# The development of anticholinergics in the management of COPD

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**Abstract:** Anticholinergics have been used to treat obstructive respiratory disease for many years from historical preparations of the deadly nightshade genus, to the more recent developments of ipratropium, oxitropium, and tiotropium. The medical treatment of airways obstruction has focused on achieving maximal airway function through bronchodilators. Of the two main bronchodilators, beta2-agonists are often the first treatment choice although there is evidence of equivalence and some suggestions of the superiority of anticholinergics in chronic obstructive pulmonary disease (COPD). The following review looks at the background of anticholinergics, their pharmacological properties, and the evidence for use with suggestions for their place in the treatment of COPD.

**Keywords:** anticholinergics, ipratropium, oxitropium, tiotropium, breathlessness, exacerbations, health related quality of life, exercise tolerance

## Background

A combination of genetic, constitutional, familial, behavioral, sociodemographic, and environmental factors predispose patients to chronic obstructive pulmonary disease (COPD), with cigarette smoking the most common cause (BTS 1997; NCCCC 2004). These factors damage the airways and impair the defense and repair mechanisms (Turato et al 2002), leading to structural narrowing of the airways, which is predominantly irreversible due to a combination of fibrosis, mucus hyperplasia, and alterations in vagal bronchomotor tone. Loss of elastic recoil in the lung caused by parenchymal destruction characterizes the emphysemic component. Increased resistance in the airways as a result of airway inflammation increases the thickness of the airway walls, and narrows the airways, which reduces the driving pressure; the obstructive element (Turato et al 2002). There is also excessive mucus secretion increased by goblet cell proliferation; the bronchitic component. For patients this means declining lung function, breathlessness and other symptoms, exacerbations, and reductions in health status or health related quality of life (HRQoL).

Few treatments have been manufactured specifically for patients with COPD. Treatments evolved from asthma treatments through a tendency to treat the two diseases as one, a misunderstanding of the pathogenesis of the diseases and a nihilistic view of COPD with treatment considered as palliative rather than curative or restorative. This was reinforced by insufficient evidence to conclude that any specific pharmacotherapeutic agents significantly altered the outcome of the disease process (Halpin 2001).

A growing evidence base now supports the use of bronchodilators in COPD to improve function, exercise tolerance and health status (Crockett 2000; Halpin 2001; NIHLBI 2001; NCCCC 2004). Inhaled therapy is the cornerstone of treatment comprising anticholinergics which relax airway smooth muscle by

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blocking cholinergic tone (the primary reversible component in COPD), and beta2-agonists which are nonspecific functional bronchodilators that work via the sympathetic pathway (Cooper and Tashkin 2005). There is increased evidence of a greater response to anticholinergics than beta2-agonists (Barnes 1999; Cooper and Tashkin 2005). This review discusses the history of anticholinergic therapy, pharmacology, dynamics and kinetics, clinical efficacy, and tolerability with conclusions and suggestions of place in therapy.

## A brief history of anticholinergics

Anticholinergics originate from botanical preparations of the deadly nightshade family (Solanaceae) used for hundreds of years in many cultures worldwide (Chapman et al 2006). Datura is a genus of the Solanaceae family and it grows worldwide (Chapman et al 2006). The burning roots, stems, and seeds of these plants release an aerosol of potent alkaloids, one of which is the antimuscarin compound, atropine. It was the inhalation of this medicinal smoke that was a treatment for obstructive airways disease for many centuries (Chapman et al 2006). In addition to atropine other alkaloids, including scopolamine and hyoscyamine, are released with additional effects including intoxication, hallucinations, and poisoning. Derived from atropine-containing plants, anticholinergics work by inhibiting the parasympathetic–cholinergic system (Gross 1995). Brewis (1990) suggests that it was the Egyptians who first used anticholinergics in respiratory medicine and there is evidence of their use in Ayurvedic medicine in the 17th century and by the Greek physicians of Hippocrates' era (Gandevia 1975).

In Britain, Sims recorded the first use of Datura to treat asthma in 1802 (Gandevia 1975) and although its use was controversial, it became a popular over the counter medication taken in the form of a cigarette or pipe tobacco. The amount of atropine reaching the lungs was dependent on deep inhalation with a small amount absorbed across the oral mucosa or swallowed and absorbed via the gastrointestinal tract.

Atropine based agents became the standard bronchodilators for respiratory disorders however, the unpleasant side effects of the emerging adrenergic drugs in the 1920s and theophyllines in the next decade led to a decline in the use of these agents for many years (Chapman et al 2006).

