REVIEW ARTICLE

# The use of inhaled anticholinergics in chronic obstructive pulmonary disease: is there cause for concern?

## A review of evidence from clinical trials

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**KEY WORDS**

anticholinergics, cardiovascular, chronic obstructive pulmonary disease, ipratropium, myocardial infarction, stroke, tiotropium

**ABSTRACT**

Chronic obstructive pulmonary disease (COPD) is a common condition affecting men and women equally that worsens quality of life and increases mortality. The burden of illness from COPD is rising rapidly and is now recognized as a global health issue. Diagnosis and management guidelines have been developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). GOLD defines disease severity according to airflow limitation and guides pharmacological therapy in a step-wise fashion. Inhaled bronchodilators – i.e., $\beta_2$-agonists and anticholinergics – are the therapeutic mainstay for patients with COPD. Current guidelines recommend that all symptomatic patients with COPD should be prescribed a short-acting bronchodilator to be used on an as-needed basis. If symptoms are inadequately controlled, a long-acting bronchodilator should be added and used regularly. Furthermore, GOLD and many other guideline groups recommend inhaled anticholinergics as one of the first-line agents for the long-term therapy of COPD patients. However, recent controversy has erupted around anticholinergics' cardiovascular safety, based on newly published data from analyses looking at older studies suggesting harm and 1 large recent trial confirming safety. This provides the facts surrounding this debate and reinforces our belief in the safety of inhaled anticholinergics.

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**INTRODUCTION** Chronic obstructive pulmonary disease (COPD) is a progressive yet treatable disease that significantly affects patients' quality of life and is a major cause of death and disability throughout the world. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has established a staging system for COPD severity based on airflow limitation.[1] It is widely used as a guide to the management of patients with stable COPD. The GOLD guideline's philosophy is to encourage non-pharmacologic interventions such as education, smoking cessation and exercise at all stages of the disease, along with stepwise addition of pharmacologic therapies. The goals are to control symptoms, decrease exacerbations, and improve patient function and quality of life. Furthermore, smoking cessation and oxygen therapy in hypoxic patients are both recommended as they have both been shown to prolong patient survival.

It is an expert consensus that inhaled bronchodilators are the therapeutic foundation of COPD therapy. They include both short- and long-acting anticholinergics and $\beta_2$-agonists. Bronchodilators have been consistently shown to reduce symptoms and airflow limitation, and to increase exercise capacity. The current philosophy endorsed by guidelines is that all symptomatic patients with COPD should be prescribed a short-acting bronchodilator to be used on an as-needed basis. Furthermore, a long-acting bronchodilator should be added and used regularly if symptoms are inadequately controlled with short-acting bronchodilator therapy alone.

Long-acting $\beta_2$-agonists (LABA's), are also used extensively in COPD, and have not been immune

to controversy. Concerns about mortality associated with the use of LABAs in COPD have been highlighted in metaanalyses conducted by Salpeter and colleagues, who reported more than a doubling of the risk of respiratory death in COPD with the use of LABA's vs. placebo, and an almost double risk with LABA's vs. anticholinergic therapy, while reporting anticholinergic therapy in COPD reduced hospitalizations by 30% and mortality by 70%.[2] A futher metaanalysis by Rodrigo added to the controversy by showing relative to placebo, no adverse effect of LABA's on mortality in COPD.[3]

Several studies have demonstrated the benefit of LABA's in patients with COPD while reinforcing the wisdom of only using inhaled corticosteroids (ICS) for more advanced disease. For example, the 3-year Toward a Revolution in COPD Health (TORCH) trial examined the long-acting $\beta_2$-agonist salmeterol and the ICS fluticasone alone and in combination.[4] The investigators randomly assigned 6,112 patients with COPD to salmeterol alone (50 μg twice daily), fluticasone alone (500 μg twice daily), combination therapy (salmeterol plus fluticasone) or placebo. Salmeterol significantly decreased exacerbation rates, improved lung function and improved health-related quality of life compared to placebo. All-cause mortality rates were 12.6% in the combination-therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group and 16.0% in the fluticasone group ($p = 0.052$ for combination therapy vs. placebo). The frequency of pneumonia also was significantly increased in both arms that included fluticasone ($p < 0.001$).

