium have been shown to be beneficial in the treatment of patients with COPD. van Noord et al (2005) have demonstrated

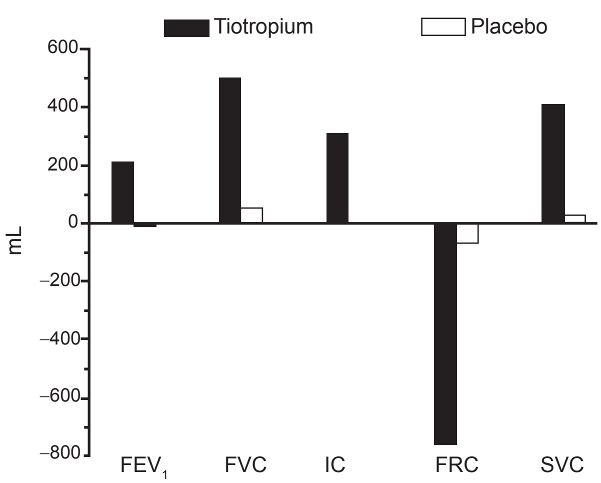

Figure 4 Tiotropium improves lung volumes compared with placebo. Reproduced from Celli B, ZuWallack R, Wang S, et al. 2003. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. *Chest*, 124:1743–8. Copyright©2003, with permission from *CHEST*.
Abbreviations: FRC, functional residual capacity; IC, inspiratory capacity; SVC, slow vital capacity.

Table 2 Stages of COPD

Stage	Findings
0: At Risk	Normal spirometry Chronic cough, sputum production, dyspnea
I: Mild COPD	$FEV_1/FVC < 70\%$ FEV_1[a] $\geq$80% predicted May have chronic cough, sputum production, dyspnea
IIA: Moderate COPD	$FEV_1/FVC < 70\%$ $50\% \leq FEV_1 < 80\%$ predicted May have chronic cough, sputum production, dyspnea
IIB: Moderate COPD	$FEV_1/FVC < 70\%$ $30\% \leq FEV_1 < 50\%$ predicted May have chronic cough, sputum production, dyspnea
III: Severe COPD	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted and either respiratory failure[b] or *cor pulmonale*

Adapted from ATS (1995).
[a]all FEV_1 values refer to post bronchodilator measurements.
[b]$PaO_2 < 60$ mmHg.

that tiotropium produces a greater improvement in daytime FEV_1 than formoterol. Interestingly, night-time change in FEV_1 was not different between the two medications. However, combination therapy with the two medications (with daily dosing) improved FEV_1 to the greatest extent. While combination therapy appears to be a trend in caring for patients with more advanced disease, it is important to recognize that individual and combination pharmacologic medications are expensive, add significantly to the cost of healthcare, and have not been found to alter the overall decline in lung function seen in patients with COPD. Additional studies will be necessary to determine the best combination(s) of bronchodilators in the treatment of patients with COPD.

The staging of COPD

Various respiratory societies, including the American Thoracic Society (ATS) and the European Respiratory Society (ERS), have developed staging systems to help identify patients at risk for COPD and to aid in standardization of therapies and clinical trials. The ATS guidelines for staging COPD are shown in Table 2 (ATS 1995). "Stage 0" disease describes a smoker with normal spirometry who has symptoms of chronic mucus production or cough. "Stage I" or "Mild COPD" describes the patient with objective spirometric evidence of airflow obstruction. Their FEV_1/FVC ratio is < 70%, and their post-bronchodilator FEV_1 is ≥ 80% of predicted. They may or may not have symptoms of airflow obstruction, chronic bronchitis, or dyspnea. "Stage II" or "Moderate COPD" is characterized by typical symptoms, airflow obstruction with the FEV_1/FVC ratio < 70%, and the FEV_1 between 30% and 80% of predicted. It is considered "IIA" disease if the FEV_1 is ≥ 50% of predicted, and "IIB" disease if the FEV_1 falls between 30% and 50% of predicted. "Stage III" or "Severe COPD" is characterized by appropriate symptomatology, a FEV_1/FVC ratio < 70%, and a FEV_1 < 30% of predicted. Evidence of respiratory failure or *cor pulmonale*, with a FEV_1 < 50% of predicted, is also consistent with "Severe" disease.

