

# Role of tiotropium in the treatment of COPD

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**Abstract:** Tiotropium is a potent, long-acting, selective anticholinergic bronchodilator. Treatment with tiotropium produces sustained improvements in lung function, particularly FEV<sub>1</sub> (peak, trough, average, and area under the curve) compared with either placebo or ipratropium in patients with moderate to severe COPD. Preliminary evidence suggests that treatment with tiotropium may slow the rate of decline in FEV<sub>1</sub>, but this finding awaits confirmation. Tiotropium reduces lung hyperinflation, with associated improvements in exercise capacity. Tiotropium, compared with either placebo or ipratropium, improves a variety of patient-centered outcomes, including subjective dyspnea ratings and HRQL scores. Tiotropium reduces the frequency of COPD exacerbations and of hospitalizations due to exacerbations, but has not been shown to reduce all-cause mortality. Compared with the long-acting bronchodilators, tiotropium provides incrementally better bronchodilation, but it is not clearly superior in terms of patient-centered outcomes. Tiotropium has a good safety profile; however patients with severe cardiac disease, bladder outlet obstruction, or narrow angle glaucoma were excluded from all studies. Medico economic analyses suggest that treatment with tiotropium may also be cost-effective, primarily by reducing costs associated with hospitalizations.

**Keywords:** tiotropium, anticholinergic bronchodilator, chronic obstructive pulmonary disease

## Introduction

It is estimated that COPD afflicts from 4% to 10% of adults and is the fourth leading cause of death worldwide (Sullivan et al 2000; World Health Organization 2000; Michaud et al 2001; Halbert et al 2003). The true global burden of COPD may be even greater as the condition is often under-diagnosed (Halbert et al 2003). Cigarette smoking is the primary cause of COPD, but environmental and genetic factors also contribute to the disease burden. The primary objective of COPD management is disease prevention through promoting smoking cessation and improving air quality. Other important goals of COPD management include efforts to slow progression of the disease, improve symptoms and overall health status, treat and prevent exacerbations, and reduce mortality.

Inhaled bronchodilators play an important role for improving chronic symptoms and management of exacerbations in COPD, but they have not been shown to reduce mortality or slow the accelerated decline in lung function over time that typifies this disease. The two major classes of inhaled bronchodilators commonly used for COPD are beta adrenergic agonists and anticholinergics. In recent years longer-acting bronchodilators of both drug classes have been widely introduced into clinical practice, either complementing or replacing shorter-acting drugs. This article focuses on tiotropium (Spiriva®, Boehringer Ingelheim), a newly developed, long-acting, potent anticholinergic agent that was approved for use in Europe in 2002 and in the United States and Canada in 2004. We

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will review what has been learned about the clinical benefits and safety of this drug, relying primarily on results from peer reviewed multi-dose, randomized, controlled trials.

## Mechanism of action

Atropine, as well as the short-acting inhaled bronchodilator ipratropium, and the long-acting inhaled bronchodilator tiotropium, are muscarinic receptor antagonists. Unlike atropine, tiotropium and ipratropium (Atrovent®, Boehringer Ingelheim) are quaternary ammonium cation compounds that are poorly absorbed across cell membranes, thus limiting their effects mainly to the airways after inhalation. Three types of muscarinic receptors have been identified in human airways. Two of these receptors,  $M_1$  located in parasympathetic ganglia, and  $M_3$  located on airway smooth muscle, mediate bronchoconstriction via the discharge of acetylcholine from vagal nerve endings (Belmonte 2005).  $M_2$  receptors are located on postganglionic cholinergic nerve endings and on smooth muscle and provide negative feedback so as to counteract smooth muscle contraction. Thus, antagonism of the  $M_1$  and  $M_3$  receptors reduce smooth muscle tone and cause beneficial bronchodilation while inhibition of the  $M_2$  receptor has the opposite effect. Ipratropium and atropine nonselectively block all three receptors, but tiotropium is more selective for the  $M_1$  and  $M_3$  receptors, from which it dissociates much more slowly (Barnes 2000). Consequently, tiotropium is a somewhat more potent bronchodilator than is ipratropium, and has a much longer duration of action. A single dose of inhaled tiotropium produces bronchodilation that is sustained for 24 hours or more (Barnes 2000).

Cholinergic-mediated pathways also modulate mucus production, vascular tone, and possibly a variety of immune pathways in the airways, raising the question as to whether any of the clinical benefits of anticholinergic therapy in COPD might be mediated via mechanisms other than bronchodilation (Koyama et al 1992; Nomura et al 2003; Belmonte 2005). The evidence for this is inconclusive. Excess mucus production is thought to be clinically important in COPD. However, efforts to show that inhaled anticholinergics reduce the volume of sputum production in patients with obstructive lung disease have yielded mixed results (Lopez-Vidriero et al 1975; Tamaoki et al 1994).

