

Research Review

Respiratory Research Review – Tiotropium (Spiriva®) review

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COPD – A worldwide burden

According to the World Health Organisation, COPD will be the third leading cause of death worldwide by 2020¹, mainly due to increased smoking rates worldwide over the last half-century. Its significance in New Zealand continues to grow and the direct healthcare cost was estimated at \$192 million in 2003².

The following publication is an independent review of the COPD treatment tiotropium. It is intended for New Zealand health professionals and presents a short summary of significant peer reviewed studies featuring the medication. Also provided is a commentary from a local specialist indicating conclusions from the studies and the implications for treatment in New Zealand. It is intended to provide readers with a concise review of advancing clinical practice in the area.

About tiotropium

Tiotropium (Spiriva) is a novel, long-acting anticholinergic bronchodilator, which is effective in the treatment of COPD. Tiotropium differs from ipratropium by its functional relative selectivity for muscarinic receptor subtypes, which result in greater duration of action and efficacy.

There is now substantive evidence that regular use of tiotropium reduces severe exacerbations and requirement for hospital admission, and improves the quality of life, symptoms and lung function in subjects with COPD, when compared with placebo and ipratropium. An indication of the clinical significance of this benefit is obtained from the hospital admission data, in which tiotropium use results in a one third reduction in admission rates. This effect is the basis for the cost effectiveness of tiotropium in the treatment of moderate and severe COPD. The side effects are those expected with an anticholinergic agent, such as dry mouth, blurred vision or urinary obstruction in older men.

While there is evidence to suggest an additive benefit of tiotropium with long-acting beta-agonist drugs, further data is required to clarify the clinical role of this therapeutic approach. Additional long-term studies are also required to determine whether the reduction in hospital admissions is associated with a reduction in mortality. It is likely that triple combination products with tiotropium, a LABA and ICS will be developed for use in moderate and severe COPD.

It is recommended that all patients with COPD who meet the PHARMAC criteria should receive tiotropium. The main restriction is the requirement for patients to have an FEV1 < 40% predicted. The normal prediction values, which have recently been established for a New Zealand reference population, are available at www.researchreview.co.nz (Respiratory Research Review section) for easy reference to allow calculation of the percent predicted³.

This PHARMAC criteria has meant that all general practices in New Zealand now need to have a spirometer, in order to assess eligibility of patients. There are a number of spirometry devices which are accurate, reliable and relatively inexpensive, and GPs are encouraged to establish lung function testing in their practices, with appropriate training of staff responsible for providing this service. In support of this approach there is now good evidence that the provision of spirometry in general practice results in better assessment and management of COPD patients.

Major studies show positive results of COPD treatment

Inhaled tiotropium for stable chronic obstructive pulmonary disease⁴

Authors: Barr RG et al

Summary: This systematic meta-analysis assessed the efficacy of tiotropium for COPD compared to placebo and other bronchodilators. The studies evaluated outcomes including COPD exacerbations, hospitalisations, symptom scales and pulmonary function.

Method: Randomised clinical trials of > 1 month in duration, comparing tiotropium to placebo, ipratropium bromide and other bronchodilators were identified from the literature. Patients were adults aged > 35 years with known, stable COPD. Weighted mean differences (WMD) or odds ratios (OR) were calculated by pooling studies and results were reported using 95% confidence intervals.

Results: A total of 9 studies (n = 6,584) which met the inclusion criteria were identified. Of these 7 were published, and 2 were available in abstract form only. The risk of a COPD exacerbation was reduced with tiotropium (OR 0.740; NNT 14) compared to placebo or ipratropium. The risk of a related hospitalisation was also decreased (OR 0.64; NNT 30). However reductions in exacerbations and hospitalisations compared to long-acting β_2 -agonists were not significant, possibly due to the small sample size. Overall improvements in respiratory health status were significantly greater with tiotropium compared to placebo and ipratropium, but not salmeterol. Improvement in bronchodilation

(mean increase in FEV1 trough from baseline) over 6-12 months was significantly greater with tiotropium vs placebo, ipratropium and salmeterol. Tiotropium-treated patients had significantly higher rates of dry mouth than those treated with placebo, ipratropium or salmeterol.