Treatment according to disease stage

Spirometry should be used to help identify and stage patients with COPD as their treatment is often predicated upon disease stage (Figure 5) (Lipson 2004). However, following stable patients with multiple repeat spirometric tests may not be useful (Wilt et al 2005). "At risk" patients must refrain from cigarette smoking, and should obtain annual influenza vaccination and should be vaccinated with the pneumococcal vaccine every 5 years. Bronchodilator therapy on an "as

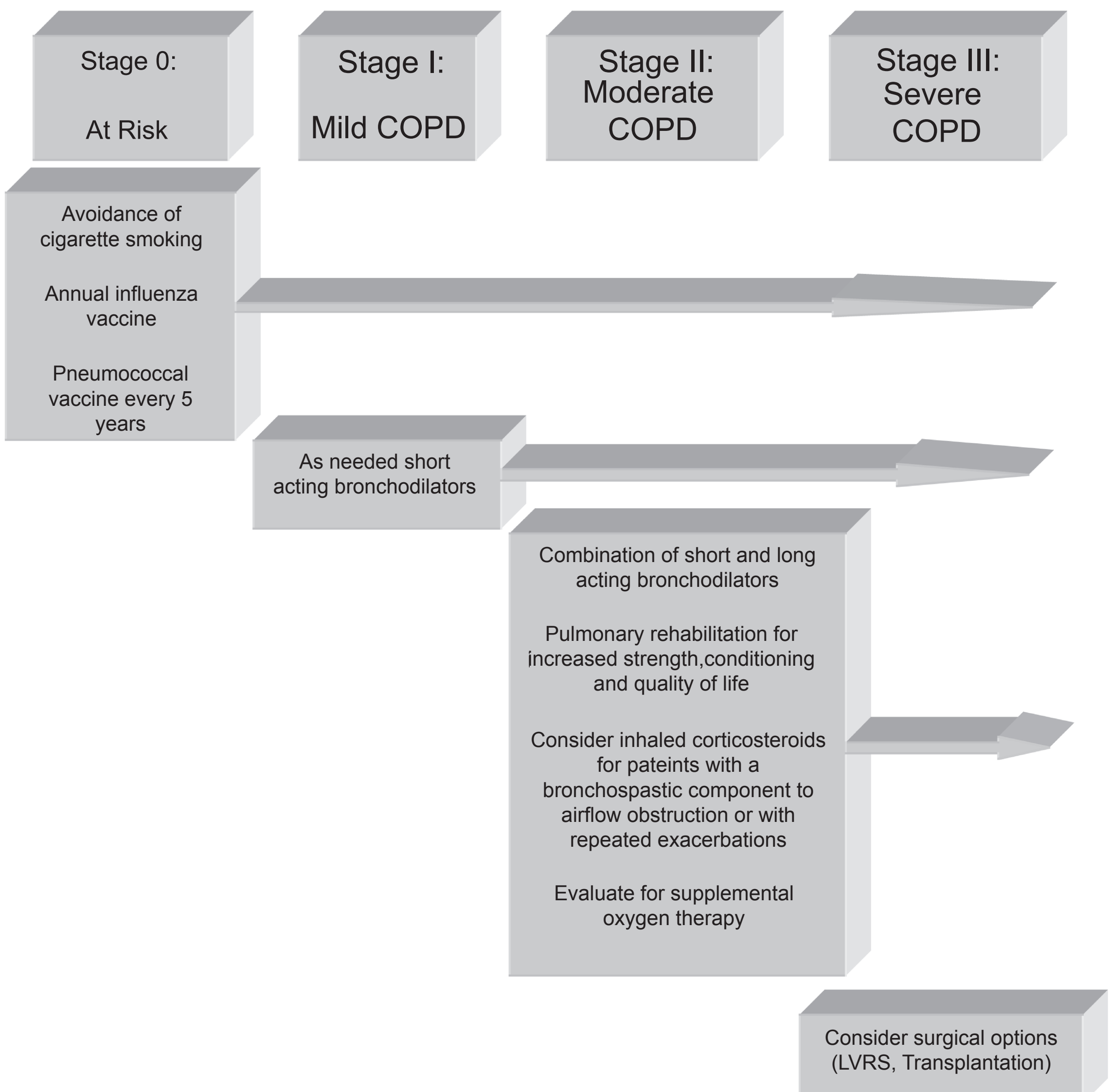

Figure 5 Treatment of COPD by stage. Reproduced from Lipson DA. 2004. Redefining treatment in COPD: new directions in bronchodilator therapy. *Treat Respir Med*, 3:89–95. Erratum in *Treat Respir Med*, 3:181. Copyright©2004, with permission from Adis International Ltd.
Abbreviations: LVRS, lung volume reduction surgery.

needed" basis with short-acting bronchodilators may be used for managing mild COPD patients (Vathenen et al 1988).

A combination of short- and long-acting bronchodilators is often used to treat moderate emphysema. Inhaled anticholinergic medications and combinations of short- and long-acting β_2-agonists are standard treatments. Inhaled corticosteroids may be useful for patients with more severe disease, or those patients with a partially reversible, bronchospastic component to airflow obstruction. These medications may also be useful in patients who have repeated exacerbations (Burge et al 2000; The Lung Health Study Research Group 2000; Sin and Tu 2001; Hattotuwa et al 2002). Medications combining an inhaled steroid and a long-acting β-agonist, such as fluticasone and salmeterol, may also be useful in this patient population (Mahler et al 2002).

Pulmonary rehabilitation is an important addition to pharmacologic therapy in patients with COPD because severe dyspnea leads to a sedentary lifestyle, subsequent deconditioning, and muscle weakness (ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel 1997). Pulmonary rehabilitation increases strength, quality of life, sense of well-being, and exercise tolerance. It is also useful in breaking the vicious cycle of progressive debilitation in patients with advanced lung disease (Fishman 1994; Celli 1997; ATS 1999).