## Characteristics of study populations

All tiotropium trials conducted to date enrolled relatively homogeneous populations of COPD patients (Table 1). Most patients had moderate to severe disease by spirometric criteria

(forced expiratory volume in one second/forced vital capacity [ $FEV_1/FVC$ ] < 0.70 and  $FEV_1$  < 65% of predicted) (National Heart, Lung and Blood Institute 2005). Patients with predominant asthma were excluded by clinical criteria. The majority of participants were men, and the average age of patients in most trials was typically in a range of 60–70 years. All trials banned concomitant use of ipratropium, and most prohibited the use of long-acting beta agonists, but inhaled corticosteroids and unlimited albuterol rescue therapy were generally permitted. Most trials also excluded patients with unstable heart disease, severe or inadequately treated urinary outflow obstruction, narrow angle glaucoma, or moderate to severe azotemia.

Delivery of tiotropium in all studies was by inhalation via a single-dose dry powder delivery device (Handihaler®, Boehringer Ingelheim) (Chodosh et al 2001). The dose of tiotropium was 18 µg/day, as dose-ranging studies indicated that higher doses increase the incidence of adverse effects without providing significant additional improvement in pulmonary function (Littner et al 2000). Tiotropium was usually given in the morning, although the time of administration has little effect on lung function over a 24-hour period (Calverley et al 2003).

## Effects on lung function and exercise Spirometry

Treatment-related bronchodilator effects, as assessed by spirometry, were evaluated in all tiotropium trials. Spirometry is a useful surrogate for clinical outcomes because airflow limitation is a defining feature of COPD and because spirometric variables such as the  $FEV_1$  correlate with the severity of respiratory symptoms, with exercise capacity, and with mortality, albeit in an imperfect fashion (Anthonisen et al 1986). The  $FEV_1$  is easily measured, and because it is more reproducible than most other efficacy outcomes in COPD, statistically significant changes can be detected with relatively modest sample sizes. Trough  $FEV_1$ , measured in the morning 23–24 hours after the last dose of study drug, was the primary outcome in a number of tiotropium studies. Other spirometric assessments included FVC, peak and area under the curve for both  $FEV_1$  and FVC, and inspiratory capacity (IC). The direction and relative magnitude of the changes seen with these measurements were generally similar to those observed with trough  $FEV_1$ .

Several short-term (4–12 weeks) studies demonstrated that tiotropium increases mean peak  $FEV_1$  by between 210 mL and 265 mL and mean trough  $FEV_1$  by between 120 mL and 184 mL (Celli et al 2003; O'Donnell et al 2004; Covelli et al 2005; Verkindre et al 2006). In a larger 12-week study,

**Table 1** Characteristics of trials and their study populations

<b>Tiotropium vs Placebo</b>	<b>N</b>	<b>Duration of trial</b>	<b>Age (yr)<sup>a</sup></b>	<b>Gender male/female</b>	<b>FEV<sub>1</sub><sup>a</sup> (% predicted)</b>	<b>FEV<sub>1</sub>/FVC<sup>a</sup> (%)</b>
Beeh 2006	1639	12 wk	62	1237/402	45	57
Calverly 2003	121	6 wk	66	75/46	41	51
Celli 2003	81	4 wk	64	50/31	38	43
Casaburi 2000	470	13 wk	65	307/163	39	46
Casaburi 2002	921	12 mo	65	599/322	39	46
Covelli 2005	196	12 wk	65	114/82	39	NA
Dusser 2006	1010	12 mo	65	889/121	48	54
Littner 2000	169	4 wk	66	96/73	42	NA
Maltais 2005	261	6 wk	63	189/72	43	44
McNicholas 2004	95	4 wk	66	66/29	32	45
Niewoehner 2005	1829	6 mo	68	1802/27	36	48
O'Donnell 2004	187	6 wk	60	138/49	42	45
Verkindre 2006	100	12 wk	60	94/6	35	40
<b>Tiotropium vs Ipratropium</b>						
Van Noord 2000	288	3 mo	64	238/47 <sup>b</sup>	41	45
Vincken 2002	535	12 mo	64	453/82	41	46
<b>Tiotropium vs LABA</b>						
Briggs 2003	653	6 mo	64	434/397	38	43
Brusasco 2003	1207	6 mo	64	920/287	38	43
van Noord 2005	71	6 wk	65	56/15	37	38
van Noord 2006	95	2 wk	64	72/23	38	41

<sup>a</sup>Data are presented as means<sup>b</sup>[sic] M/F numbers do not add up to total subjects in original report**Abbreviations:** LABA, long-acting beta agonists.

Beeh and associates showed that tiotropium increased mean trough FEV<sub>1</sub> by an average of 79 mL, compared with placebo (Beeh et al 2006). They found larger improvements in average trough FEV<sub>1</sub> (113 mL) in the subgroup of patients with milder COPD (FEV<sub>1</sub> 50%–70% predicted) compared with the group as a whole. In one trial, mean steady state trough FEV<sub>1</sub> occurred within 48 hours of treatment initiation, but mean FVC (trough and peak) continued to increase over the first week of continuous treatment (van Noord et al 2002).