Comment: This meta-analysis provides a timely overview of the efficacy of tiotropium in the treatment of COPD. The main finding is that tiotropium reduces severe exacerbations resulting in hospital admissions by about a third when compared with either placebo or ipratropium. When this effect is applied to a one year rate of hospitalisations of 10%, the NNT for tiotropium is about 30. It would be expected that this effect would be associated with some survival benefit, although there is insufficient data in this regard.

Based on these findings it can be recommended that all patients with severe COPD should receive a trial of tiotropium. To be eligible the patients would need to meet the PHARMAC criteria of an FEV1 < 40% predicted. Implementation of this recommendation represents a priority in primary and secondary respiratory care in New Zealand.

Compared with other commonly used drugs in COPD, such as long-acting beta-agonists, there was not enough evidence from this meta-analysis to draw conclusions regarding comparative efficacy. However, there is substantive evidence that the use of tiotropium together with a LABA results in an additive bronchodilator response.

Long term evaluation of once-daily inhaled tiotropium in COPD⁵

Authors: Casaburi R et al

Summary: Two identical 12-month randomised, double-blind, placebo-controlled clinical trials assessed the long-term efficacy and safety of once-daily inhaled tiotropium in COPD.

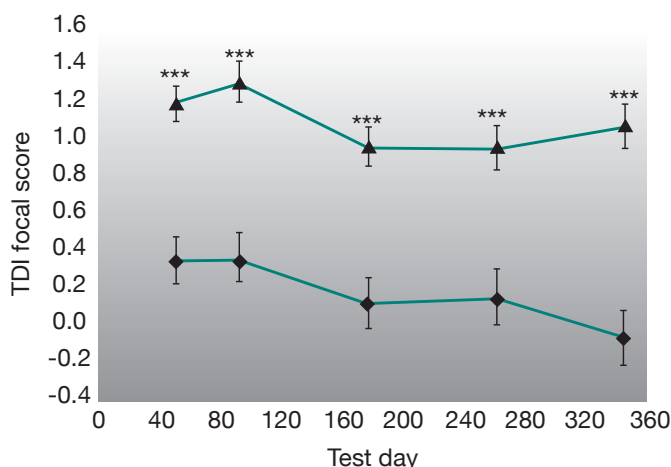
Method: 921 outpatients aged > 40 years with a diagnosis of stable COPD were randomised to 12-months treatment with inhaled tiotropium (18 μ g) or placebo once daily. Trough FEV1 (prior to dosing) was the primary outcome measure. Dyspnea was assessed with the Transition Dyspnea Index (TDI) and health status was measured with the St George's Respiratory Questionnaire Index (SGRQ) and the Short Form 36 (SF-36).

Results: Bronchodilation was significantly greater with tiotropium compared to placebo as measured by trough FEV1 (p < 0.01) and mean response during the 3 hours after dosing (p < 0.001). Dyspnea was significantly reduced in tiotropium-treated patients at the first assessment (day 50) and at all subsequent timepoints (p < 0.001). Fewer patients in the tiotropium group experienced COPD exacerbations (0.76 vs 0.95 events patient-year⁻¹; p = 0.045). The rate of hospitalisation for exacerbation was lower in tiotropium-treated patients (5.5% vs 9.4%; p < 0.05), as was the number of days spent in hospital for exacerbations (0.6 vs 1.2 days patient-year⁻¹; p = 0.023). Disease-specific and general health status were significantly improved in patients treated with tiotropium compared to placebo (p < 0.05). Similar numbers of patients in both groups experienced adverse events. The proportion of patients with dry mouth was significantly greater in the tiotropium group (16%) compared to placebo (2.7%).

Comment: This study reports the findings of two of the main double-blind placebo controlled, long-term studies which demonstrated the efficacy of tiotropium in COPD. The manuscript reports that tiotropium has bronchodilator efficacy over a 12 month period, with no reduction in effect during this period, i.e. there is no tachyphylaxis with its regular use.