Following studies describing the role of the parasympathetic system in controlling the calibre of the airways there was an emerging interest in anticholinergic therapies (Widdicombe 1966; Gandevia 1975; Barnes 1986). This led to the recognition that inhibiting the parasympathetic-cholinergic system could be an alternative therapeutic approach to improving airflow, and revived an interest in using anticholinergics. Available anticholinergics include ipratropium bromide, oxitropium, and tiotropium, which work by blocking the muscarinic receptors for the neurotransmitter acetylcholine released from cholinergic nerve endings in the airways.

## Pharmacology, dynamics, and kinetics

All cells communicate by chemical and electrical signaling. Although a complex process, the relevant features of intercellular signaling are achieved by the secretion of a chemical molecule by the transmitting cell. The signaling molecule, known as a ligand, travels to the receiving cell, which recognizes the ligands that are relevant to it and binds the cell with a reversible bond. The process of chemical binding changes the receptor protein activating it, causing the appropriate alteration in cell function and producing an appropriate, graded response. Many drugs mimic endogenous chemical signals by binding as ligands at receptors on cell membranes. Those drugs that bind to such recognition sites without causing a response, but which prevent access to the site by the natural agonist are known as antagonists or receptor blockers. The speed with which the reversible bond breaks down gives the duration of a drug's action.

Anticholinergics are antagonists of muscarinic receptors and, in therapeutic use, have no other significant pharmacological effects (Barnes 2004). In animals and humans there is a small degree of resting bronchomotor tone due to tonic vagal nerve impulses that release acetylcholine in the vicinity of airway smooth muscle (Barnes 2004). Anticholinergic drugs can block this release. Acetylcholine may also be released from other cells apart from nerve cells, but the mechanism for this is not well documented. The synthesis of acetylcholine in epithelial cells is increased by inflammatory stimuli increasing the expression of choline acetyltransferase that may contribute to cholinergic effects in airways disease, Muscarinic receptors are expressed in the airway smooth muscle of small airways not innervated by cholinergic nerves, but may be an important mechanism of airway narrowing in peripheral airways (Barnes 2004). Anticholinergics therefore inhibit reflex cholinergic bronchoconstriction and have no direct blocking effect on inflammatory mediators such a histamine and leukotrines in bronchial smooth muscle.

There are several subtypes of muscarinic receptors, three of these found in the airways have different functioning

effects (Barnes 1986, 1993). These receptors principally $M_1$, $M_2$, and $M_3$ are predominantly localized in the smooth muscle of the airways, although higher in density in the proximal airways and in high density to the submucosal glands (Barnes 1986, 1993). Anticholinergic drugs work by blocking the receptors (muscarinic receptors) from the neurotransmitter acetylcholine, which is released from cholinergic nerve endings in the airways.

### $M_1$ receptors

$M_1$ receptors are localized to parasympathetic ganglia in the airways, where they appear to function as regulators of ganglionic transmission. Preganglionic nerves release acetylcholine, which acts on the nicotinic receptors on ganglionic cells to activate postganglionic nerves. Only a proportion of preganglionic signals are translated into postganglionic impulses. $M_1$ receptors facilitate transmission through these ganglia and enhance cholinergic reflex bronchoconstriction (Celli 2004).

### $M_2$ receptors

$M_2$ receptors are located on the ends of cholinergic nerve endings and act as feedback inhibitors of acetylcholine release from the nerve. Blocking these receptors leads to an increased release of acetylcholine and increased bronchoconstrictor response to cholinergic nerve stimulation. Ipratropium and oxitropium bromide are nonselective blockers and therefore block the $M_2$ receptors, which increases acetylcholine release and reduces the degree of blockade or the duration of action on the $M_3$ receptors. These possibly explain reported paradoxical bronchoconstriction after the use of ipratropium bromide (Celli 2004).

### $M_3$ receptors

The $M_3$ receptors mediate the bronchoconstrictor response to cholinergic nerve stimulation and cholinergic agonists. Tiotropium alone of the anticholinergics exhibits kinetic receptor subtype selectivity in which the dissociation from $M_3$ receptors is approximately 35 hours thus giving sustained bronchodilation with a once daily dosing (Disse et al 1999).