Longer-term studies demonstrated similar sustained improvements in lung function with tiotropium. At the end of one 13-week study in patients with severe COPD (mean baseline FEV<sub>1</sub> 38% predicted), treatment with tiotropium increased peak FEV<sub>1</sub> by an average of 220 mL and trough FEV<sub>1</sub> by an average of 150 mL compared with placebo (Casaburi et al 2000). In a 1-year study of 921 patients with severe COPD (mean baseline FEV<sub>1</sub> 38%–39% predicted), treatment with tiotropium, compared with placebo, improved mean trough FEV<sub>1</sub> by between 120 and 150 mL on the various assessment days (Casaburi et al 2002). Similar results were reported in other 6-month and 12-month studies (Brusasco et al 2003; Niewoehner et al 2005). The MISTRAL study, performed in patients with somewhat milder COPD (mean FEV<sub>1</sub> 48% predicted), showed similar effects from tiotropium

on both peak and trough FEV<sub>1</sub> (Dusser et al 2006). Rodrigo and associates calculated that tiotropium, compared with placebo, conferred weighted mean improvements of 120 mL in the trough FEV<sub>1</sub> and 210 mL in the peak FEV<sub>1</sub> among 4214 patients entered in eight trials (Rodrigo et al 2006).

Overall, the correlation of FEV<sub>1</sub> changes with clinically relevant outcomes, such as dyspnea and health-related quality of life (HRQL), is relatively weak in COPD patients and no general consensus exists as to what constitutes a clinically meaningful improvement. Anchoring of FEV<sub>1</sub> changes to clinical outcomes, such as dyspnea and exacerbation, suggests that increases on the order of 100 mL are clinically noticeable in certain settings (Redelmeier et al 1996; Niewoehner et al 2000; Donohue 2005). Thus, it is expected that the bronchodilator effects with tiotropium should be sufficiently large to provide some meaningful impact on clinical outcomes.

## Acute bronchodilator responses as predictors of long-term tiotropium responses

Although asthma patients were excluded by clinical criteria in all of the tiotropium trials, none were excluded because the acute bronchodilator response exceeded some arbitrary upper

**Table 2** Effect of tiotropium on spirometry

Tiotropium vs Placebo	FEV <sub>1</sub> trough (mL)	FEV <sub>1</sub> peak (mL)	FVC trough (mL)	FVC peak (mL)
Beeh 2006	79	128	116	176
Calverly 2003	210	-	320	-
Celli 2003	160	220	330	480
Casaburi 2000	150	220	280	410
Casaburi 2002	120–150 <sup>a</sup>	190–220 <sup>a</sup>	260–290 <sup>a</sup>	420–510 <sup>a</sup>
Covelli 2005	184	265	213	388
Dusser 2006	120	-	170	-
Littner 2000	150	-	370	-
Maltais 2005	150	230	300	410
Niewoehner 2005	100	170	-	-
O'Donnell 2004	120	220	250	430
Verkindre 2006	110	210	80	-
<b>Tiotropium vs Ipratropium</b>				
Van Noord 2000	130	50	210	60
Vincken 2002	150	-	210	-
<b>Tiotropium vs LABA</b>				
Briggs 2003	18	46	120	64
Brusasco 2003	30	-	-	-
van Noord 2005	41	-3	74	-7

**Notes:** Data are presented as mean change from baseline.

<sup>a</sup>Range of change on different study days.

**Abbreviations:** LABA, long-acting beta agonists.

limit. Consequently, individual bronchodilator responses to a short-acting bronchodilator varied over a fairly wide range in those studies where that information is provided (Cazzola et al 2004a, b; Beeh et al 2006; van Noord et al 2006). None of the aforementioned studies reported whether initial responses to short-acting bronchodilators predicted long-term bronchodilator responses to tiotropium. In a secondary analysis of two 1-year trials, patients who had larger responses ( $\geq 12\%$  increase and  $\geq 200$  mL in FEV<sub>1</sub>) to tiotropium on study day 1 were compared with patients with poorer responses to tiotropium (Tashkin et al 2003). Responsive patients, compared with less responsiveness patients, exhibited greater improvement in mean trough FEV<sub>1</sub> at the end of the 1-year follow-up ( $212 \pm 17$  mL vs  $94 \pm 17$  mL, respectively), but differences in various clinical outcomes tended to be small and mostly statistically insignificant. Neither the initial response to a short-acting bronchodilator nor the initial response to tiotropium has been shown to provide useful information about long-term clinical outcomes with tiotropium. This is consistent with other evidence demonstrating the futility of using acute bronchodilator responses as a guide to therapy in COPD (Calverly et al 2003).

## Disease modification – FEV<sub>1</sub> decline over time

Accelerated age-related decreases in the FEV<sub>1</sub> typify the natural history of COPD. Though the FEV<sub>1</sub> is a surrogate out-

come, it is widely accepted that slowing the decline in FEV<sub>1</sub> over time can be viewed as “disease modifying”, as there is the expectation of eventual reductions in morbidity and mortality. To date, smoking cessation is the only intervention that is known to slow the annual rate of decline in FEV<sub>1</sub> in patients with COPD (Anthonisen et al 2002a). Pharmacologic interventions have been mostly unsuccessful. Several large randomized trials failed to show a statistically significant effect of high dose inhaled corticosteroids on FEV<sub>1</sub> decline over 3 years in patients with mild to moderate COPD, though summary estimates do not exclude a small effect (Highland et al 2003; Sutherland et al 2003). Similarly, the Lung Health Study found that regular treatment with ipratropium over a 5-year period had no effect on the rate of decline in FEV<sub>1</sub> in patients with mild COPD (Anthonisen et al 1994).