This study also showed that patients with COPD may have substantial bronchodilator responsiveness, which underlies the therapeutic use of bronchodilators in COPD. The subjects with COPD had a mean increase in FEV1 of 22% three hours after tiotropium administration, equivalent to a mean increase in FEV1 from 1.0 litres to 1.2 litres.

These findings challenged the dogma that existed at the time that airflow limitation in COPD was irreversible. This issue has now been clarified in the GOLD guidelines, in which the diagnosis of COPD is made by the demonstration of a post-bronchodilator FEV1/FVC of < 0.7, without regard to the magnitude of the bronchodilator response.



Mean Transition Dyspnea Index (TDI) focal score at the five assessment points over the course of the 1-yr trial (▲:tiotropium (n=507);◆: placebo (n=325)). Data are presented as mean±SEM. Means were adjusted for treatment, centre and Baseline Dyspnea Index. A higher score denotes less dyspnea. ***:p<0.001.

Research Review

Improvements in symptom-limited exercise performance with tiotropium in COPD⁶

Authors: Maltais F et al

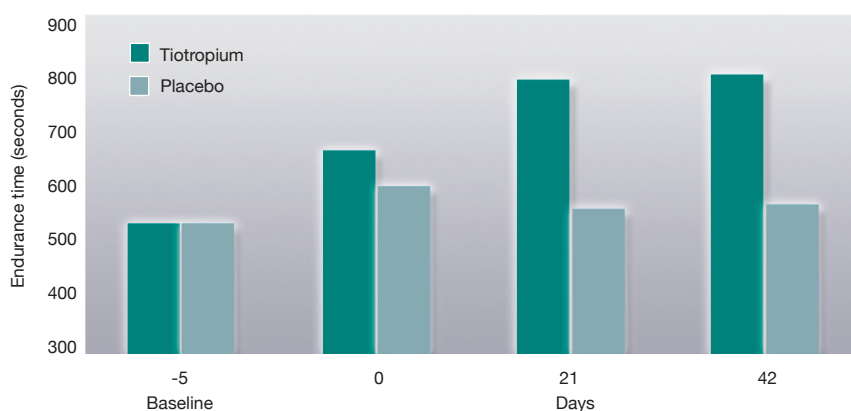
Summary: A randomised, double-blind, placebo-controlled, parallel-group study in patients with COPD. The study aimed to assess the duration of improvements in exercise performance in COPD patients treated with tiotropium.

Method: Following a 2-3 week run-in period, 261 subjects (mean age 62.5) were randomised to 6 weeks treatment with once-daily tiotropium (18µg) or placebo. Pulmonary function tests were conducted before and at 90 minutes after dosing on days 0, 21 and 42 of treatment. Symptom limitation was assessed using a constant work rate cycle ergometry test at 2.25 hours after dosing on days 0, 21 and 28, and at 8 hours after dosing on day 42.

Results: Mean performance time was significantly longer in the tiotropium group, at both 2.25 hours ($p = 0.0001$) and 8 hours post-dose. ($p = 0.0035$). Significant improvements in dyspnea (adjusted mean intensity), and pre-exercise inspiratory capacity (IC) were also observed in tiotropium-treated patients at both time points ($p < 0.001$). Improvements in IC were maintained during exercise.

Comment: One of the difficulties in assessing the efficacy of bronchodilator therapy in

COPD is in interpreting the clinical relevance of small but statistically significant increases in FEV1. This study addresses this issue by measuring the effects of tiotropium on exercise performance and lung volumes. It reports that tiotropium use results in an increase in endurance from around 9 minutes to 13 minutes – an improvement worth having! Interestingly the reduction in exertional dyspnoea was sufficient to shift the basis of symptom limitation from breathlessness to leg discomfort. The other important observation of this study was that the improvement in exercise tolerance related in part to the reduction in hyperinflation.