Ipratropium, oxitropium, and tiotropium are quaternary ammonium compounds, which effectively means that they are electrically charged and as such are not absorbed from the gastrointestinal tract and do not pass the blood–brain barrier. This reduces any potential anticholinergic side effects. As the vagal tone on the airway appears to be the major reversible element in COPD, even a small effect on vagal tone through bronchodilatation may benefit the patient (Gross 1993). Anticholinergics are effective bronchodilators in COPD where the effects of bronchoconstriction are inflated by airways resistance in narrowed airways. Cholinergic nerves also encourage mucus secretion so anticholinergics may be seen to be useful in reducing airways mucus secretion although this has only be shown in one study with oxitropium (Coe and Barnes 1986).

Anticholinergic bronchodilators have also been documented as having a beneficial effect on the quality of patients' sleep in asthma (Coe and Barnes 1986).

## The role of anticholinergics in COPD

Achievement of maximal airway function through regular use at the maximum tolerated levels of bronchodilators. improves symptoms and exercise tolerance (Gross 1993; Barnes 2004; Pauwels et al 2001; NCCCC 2004). The short-acting bronchodilators, ipratropium and oxitropium, are slower in onset for bronchodilatation than the beta2-agonists, but have a sustained mode of action and may be considered at least as effective and possibly more so in COPD (Table 1) (Chapman 1991). Guidelines advocate that, for severe COPD, combination therapies with regular $\beta_2$-agonist and anticholinergic therapy should be given (Gross 1993; Pauwels et al 2001; Barnes 2004; NCCCC 2004).

### Ipratropium bromide

Ipratropium bromide was introduced in 1974 and made it possible to give local anticholinergic effects to the lung whilst avoiding the systemic side effects of atropine due to its poor absorbtion (Chapman 1993). Ipratopium has been studied in patients with acute exacerbations of COPD either in an inhaled or nebulized form. Ipratropium starts to act within 15–30 minutes, but maximal bronchodilatation may take up to 90 minutes in COPD (Rebuck et al 1987; Karpal et al 1990). The duration of action is approximately six hours so in comparison with beta2-agonists it has a slower onset of action, probably a longer duration of action, and does not cause tachyphylaxis or the drop in oxygenation that can occur with beta2-agonists (Karpal 1993). This fall in oxygenation could be due to an initial worsening of ventilation-perfusion mismatch resulting from pulmonary vasodilatation and/or increased cardiac output with beta2-agonist use or it may be that anticholinergic agents have less effect on pulmonary circulation, are not systemically absorbed, and therefore do

**Table 1** The beta2-agonists and anticholinergics

| Medication | Mode of action | Reported side effects |
|---|---|---|
| Salbutamol | Rapid onset of action | Fine tremor |
| | Duration of action 3–5 hours | Headache |
| Terbutaline | Rapid onset of action | Nervous tension |
| | Duration of action 3–5 hours | Muscle cramps |
| Salmeterol | Maximum effect after 40 minutes | Tachycardia |
| | Duration of action 12 hours | Arrythmias |
| Formoterol | Rapid onset of action | Paradoxical bronchospasm |
| | Duration of action 12 hours+ | Hypokalemia |
| | | Urticaria |
| | | Angioedema |
| | | Sleep and behaviour disturbance in children |
| | | Fall in oxygen saturations |
| Ipratropium | Maximum effect after 15–90 minutes | Dry mouth |
| | | Nausea |
| | Duration of action 3–6 hours | Headache |
| Oxitropium | Maximum effect after 30–60 minutes | Urinary retention |
| | | Blurred vision |
| | Duration of action 6 hours* | Glaucoma risk |
| | (*little evidence of longer duration than 6 hours) | Paradoxical bronchospasm |
| Tiotropium | Onset of action | Tachycardia and atrial fibrillation |
| | Duration of action 35 hours | has been reported |

not cause deterioration in blood oxygen tension (Gross and Bankwala 1987). Oral anticholinergics are not a treatment option for COPD because of unacceptable side effects, whereas inhaled anticholinergics have virtually no systemic absorption.

## Oxitropium bromide

Oxitropium bromide became available in the early 1990s and was promoted as having a longer mode of action than ipratropium bromide. However, a review of studies by Hardy and colleagues (1992) concluded that there was little evidence of this longer mode of action using equivalent doses. The published studies were small and either did not show any significant differences or were in asthmatic patients (Peel et al 1984; Ikeda et al 1995). Oxitropium use in the UK was minimal and it is no longer on formulary.