Preliminary evidence suggests that treatment with tiotropium might alter the progression of COPD. A post-hoc analysis of data from a previously published study (Casaburi et al 2002) found that treatment with tiotropium between study days 8 and 344 statistically significantly reduced the mean rate of decline in trough FEV<sub>1</sub> by 46 mL/year compared with placebo (Anzueto et al 2005). In a systematic review, Barr and colleagues confirmed that result and also reported a similar effect from tiotropium when it was compared with ipratropium (Barr et al 2006a; Vincken et al 2002). A mean effect size of 46 mL/year is substantially larger than that reported in the ICS trials (5–8 mL/year) and would be viewed

as clinically meaningful, if confirmed. These preliminary results formed the basis of the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial. The study has completed enrollment of 6000 patients with COPD and the primary objective is to determine whether tiotropium slows the decline in lung function (as measured by FEV<sub>1</sub>) over a 4-year period (Boehringer Ingelheim 2004). Results of the study are expected in 2008.

## Dynamic hyperinflation and exercise performance

Along with airflow limitation, hyperinflation is thought to play an important role in the genesis of exertional dyspnea, the symptom that is so characteristic of more advanced COPD (Calverley et al 2006). In contrast to normal subjects, end-expiratory lung volume (EELV) increases during exercise in patients with severe COPD. Hyperinflation can be assessed indirectly without resorting to plethysmography by measuring the reduction in IC (O'Donnell et al 1998). Hyperinflation is essential for maintaining the higher expiratory flow and minute ventilation rates that allow the COPD patient to meet the increased metabolic demands of exercise (Calverley et al 2006). However, dynamic lung hyperinflation also carries a penalty because the respiratory system becomes progressively less compliant at larger lung volumes. It is thought that the resultant increase in the elastic component of respiratory muscle work has an important bearing on the sensation of breathlessness.

O'Donnell et al (2004) compared tiotropium with placebo for 6 weeks and found that tiotropium increased resting and end-exercise IC and VC, decreased resting residual volume and functional residual volume, and improved mean exercise endurance time by an average of 105 sec (21%). In a 4-week study Celli et al (2003) showed that treatment with tiotropium, compared with placebo, improved resting trough IC (by an average of 220 mL), and reduced trough thoracic gas volume (by an average of 540 mL). Similar effects on lung hyperinflation and exercise have been reported in other trials (Maltais et al 2005; Beeh et al 2006; Verkindre et al 2006).

Studies of dynamic hyperinflation during exercise provide interesting new insights into the mechanism of dyspnea relief from bronchodilators in COPD patients. It has been suggested that bronchodilator-induced increases in IC and EELV may be better predictors of improvement in exertional dyspnea and exercise times than changes in FEV<sub>1</sub>, though this claim has not been fully substantiated (Belman et al 1996; O'Donnell et al 1998). IC measurements are substantially less reproducible than more conventional measurements,

such as the FEV<sub>1</sub> (ATS/ERS 2005), and their capability for distinguishing small bronchodilator effects is correspondingly weaker. It also bears emphasizing that the capability for reducing dynamic hyperinflation, though best studied with tiotropium, is most likely a generic effect common to all bronchodilators (Belman et al 1996).

Tiotropium may also provide a useful adjunct to pulmonary rehabilitation. Casaburi et al (2005) demonstrated that tiotropium amplified the benefits of endurance training in patients with severe COPD (FEV<sub>1</sub> 35% predicted). Over an 8-week program, patients receiving tiotropium improved their mean constant work rate endurance time by 80% as compared with only 57% in patients receiving placebo. This difference was well maintained over a subsequent 12-week period when all patients continued study drug but received no further formal endurance training.

## Arterial blood gases and sleep-related oxygen desaturation

The effect of tiotropium on resting awake arterial blood gases has not been well studied, although tiotropium does improve sleep-related oxygen desaturation (S<sub>a</sub>O<sub>2</sub>) in patients with COPD. After 1 month of treatment with tiotropium, administered once a day in the evening, mean S<sub>a</sub>O<sub>2</sub> during REM was modestly (3.1%) but statistically greater than placebo, with a similar trend for patients who took tiotropium in the morning (McNicholas et al 2004). The improvement in S<sub>a</sub>O<sub>2</sub> was most strongly correlated with increases in end-of-treatment FEV<sub>1</sub>. Tiotropium had no effect on the S<sub>a</sub>O<sub>2</sub> while subjects were awake, the amount of time they spent in REM, or self-reports of sleep quality or daytime sleepiness.