In addition, a very recently published review and meta-analysis showed 1 year of treatment with inhaled corticosteroids does not improve survival and is associated with an increased risk of pneumonia.[5]

The GOLD guidelines[1] and our Canadian guidelines[6] recommend inhaled anticholinergics as one of the first-line agents for the long-term therapy of COPD patients. In accordance with current guidelines and in appreciation of their favorable side-effect profile, ipratropium and tiotropium have become widely prescribed agents for maintenance therapy of COPD. Ipratropium is a short-acting anticholinergic medication that has proven in randomized clinical trials (RCTs) to consistently improve lung function, exercise tolerance, gas exchange and symptoms. The more recently introduced, long-acting anticholinergic medication tiotropium has demonstrated additional benefits, as will be discussed later in this article.

**Systemic therapy in COPD** It has become increasingly accepted that COPD is a disease characterized not only by pulmonary inflammation, but also by systemic inflammatory events that contribute substantially to the total disease burden in COPD patients. The recognition that COPD may be one manifestation of a widely expressed inflammatory process is likely to increase attention on agents capable of blunting these events in both the lungs and the rest of the body. Oral steroids, although beneficial in acute exacerbations, have been associated with increased mortality when used for chronic therapy and hence are best avoided.

Oral theophylline therapy is still widely used around the world – as demonstrated by the fact that 28% of patients in the Understanding the Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial were using this treatment[7] – but it is not commonly prescribed for acute or chronic COPD management in North America. This is because theophylline has a narrow therapeutic index, coupled with significant drug interactions and life-threatening toxicity when it is used in supra-therapeutic doses. New phosphodiesterase type 4 inhibitors may be particularly useful agents for addressing the inflammatory processes associated with COPD. For example, the results from the 2 large-scale, controlled clinical trials of roflumilast published to date show reduced exacerbations and improvements in health-related quality of life.[8,9] This new phosphodiesterase type 4 inhibitor is also well-tolerated by COPD patients, including having a low rate of gastrointestinal adverse events that declines with continued treatment.

Statins, which are 3-hydroxy-3-methyl-glutaryl co-enzyme A reductase inhibitors, also appear to have anti-inflammatory properties. In a case-control study of 418 smokers and former smokers, those who used statins had a lower rate of decline in their forced expiratory volume in one second ($FEV_1$) than patients who did not use statins (–0.005 l vs. + 0.085 l per year).[10] Prospective studies are needed to confirm these findings.

## Recent concerns regarding anticholinergics

The Lung Health Study that was conducted over a decade ago reported that ipratropium was associated with more than twice as many cardiovascular deaths in COPD patients as placebo.[11] Recently this issue was addressed by the U.S. Food and Drug Administration, which determined from a pooled analysis of 29 trials involving 13,500 COPD patients that the rate of stroke associated with inhaled tiotropium was 8/1,000 people per year compared with 6/1,000 people per year with placebo.[12] This was contrary to a 2006 pooled analysis of 19 short-term, placebo-controlled trials that revealed no significant increase in the risk of cardiovascular adverse events with inhaled tiotropium.[13] Also, 3 other meta-analyses failed to show any effect of anticholinergics on all-cause mortality.[14-16]

**The controversy of increased cardiac events and anticholinergics** Singh et al. recently performed a systematic review and meta-analysis of ipratropium and tiotropium, focusing on the cardiovascular

safety of these drugs.[17] They included 17 RCTs encompassing 14,783 patients and lasting between 6 weeks and 5 years. Some of the trials were published while others were unpublished and obtained from government and corporate sources. There was no evidence of statistical heterogeneity among the included trials ($I^2 = 0\%$).

The team's analysis of all 17 studies showed inhaled anticholinergics were associated with a 1.8% risk of the primary endpoint – a composite of cardiovascular death, and non-fatal myocardial infarction and stroke – while control therapy was associated with a 1.2% risk (total 221 events, relative risk [RR] 1.58, 95% confidence interval [CI] 1.21–2.06, $p < 0.001$). Additional analyses revealed that the increased risk for the primary endpoint was present only in the 5 RCTs that lasted longer than 6 months and, furthermore, that it was seen with both ipratropium (RR 1.57, 95% CI 1.08–2.28, $p = 0.02$) and tiotropium (RR 2.12, 95% CI 1.22–3.67, $p = 0.008$).