## Tiotropium bromide

Tiotropium bromide is a once-daily, long-acting anticholinergic with high potency as a selective antagonist at the muscarinic acetylcholine receptors and with kinetic selectivity (Barnes 2000; Littner et al 2000). Tiotropium rapidly dissociates from the autoinhibitory $M_2$ receptors, but slowly dissociates from $M_1$ and $M_3$ receptors, which mediate acetycholine-mediated bronchoconstriction and mucus secretion. This increased duration of binding at the $M_3$ receptors results in prolonged bronchodilatation, allowing a once-daily dose compared with the three to four doses per day previously necessary with ipratropium (Barnes 2000; Littner et al 2000). Tiotropium is rapidly absorbed into the circulation with a peak plasma concentration within 5 minutes followed by a rapid fall within an hour to a steady state and a terminal half life of 5–6 days that is independent of dose. Calculations are that this concentration would occupy <5% of muscarinic receptors and would account for the low incidence of side effects (Barnes 2000; Littner et al 2000).

Tiotropium has a good safety profile with relatively few side effects. Those documented effects are mainly oral problems, particularly an unpleasant taste, and potential problems are urinary problems and glaucoma.

Tiotropium bromide is delivered to the lungs by inhalation through a device known as the Spiriva® HandiHaler® (Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT, USA) (Figure 1). a device developed specifically for use by

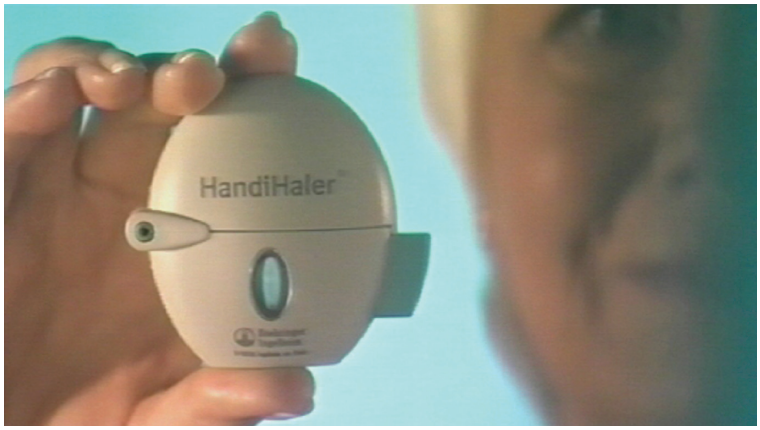


**Figure 1** The Spiriva® HandiHaler® (Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT, USA).

patients with COPD and tested at variable inspiratory flow rates, which enables use by patients at all levels of disease severity. The device delivers individual doses by means of a capsule inserted into the device that is then activated and subsequently inhaled. It is a once daily dose, which may be beneficial in terms of adherence with treatment.

## Clinical findings

In published clinical trials, anticholinergics have been compared with placebo, the beta2-agonists, and each other. The relevant findings from the trials relate to improvements in spirometric measurements, breathlessness, exacerbation rates, HRQoL, and exercise tolerance during rehabilitation. More recently long acting beta2-agonists and anticholinergic have been combined to look at effectiveness (Di Marco et al 2006).

### Spirometric measurements

In COPD bronchodilators are the mainstay of treatment and clinical trials have been based on demonstration of improvements in lung function although this is by definition relatively fixed in this disease.

In a review of seven clinical trials comparing ipratropium with a beta2-agonist long-term therapy with ipratropium improved baseline forced expiratory volume at one second ($FEV_1$) whilst the beta2-agonist did not (Rennard et al 1996). For tiotropium, improvements in trough $FEV_1$ by 12% over baseline in comparison with placebo were found (Casaburi et al 2002). Trough forced vital capacity (FVC) and morning and evening peak expiratory flow rate (PEFR) also improved (Casaburi et al 2002; Serby 2002). Bronchodilation was also consistent over the year, which showed that patients did not become resistant to the effects (Casaburi et al 2002).

Compared with ipratropium, tiotropium improved spirometric values (Serby 2002). Trough $FEV_1$ improved from baseline by 120 ml with tiotropium, and declined by 30 ml with ipratropium after 1 year, implying that the effects of tiotropium were sustained (Serby 2002).

In comparison with salmeterol, tiotropium improved lung function measured over 12 hours and was sustained at 6 months (Donahue et al 2002). However the combined studies of Donohue and colleagues (2002) and Witek and Mahler (2002) looking at spirometry at 13 and 3 hours in comparison with salmeterol, did not report any spirometric outcomes. This supports the fixed nature of lung function in COPD.