**Table 3** Summary of tiotropium effects

Benefits	
• Sustained effects for at least 24 hours from a single dose	
• Improved lung function, exercise capacity, and health-related quality-of-life	
• Reduced frequency of COPD exacerbation and related hospitalizations	
• Better bronchodilation compared with ipratropium or long-acting beta agonists	
• Additive bronchodilation when combined with a long-acting beta agonist	
Adverse effects	
• Dry mouth	
• Urinary retention	
• Safety in patients with severe cardiac disease, renal failure, untreated bladder outlet obstruction or narrow angle glaucoma is not established	



## Patient-centered outcomes

Direct measurement of patient-centered outcomes, such as health related quality of life, respiratory symptoms, exacerbations, mortality, adverse drug events, and costs, are increasingly recognized as the most important components in COPD trials (Tashkin 2006). Tiotropium has been shown to improve many of these outcomes.

## Health-related quality of life (HRQL)

The St. Georges Respiratory Questionnaire (SGRQ) is the most widely used and arguably the best validated instrument for assessing health status in COPD patients. An improvement of at least 4 points in the SGRQ score is judged to be the clinically meaningful difference (Jones et al 1997). In a summary analysis of 3 controlled trials, Barr et al (2006b) reported that tiotropium, compared with placebo, improved total SGRQ score by a weighted mean difference of  $-3.3$  units (95% CI,  $-5.6$  to  $-1.0$ ). While the mean change fell short of the 4-unit change that is considered clinically noticeable, treatment with tiotropium, compared with placebo, did significantly increase the likelihood that an individual patient would achieve an improvement of 4 units or more (odds ratio, 1.9; 95% CI, 1.4–2.7).

## Dyspnea

Dyspnea plays a central role in the disability of patients with advanced COPD (Ries 2006). Dyspnea evaluation is a component of the SGRQ, but the Transitional Dyspnea Index (TDI) provides a more specific assessment of functional impairment due to breathlessness (Mahler et al 1984). The clinically meaningful difference for the TDI score has been reported to be a 1 unit change (Witek et al 2003). Compared with placebo, tiotropium affected statistically significant mean improvements of 1.1 units in a 6-month trial and 0.8–1.1 units at various time points in a 1-year trial (Casaburi et al 2002; Brusasco et al 2003).

## Exacerbations

Results from multiple trials consistently show that tiotropium, compared with placebo, reduces the frequency and severity of COPD exacerbations (Casaburi et al 2002; Brusasco et al 2003; Niewoehner et al 2005; Verkindre et al 2005; Beeh et al 2006; Dusser et al 2006). Most trials were not clearly designed with exacerbation as the primary outcome and much of the information about exacerbations was collected through adverse event reporting. The single trial that was designed specifically to evaluate exacerbation frequency was also the largest of the trials and it fully confirmed the results

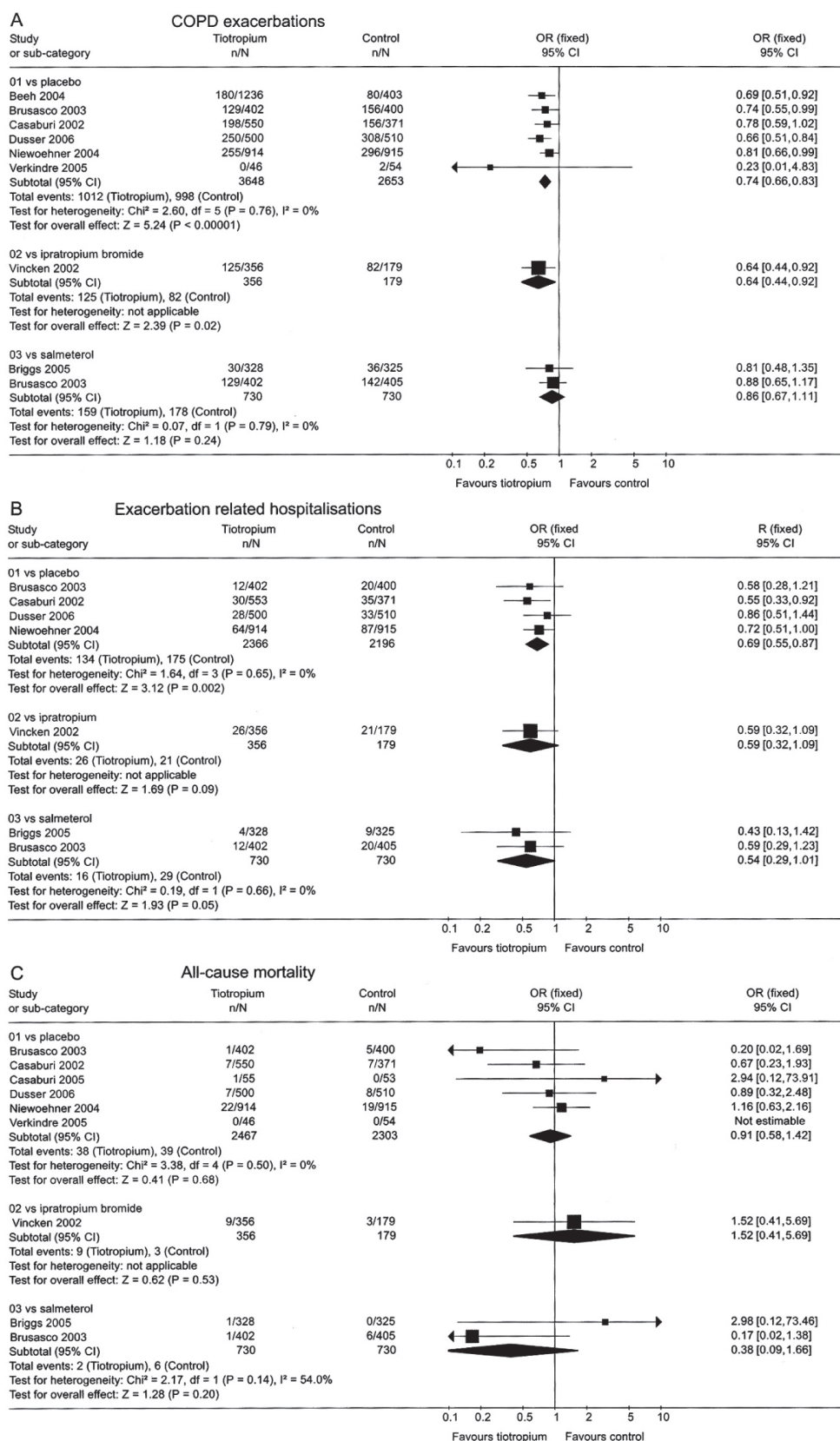
obtained in other studies (Niewoehner et al 2005). Though there was some variation from trial to trial, most used an “event-based” definition of exacerbation that required the occurrence of typical symptom complexes coupled with some form of medical intervention, such as antibiotic or systemic corticosteroid use.