ET during constant work rate cycle ergometry to symptom limitation at 75%Wmax. Baseline (day - 5) and 2.25 h after dosing on days 0, 21, and 42.

Effects of combination therapy with tiotropium plus formoterol on airflow obstruction and resting hyperinflation in patients with COPD⁷

Authors: van Noord JA et al

Summary: This randomised, open-label, placebo-controlled, 3-way cross-over study, found tiotropium plus formoterol was more effective than tiotropium alone in patients with stable COPD.

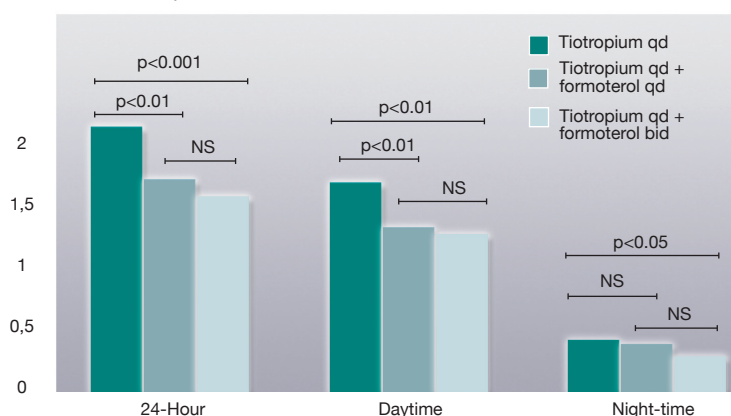
Method: The trial consisted of a 2-week run-in period, plus a 3 x 2 week crossover treatment phase. Patients ($n = 95$) received tiotropium (18µg qd) during the run-in, and then continued to receive tiotropium (18µg qd), plus either placebo (PBO) or formoterol (12µg qd) once (FOD) or twice daily (FBD) during the treatment phase. Assessment of lung function (FEV1, FVC and resting inspiratory capacity [IC] measured serially over 24 hours) was carried out at baseline and at 2 weeks following each treatment.

Results: Following treatment, significant improvements ($p < 0.01$) in bronchodilation were observed in each treatment group (0.08L, 0.16L and 0.20L in the PBO, FOD and FBD groups respectively, compared to a baseline FEV1 of 1.05L). Patients receiving FOD had significant improvements in bronchodilation (FEV1, FVC and IC) lasting >12 hours compared to those receiving PBO ($p < 0.05$). Following the second daily dose of formoterol, a further improvement in FEV1 lasting >12 hours occurred, but improvements in FVC and IC lasted <12 hours. Rescue use of salbutamol was significantly reduced during daytime in the FOD group ($p < 0.01$) and also at night in the FBD group ($p < 0.05$). Tolerability was comparable across the three different treatment regimens.

Comment: This study provides evidence that the addition of formoterol to tiotropium results in additional clinical benefit. The magnitude of the improvement in FEV1 was similar with tiotropium and formoterol, suggesting similar efficacy with this outcome measure.

The interesting comparison which was not investigated in this study, was the relative efficacy of a second daily dose of tiotropium compared with formoterol. As a result it remains uncertain as to whether a twice daily regime of both tiotropium and formoterol results in significantly greater benefit than once daily tiotropium with the twice daily formoterol regime.

Due to the restriction in the availability of tiotropium in New Zealand it is likely that patients will receive tiotropium rather than LABA as the add-on therapy. Currently the likely progression of therapy for COPD in New Zealand is initiation with an ipratropium salbutamol (Combivent) combination therapy for relief of symptoms first, then the addition of ICS and LABA with progressively increasing severity, with tiotropium added in patients with the most severe forms of the disease.



Mean 2-weekly number of puffs of rescue salbutamol per day. NS - not significant.

Research Review

Improvements in exercise tolerance with tiotropium plus pulmonary rehabilitation in COPD patients⁸

Authors: Casaburi R et al

Summary: This randomised, double-blind, placebo-controlled trial investigated the effect of tiotropium plus pulmonary rehabilitation (PR) on exercise tolerance.