Trough $FEV_1$ has been criticized as a measure in tiotropium trials. Baseline $FEV_1$ was calculated as the mean of two readings measured in the morning of the randomization visit prior to the administration of the study medication. Trough $FEV_1$ is the predose $FEV_1$ defined as the mean of the two $FEV_1$ readings taken at one hour and at five minutes before administration of the study medication. The trough $FEV_1$ response was defined as the difference between baseline and trough $FEV_1$ and was the primary bronchodilator efficacy endpoint in the studies. As tiotropium has a sustained action of around 35 hours this would influence measurements taken at 24 hours.

Forced expiratory volume at one second measurements do not correlate well with the symptoms experienced by patients and may be at best a surrogate measure for many of the goals of COPD management. Patients are individual and some endure a substantial loss of lung function with little in the way of symptoms or impact on their lives. At the other end of the scale, there are patients sensitive to small changes in lung

function that will report symptoms and impact on quality of life at an earlier level of physiological functioning.

## Breathlessness

Patients with COPD report a number of symptoms, principally breathlessness. In severe COPD, breathlessness occurs on minimal exertion and when undertaking simple everyday tasks. Increasing breathlessness often encourages the patient to seek medical help, although this is often at a late stage of the disease by which time the damage is largely irreversible (BTS 1997; Pauwels et al 2001; NCCCC 2004). Patients often report disturbed breathing patterns, particularly at night when lung function is suboptimal. Increased vagal tone is the likely reason for an increase in nocturnal bronchoconstriction (Coe and Barnes 1986).

Breathlessness appears to be linked physiologically to dynamic hyperinflation in the lungs. In patients, dynamic hyperinflation means an increased residual volume in the lung; inspiratory capacity (IC) is reduced and increasing the tidal volume is ineffective at reducing dynamic hyperinflation. Lung hyperinflation will influence inspiratory muscle function, breathing patterns, the ability of the body to eliminate carbon dioxide, and the feelings of breathlessness (O'Donnell et al 2004).

Breathlessness is a useful outcome measure in clinical trials. Tiotropium in comparison with placebo, improved breathlessness measured on the baseline dyspnea index (BDI) and on the transitional dyspnea index (TDI) in comparison with ipratopium (Serby 2002; Vincken et al 2006). The tiotropium group used less salbutamol, which may be a proxy measure of reduced breathlessness (Casaburi et al 2002). The BDI and TDI are validated multidimensional measurements based on activities of daily living of patients and provide data on the progression of disease; these instruments can be used to evaluate symptoms, which are important in clinical trials (Witek and Mahler 2002).

## Exacerbations

Patients report symptoms including cough, sputum production, wheeze, and chest tightness, and these are often linked to a periodic worsening of symptoms, known as exacerbations that vary in severity and duration. This worsening of symptoms regularly leads to general practitioner consultations and frequently to hospitalization, and has a detrimental effect on lung function, symptoms, general well-being, and quality of life (Wedzicha et al 2001). Reducing exacerbation rates is an important outcome measure in disease management (Dusser et al 2006).

Exacerbations in the tiotropium studies were defined as changes in cough, wheeze, sputum production, and dyspnea lasting more than 3 days. When compared with placebo and ipratropium, tiotropium bromide delivered a significant reduction in exacerbations (Casaburi et al 2002; Vincken et al 2006). In comparison with placebo, tiotropium reduced exacerbations by 20%, delayed the onset of exacerbations, reduced hospitalizations by 47% and demonstrated a 50% reduction in actual days in hospital (Casaburi et al 2002). Tiotropium also reduced exacerbations by 24% at 1 year hospital in comparison with placebo (O'Donnell et al 2004). When compared with placebo, tiotropium reduced exacerbations, associated healthcare resource use, and improved airflow over a year (Dusser et al 2006).

A recent meta-analysis pooling data from 22 studies that compared anticholinergics and beta2-agonists concluded that inhaled anticholinergics, but not beta2-agonists significantly reduced severe exacerbations and respiratory deaths in COPD patients and that the beta2-agonists were associated with a greater risk of death and possible worsening disease control (Salpeter et al 2006).

Rees (2002) suggests that in the Vincken (2006) study nine patients need to be treated with tiotropium rather than ipratropium for I year to prevent one exacerbation and 23 patients treated to prevent one hospital admission, although patients had low exacerbation rates overall. In the Casaburi study seven patients needed to be treated to keep one patient exacerbation free and 26 to prevent one hospital admission (Rees 2002). The cost-benefit analysis of these studies requires further evaluation and low overall exacerbation rates may not reflect what currently happens in practice.

Whilst exacerbations and mortality are useful clinical outcomes, exacerbation data from clinical trials may vary in the definition of an exacerbation, which can influence the interpretation of the clinical findings. The findings will also be dependent on the average number of exacerbations of patients entering the trials.