Several meta-analyses summarized the results from available trials (Sin et al 2003; Wilt et al 2005; Barr et al 2006a, b; Rodrigo et al 2006). A recent systematic review included 6 placebo-controlled trials of greater than 12 weeks duration and involving 6301 patients (Barr et al 2006b). The summary odds ratio of having one or more exacerbations for tiotropium, compared with placebo, was 0.74 (95% CI, 0.66–0.83) (Figure 1). No subgroups have been clearly identified to whom treatment is more effective or less effective.

There is also solid evidence that tiotropium reduces the frequency of hospitalizations among those patients who suffer a COPD exacerbation. Hospitalization is very important in human terms, because of its morbidity and increased risk of mortality, and in economic terms because of the inordinately high costs. In the United States, hospital admissions are the single largest source of medical expenditures for COPD, accounting for up to 70% of the total costs of medical care for this disease (Hilleman et al 2000).

Information about COPD hospitalization rates were provided in four large placebo-controlled trials (Casaburi et al 2002; Brusasco et al 2003; Niewoehner et al 2005; Dusser et al 2006). All studies are consistent in showing fewer hospitalizations among subjects who received tiotropium with the relative reduction in individual trials ranging between 13% and 42%. Barr et al (2006b) calculated the summary odds ratio for tiotropium relative to placebo in these 4 trials as being 0.69 (95% CI, 0.55–0.87) (Figure 1).

Since most COPD exacerbations are thought to be caused by infections, the mechanism by which tiotropium reduces the frequency and severity of COPD exacerbations is uncertain. Improvements in lung function and dyspnea could reduce patients’ perception of the severity of exacerbations, thereby decreasing the likelihood that they would seek medical attention. That event would not be counted as an exacerbation, as exacerbation has been defined in most of the tiotropium trials. Other possible mechanisms might include more efficient cough and clearance of respiratory secretions due to better bronchodilation, protection against lung injury due to hyperinflation, or specific anticholinergic effects on mucus secretion or bronchial inflammation (Niewoehner et al 2005; Turino 2005).



**Figure 1** Summary effects of tiotropium on (A) COPD exacerbations, (B) hospitalizations, and (C) all-cause mortality. Reproduced with permission from Barr RG, Bourbeau J, Camargo CA, et al. 2006. Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. *Thorax*, 61: 854–62. Copyright © 2006 BMJ Publishing Group Ltd. and the British Thoracic Society.

## Mortality

Salpeter and associates reported that inhaled anticholinergics (tiotropium and ipratropium trials combined), compared with placebo, reduced the risk of *respiratory* deaths (RR 0.27, 95% CI 0.09–0.81) based on a meta-analysis of 5 trials with 7881 participants (Salpeter et al 2006). However, the total number of respiratory deaths were few and ascertainment of disease-specific mortality is fraught with uncertainties. In 6 trials involving 4770 patients, Barr and colleagues found that treatment with tiotropium, compared with placebo, did not significantly reduce *all-cause* mortality (OR, 0.91; 95% CI, 0.58–1.42) (Barr et al 2006b) (Figure 1). Because of its large size and long duration, the UPLIFT study should provide more definitive information about the effect of tiotropium on mortality.