Method: 91 patients aged > 40 years, with a diagnosis of COPD, a history of smoking, and eligibility for a PR programme were entered into the study. Treatment with tiotropium (18µg qd) or placebo was given for a total 25 weeks. After the first 5 weeks, all subjects participated in an 8-week PR programme consisting of > 30 minutes of treadmill training three times per week. The primary study endpoint was treadmill walking endurance time. Secondary endpoints included the transition dyspnea index (TDI), the St George's respiratory questionnaire (SGRQ) and rescue use of albuterol.

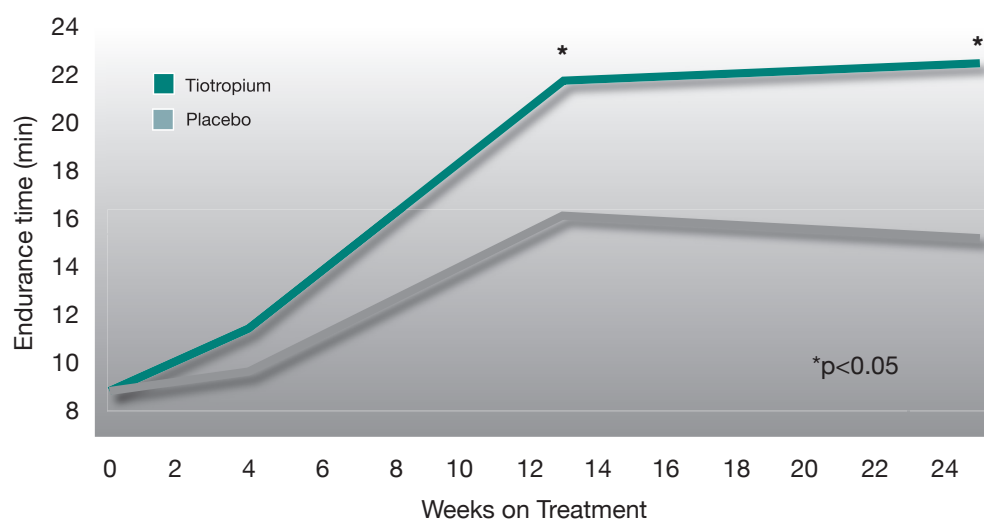
Results: Mean difference in endurance time (tiotropium minus placebo) was not significantly different before PR (1.65 min; $p = 0.183$). However, tiotropium-treated patients had significantly greater endurance times at the end of PR, (5.35 min; $p = 0.025$) and at 12 weeks after PR (6.60 min; $p = 0.018$). Dyspnea (mean TDI focal score) was not significantly different at the end of PR, but the tiotropium group had a significantly greater score at 12 weeks after PR (1.75 vs 0.08; $p < 0.05$). Overall respiratory health status (SGRQ total) was significantly improved in tiotropium-treated patients both at the end of PR, and at 12 weeks after PR ($p > 0.05$). A significant decline in rescue albuterol use was observed in tiotropium-treated patients ($p < 0.05$ for 17/25 weeks).

Comment: This study takes a novel look at the potential

benefits of tiotropium treatment in patients with COPD. It reports that tiotropium use allowed patients undergoing pulmonary rehabilitation to achieve greater benefits in terms of exercise capacity and health status. These benefits were maintained for up to three months after the rehab programme had stopped.

While the focus of this study was on the benefits of tiotropium, perhaps the more important comparison was that pulmonary rehabilitation itself produced an increase in effort capacity that was at least as good as tiotropium treatment. These findings are relevant to New Zealand, where there has been insufficient provision of pulmonary rehab programmes. This may be due in part to the traditional hospital base for these programmes, which have had limited access to COPD patients in the community.

The development of community based rehab programmes represents an important initiative for GP practices to consider. Such programmes do not need to be restricted to patients with respiratory disease but could include patients with cardiovascular and neurological disability, for which many of the principles and practical features of rehabilitation are similar.



Treadmill endurance times at baseline and at all post-treatment clinic visits in the tiotropium and placebo groups.

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