The investigators also examined the individual components of the primary endpoint in a series of meta-analyses. Their meta-analysis of 11 trials involving 10,598 patients showed inhaled anticholinergics significantly increased the risk of myocardial infarcion (MI) (total of 111 events, RR 1.53, 95% CI 1.05–2.23, $p = 0.03$), and a meta-analysis of 12 trials involving 12,376 patients indicated the agents significantly increased the risk of cardiovascular death (total of 88 events RR 1.80, 95% CI 1.17–2.77. $p = 0.008$).

In another meta-analysis of all 17 RCTs, the team found no increased risk associated with anticholinergics for the secondary endpoint of all-cause mortality (total of 264 deaths, RR 1.26, 95% CI 0.99–1.61, $p = 0.06$).

The investigators concluded that anticholinergics significantly increase the risk of MI and cardiovascular death but do not significantly increase the risk of stroke or all-cause mortality.

However, while this publication provides a signal about the possibility of increased cardiovascular risk with inhaled anticholinergics in people with COPD, the study's significant limitations mean it cannot be regarded as definitive. Some of these limitations were acknowledged by the authors. None of the RCTs were designed to examine cardiovascular outcomes, and thus there may have been important discrepancies between the trials in reporting of these outcomes. In addition, there was a mix of treatments in the control arms, and the investigators could not perform stratified analyses involving factors such as diabetes, smoking history, and use of statins and other drugs. Furthermore, the number of events was small and the resulting confidence intervals were wide; thus the precise magnitude of the observed risk is somewhat uncertain. Other factors limiting the implications of the paper are:

**1** a small possibility of an inclusion bias i.e. the possibility that important information may not have been included, despite the rigorous search strategy;

**2** in most of the trials, more patients taking placebo dropped out than did those on active medication, but the investigators did not take this into account – even though most of the excess risk appeared to come from studies in which the drugs ipratropium and tiotropium were taken for at least 6 months;

**3** there were few cardiovascular deaths in the meta-analyses, suggesting potentially that any such increased risk may not be that clinically important despite reaching statistical significance.

### Risk of death associated with anticholinergics in COPD patients: A nested case-control study

A nested case-control study by Lee et al. yielded similar findings.[18] The study involved 32,130 newly diagnosed patients and 320,501 control participants from the U.S. Veterans Affairs health care system. The adjusted odds ratios (OR) for all-cause mortality were 0.80 (95% CI 0.78–0.83) for inhaled corticosteroids, 1.11 (95% CI 1.08 to 1.15) for ipratropium, 0.92 (95% CI 0.88 to 0.96) for long-acting $\beta_2$-agonists and 1.05 (95% CI 0.99–1.10) for theophylline. Ipratropium was associated with an increased risk for cardiovascular death (OR 1.34, 95% CI 1.22–1.47). The results were maintained in sensitivity analyses.

However this study had some significant limitations, as the authors acknowledged, including: the analysis was restricted to patients ≥65 years, the investigators did not measure current smoking status and lung function, and they did not examine the validity of the death certificates.

**The UPLIFT Study** The Understanding Potential Long-term Impacts on Function With Tiotropium (UPLIFT) study was a 4-year, 490-site, 37-country, randomized, double-blind, placebo-controlled, parallel-group trial.[7] The study included 5,993 COPD patients and was sponsored by Boehringer Ingelheim and Pfizer. Patients were randomized 1:1 to receive either 18 µg tiotropium or placebo once daily. In both arms, patients were allowed to use all other prescribed respiratory medications except inhaled anticholinergics. The primary endpoint of the study was a composite measure to identify whether treatment with tiotropium slowed the rate of decline of lung function. The study included safety parameters and mortality as secondary endpoints. Forty-six percent of the patients in the UPLIFT trial were GOLD Stage II and 44% were Stage III. The results indicated that there were significant mean absolute improvements in $FEV_1$ in the tiotropium group compared to the placebo group throughout the trial – of 87–103 ml before bronchodilation and of 47–65 ml after bronchodilation ($p < 0.001$) – although after day 30 the differences between the 2 groups in further rate of decline were not significant. Tiotropium also extended a median delay in time to first exacerbation to 16.7 months (95% CI 14.9–17.9) compared to 12.5 months (95% CI. 11.5–13.8) in the placebo group, and