## Comparisons with active controls

One randomized trial compared tiotropium to inhaled ipratropium (40 µg qid) as an active control over a 1-year period in 535 patients (Vincken et al 2002). Results were closely similar to those trials in which tiotropium was compared with placebo. At the end of 1 year, trough FEV<sub>1</sub> was significantly increased by a mean of 120 mL in the tiotropium arm, compared with ipratropium. Additionally, tiotropium, compared with ipratropium, improved the average TDI score by nearly 1 unit, improved average total SGRQ score by 3.3 units, and reduced the proportion of patients who experienced one or more exacerbations (35% vs 46%), all differences being statistically significant ( $p < 0.05$ ). There was no significant effect on mortality (Figure 1). Dry mouth was the only adverse event that was significantly increased in the tiotropium arm (12% vs 6%).

Two trials, one of 12 weeks' duration and involving 653 patients and the other of 6 months' duration and involving 807 patients, compared tiotropium with inhaled salmeterol (50 µg bid) (Brusasco et al 2003; Briggs et al 2005). Summary analyses of these two trials indicate that tiotropium was superior to salmeterol in terms of trough FEV<sub>1</sub> at the conclusion of the trials (weighted mean difference, 29 mL; 95% CI, 6–51 mL) (Barr et al 2006b). Though trends favored tiotropium in certain other outcomes, SGRQ scores, TDI scores, exacerbation rates, and mortality did not differ statistically between the two treatment arms (Figure 1). As in other trials, there were more reports of dry mouth with tiotropium compared salmeterol.

## Combination therapy with long-acting beta agonists

International guidelines for COPD treatment recommended long-acting bronchodilators, either a beta agonist or an anticholinergic, for patients with moderately severe COPD or respiratory symptoms that persist despite the administration of short acting bronchodilators (Canada Thoracic Society 2003; ATS/ERS 2004; National Clinical Guideline UK 2004; National Heart, Lung and Blood Institute 2005). As with tiotropium, long-acting beta agonists increase the FEV<sub>1</sub>, improve HRQL and dyspnea scores, and reduce exacerbation rates (Wilt et al 2005). The guidelines state no preference of one class of long-acting bronchodilator over the other, nor do they recommend combination treatment with these agents.

There is limited information about the clinical benefits of combining tiotropium with a long-acting beta agonist. Small, single-dose trials demonstrated additive FEV<sub>1</sub> improvements when tiotropium is combined with either salmeterol or formoterol (Cazzola et al 2004a, b). Van Noord et al (2005) showed in a 6-week study that, compared with baseline, average daytime FEV<sub>1</sub> improvements over 12 hours with tiotropium alone, formoterol (12 µg) twice daily, and tiotropium plus once-daily formoterol were 127 mL, 86 mL, and 234 mL, respectively. Average 12 hour night-time FEV<sub>1</sub> improvements were 43 mL, 38 mL, and 86 mL, respectively. In another study of tiotropium alone or in combination with formoterol, the authors found that, compared with baseline, average FEV<sub>1</sub> improvements over 24 hours with tiotropium alone, tiotropium plus once-daily formoterol, and tiotropium plus twice-daily formoterol were 80 mL, 162 mL, and 198 mL, respectively (van Noord et al 2006). There was also a significant reduction in albuterol rescue medication in the patients receiving both tiotropium and formoterol, but the trial was not powered to show differences for most relevant clinical outcomes. In contrast with the two previous trials, investigators in another study (van Noord et al 2006) found that, after 7 days of treatment, the difference in average FEV<sub>1</sub> improvement 2 hours after a dose of formoterol was 124 mL greater than with tiotropium; at 12 hours there was no significant difference.

The Canadian Optimal Therapy of COPD trial is a 3-arm study in 449 patients that compared tiotropium alone, tiotropium plus salmeterol, and tiotropium plus salmeterol plus fluticasone for 52 weeks (Aaron et al 2007). Although there was no significant difference in the primary outcome of the proportion of patients with exacerbations that required treatment with systemic steroids or antibiotics, other



outcomes including lung function, disease-specific quality of life, hospitalizations for COPD, and all-cause hospitalization favored treatment with tiotropium plus salmeterol plus fluticasone compared with tiotropium plus placebo. There was no significant differences in these outcomes, comparing tiotropium plus salmeterol with tiotropium alone.

## Safety and adverse effects

Tiotropium has a quaternary ammonium structure so that it is poorly absorbed across cell membranes, thus limiting its activity to local bronchodilating effects and minimizing anticholinergic effects due to systemic absorption. Dry mouth is the most commonly reported adverse drug reaction from tiotropium (Kesten et al 2006). Approximately 4%–16% of patients experience this side-effect, although it tends to improve over time and it rarely (<1%) necessitates discontinuation of the drug (Tashkin et al 2003; Dusser et al 2006). In an analysis of pooled studies including 4435 tiotropium patients and 3384 placebo patients with 2159 and 1662 patient years of exposure, respectively, Kesten et al (2006) reported the relative risk for dry mouth in tiotropium patients was 3.60 (95% CI, 2.56–5.05).