All patients with moderate COPD should be evaluated for the need for supplemental oxygen. Patients who exhibit oxyhemoglobin desaturation at rest, or with exertion, should be prescribed supplemental oxygen to maintain oxyhemoglobin saturations greater than 90%. Long-term oxygen therapy, in COPD patients who require it, has been shown to improve survival, exercise tolerance, and quality of life (Nocturnal Oxygen Therapy Trial Group 1980; Medical Research Council Working Party 1981; Tarp and Celli 1995). A patient requires supplemental oxygen if they demonstrate an oxyhemoglobin saturation ≤88% or a $PaO_2 \leq 55$ mmHg. Additionally, an oxyhemoglobin saturation <89% or a PaO_2 <60 mmHg also qualifies a patient for supplemental oxygen if there is evidence of *cor pulmonale*, a hematocrit >56%, dependent edema, or other signs suggestive of heart failure.

The treatment of severe COPD is equivalent to that of moderate disease, except patients in this stage should also be evaluated for potential surgical treatments such as lung volume reduction surgery or lung transplantation (Cooper et al 1996; Sciurba et al 1996; Arcasoy and Kotloff 1999; Criner et al 1999; Geddes et al 2000; Flaherty et al 2001; Kotloff et al 2001; National Emphysema Treatment Trial Research Group 2001, 2003).

Conclusions

Anticholinergic medications are safe and useful adjuncts in the care of patients with COPD. While they have not been shown to alter the rate of decline in the FEV_1, or alter survival, they improve exercise tolerance, dynamic hyperinflation, and breathlessness. These medications improve quality of life measures and reduce the risk of exacerbation (Barr et al 2005). Newer anticholinergics, such as tiotropium, have the added advantage of once-daily dosing and more specific cholinergic receptor targets.

Clearly, the best treatment of COPD remains smoking cessation and abstinence from smoking. Evaluation and care of the patient with COPD must include respiratory and rehabilitative therapy, nutrition services, psychosocial counseling, and evaluation for the need for long-term oxygen therapy. Physicians, and persons charged with caring for patients with COPD, await the development of novel therapies that will further improve survival, and the quality of the lives of patients with lung disease.

Disclosures

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