## Health-related quality of life

One of the goals of COPD management is to improve health status and there are many published and well validated instruments for measuring this. It is important is that the authors of the tools specify what constitutes a meaningful outcome from using their measurements to allow for the significance of the findings to be evaluated.

Tiotropium when compared with placebo was reported as having a positive effect on HRQoL (Casaburi et al 2002;

Serby 2002). In the Saint George's Respiratory Questionnaire (SGRQ), there were improvements both in the total score and in the symptom, activity, and impact on life scores (Casaburi et al 2002). In comparison with ipratropium, both groups improved although tiotropium had a statistically significant impact over ipratropium using the SGRQ, indicating that the HRQoL improved and this was still evident at 12 months so the effect was sustained (Vincken et al 2006).

## Exercise tolerance and pulmonary rehabilitation

In COPD, changes in IC, a surrogate measure for hyperinflation, correlate to patient-focused outcomes such as dyspnea on exercise. When tiotropium was compared with placebo, there was a positive effect on IC maintained over a 24 hour period (Celli et al 2003).

O'Donnell and colleagues (2004) tested the hypothesis that using tiiotropium would be associated with a sustained reduction in lung hyperinflation improving exertional dyspnea and exercise performance. This randomized double-blind placebo-controlled, parallel-group study compared tiotropium and placebo over 42 days of treatment and concluded tiotropium was associated with sustained reductions of lung hyperinflation both at exercise and rest. They hypothesized that the resultant increases in IC permitted greater expansion of tidal volume and contributed to improvements in both exertional dyspnea and exercise endurance. The study was seen as supporting the hypothesis that lung hyperinflation, mechanical restriction, respiratory discomfort and exercise intolerance are closely related in COPD (O'Donnell et al 2004).

As exercise tolerance and the ability to undertake everyday activities are often compromised in COPD, primarily due to dyspnea, any reduction in dyspnea will be an important treatment goal. Pulmonary rehabilitation has a proven benefit in COPD showing improvements in exercise tolerance. Casaburi and colleagues (2005) tested the hypothesis that tiotropium would be beneficial in improving ventilatory mechanics and augment the exercise tolerance benefits of pulmonary rehabilitation. Tiotropium was compared with placebo over an eight week programme of pulmonary rehabilitation and improved endurance at a constant work rate treadmill task with clinically meaningful improvements in dyspnea and health status compared with pulmonary rehabilitation alone (Casaburi et al 2005). Effects were sustained for 3 months following rehabilitation (Casaburi et al 2005). Short acting beta2-agonists, inhaled steroids, and theophylline were allowed in the study, but not long acting beta2-agonists or short acting anticholinergics so patients could be seen as not optimally managed in the placebo group.

## Adverse effects

Adverse effects of medications have to be balanced against positive effects. Side effects of anticholinergics, including dry mouth, glaucoma, and urinary retention are mediated principally by the $M_3$ receptors. Tiotropium appears to be well tolerated, with dry mouth being the only significant adverse event, which led to 1% of patients withdrawing from the study in the Casaburi and colleagues (2002) study.

# Conclusions and place in therapy

In the past, the care, management, and treatment of COPD has not been optimal. Treatment has often followed asthma treatment, although the causes, disease process, management and treatments differ. COPD is increasingly seen as a separate disease so studies into specific treatments increase and our knowledge improves. From available evidence anticholinergic therapy is better than placebo and appears in some studies to be superior to the beta2-agonists. Whilst oxitropium and specifically ipratropium have shown benefits, tiotropium has an edge over its precursors in terms of its selectivity and clinical effects, specifically in terms of patients' symptoms.

Although guidelines support long-acting bronchodilators if patients remain symptomatic after short-acting bronchodilators (NCCCC 2004), it may be that earlier use of these agents and specifically tiotropium may lead to objective and subjective improvements. Whilst there is evidence that anticholinergics may be the preferential treatment of choice over beta2-agonists (Rees 2002), increasingly the long acting bronchodilators are being tested together and there is some evidence of synergism (Di Marco et al 2006).

Clearly anticholinergics have been used in obstructive disease for many years and they still have a relevant and useful place in therapy. Benefits now require further evaluation in clinical practice and the place of the therapies substantiated over the long term. Additionally patients enrolled in clinical trials, the level of severity of their disease, and exacerbation rates requires examination to ascertain if they are truly representative of the patient groups we see in clinical practice.

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