Only miniscule amounts of tiotropium are absorbed systemically, but as a drug class, anticholinergics have a potential for causing adverse cardiac effects, particularly tachyarrhythmias. One published article reported a small excess number of tachyarrhythmias among patients with mild COPD who received ipratropium for several years (Anthonisen et al 2002). However, an excess number of serious cardiac side-effects in patients receiving tiotropium has not been reported in any of the published trials. Barr et al (2006b) found no significant difference in the incidence of chest pain, myocardial infarction, congestive heart failure, arrhythmias, or atrial fibrillation with tiotropium compared with controls in their meta-analysis. Caution should be taken before applying these results to all patients with COPD, however, as many studies excluded patients with serious cardiac arrhythmias, recent myocardial infarctions, or hospitalizations for congestive heart failure.

Two studies provide more detailed information regarding potential adverse cardiac effects. One study found no evidence of cardiac toxicity after 6 weeks of tiotropium, as measured by 24-hour electrocardiographic (ECG) monitoring (Calverley et al 2003). A 12-week study found no significant differences in heart rate, conduction abnormalities, rhythm, or QTc duration on 24-hour ECG monitoring over a 12-week period in patients receiving tiotropium, compared with placebo (Covelli et al 2005).

Adverse effects of tiotropium on urinary, renal, gastrointestinal, or ocular function appear to be infrequent. A small but statistically significant increase in urinary tract infections with tiotropium was reported by Barr et al (2006b) in their meta-analysis, although there was no significant increase in cases of urinary retention. In the analysis by Kesten et al (2006) the relative risk of urinary retention was 10.93 (95% CI, 1.26–94.88). Again, these results may not be generalizable to all patients with COPD, however, as patients with symptoms of moderately severe prostatic hypertrophy or bladder neck outlet obstruction were excluded from participation.

Patients with severe renal impairment were also excluded from most studies. An exception was one study in which tiotropium (4.8 µg) was administered intravenously over 15 minutes to patients with levels of renal insufficiency ranging from mild to severe (creatinine clearance of <30 mL/min) (Turck et al 2004). Blood levels of tiotropium, which is secreted mainly by the kidney in unchanged form, doubled in patients with severe renal impairment compared with those with normal renal function, but no adverse clinical effects were observed.

A substantial proportion of inhaled tiotropium is ingested and could in theory cause gastrointestinal dysmotility. In their meta-analysis, Barr et al (2006b) found no increase in reports of tiotropium-associated constipation. One case of postoperative paralytic ileus attributed to tiotropium has been reported (Praetorius et al 2005).

Due to its anticholinergic effects, tiotropium might also worsen the signs and symptoms of narrow-angle glaucoma, if drug were inadvertently deposited in the eye. One such case has been reported after self application directly in the eye, but exacerbation of glaucoma has not been reported when tiotropium is taken by inhalation as directed (Oksuz et al 2006). Nonetheless, tiotropium should be used with caution in patients with narrow angle glaucoma, since they were excluded from all trials.

## Cost effectiveness

The cost effectiveness of tiotropium has been formally evaluated based on data from studies performed in Europe and the United States. An economic analysis by Oostenbrink et al (2004) performed alongside a clinical trial in the Netherlands (Vincken et al 2002) showed that substituting tiotropium for ipratropium increased mean annual healthcare costs (including acquisition costs for tiotropium) by the equivalent of €180; the additional cost to prevent one COPD exacerbation was €667,

and the cost to improve the SGRQ by at least 4 units was €1084. In a retrospective analysis of 2 studies performed in the United States (Casaburi et al 2002), Friedman et al (2004) found that treatment with tiotropium reduced average total annual healthcare costs by \$US1043 (95% CI, -\$US2136 to \$US48), although this analysis excluded the costs of anticholinergic drug acquisition (Friedman et al 2004). The reduction in healthcare costs with tiotropium in this analysis was entirely due a reduction in the costs of hospitalizations. In a recent systematic review of the pharmacoeconomic evidence of maintenance treatment for COPD, D'Souza et al (2006) concluded that treatment with tiotropium is cost-effective relative to ipratropium. These authors also found that treatment with inhaled corticosteroids is cost effective in patients with moderate-to-severe COPD, but data are lacking regarding the cost-effectiveness of long-acting beta agonists.

## Clinical implications

Tiotropium should be considered for maintenance therapy in patients with moderate to severe COPD. Improvements in pulmonary function with tiotropium are accompanied by improvements in dyspnea, exercise capacity, and HRQL, and a reduction in exacerbations. Although tiotropium has an excellent safety profile in selected patients, the risks and benefits should be carefully weighed in patients with closed angle glaucoma, bladder outlet obstruction or severe cardiac disease. Limited data support the superiority of tiotropium compared with ipratropium; there is insufficient *clinical* evidence to support the choice of tiotropium over long-acting beta agonists. Tiotropium may reduce the economic burden of COPD by reducing the frequency of COPD exacerbations and COPD-related hospitalizations.

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