provided a 14% reduction in the number of exacerbations per patient-year ($p < 0.001$). Furthermore, tiotropium was associated with an average 2.7-point improvement across all time-points in health-related quality of life, as measured by the St. George's Respiratory Questionnaire total score (95% CI 2.0–3.3, $p < 0.001$).

Among subjects for whom vital-status information was available, during the 4-year study period up to day 1,440, 921 patients died, including 14.4% of those on tiotropium and 16.3% of those on placebo (HR 0.87, 95% CI 0.76–0.99). The investigators also examined the period of 4 years plus 30 days (1,470 days) included in the intention-to-treat analysis. During that period 941 patients died: 14.9% in the tiotropium group and 16.5% in the placebo group (hazard ratio [HR] 0.89, 95% CI 0.79–1.02).

Myocardial infarction developed in 67 patients in the tiotropium group and 85 patients in the placebo group (RR 0.73, 95% CI 0.53–1.00). Stroke developed in 82 patients in the tiotropium group and 80 in the placebo group (RR 0.95, 95% CI 0.70–1.29).

The limitations of this study include that it was not specifically designed to address cardiovascular adverse events. Furthermore, as with many other long-term COPD trials, despite the investigators' best efforts approximately 40% of the enrollees dropped out before completing the study.

Donald Tashkin, the primary investigator of the study, presented some additional data from the trial at the American College of Chest Physicians' 2008 annual meeting, held in Philadelphia a few weeks after the study was published. These data indicated that tiotropium was not associated with an increased rate of cardiac death, myocardial infarction or stroke compared to placebo. Also, there was no increase in the rate of a composite of cardiovascular events that included non-fatal MI, non-fatal stroke and cardiovascular death including sudden death.

### Sponsors' response: Another meta-analysis

Boehringer Ingelheim and Pfizer have responded publicly to the paper by Singh. et al published in the *Journal of the American Medical Association*,[17] but they have not done so in the peer-reviewed literature. Instead, they released a new analysis of 30 "rigorously-controlled" clinical trials, including UPLIFT. That analysis, which included 19,545 COPD patients, demonstrated that tiotropium is not associated with an increased risk of all-cause mortality (RR 0.88, 95% CI 0.77–0.999), nor with an increased risk of mortality due to cardiac events (RR 0.77, 95% CI 0.55–1.03) or vascular events (RR 0.44, 95% CI 0.19–1.02). There also was no increased risk of stroke (RR 1.03, 95% CI 0.79–1.35) or MI (RR 0.78, 95% CI 0.59–1.02) with tiotropium. However this meta-analysis has not been published even in the U.S. Food and Drug Administration trial database or in the sponsors' trial registeries. We hope to see the new information in the literature soon, including the full methodology and results.

**SUMMARY** This paper has outlined important recently published information and concerns regarding the safety of anticholinergics in COPD. It is therefore reassuring to have a large RCT with excellent safety data to allay most fears regarding mortality associated with tiotropium. Even the most conservative interpretation of the UPLIFT data that the investigators included in their analyses revealed no increased risk for mortality over the 4 years of study follow-up. In our opinion it provides supports to a conclusion that anticholinergic therapy is safe, well-tolerated and effective. It also supports the adoption of this class of medications as one of the main elements of therapy for COPD in national and international guidelines.

We expect the flow of information and debate to continue on the risks and benefits of all COPD therapies. For now, in our opinion, we should be comfortable with, and supportive of, our current guidelines, including when we are discussing them with our colleagues in primary care and our patients[1,6,19]. We acknowledge that some may interpret data in less definitive way and advocate consideration of both known benefits and potential risks associated with any regular bronchodilator therapy, especially in people with higher cardiovascular risk.

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