Tiotropium Bromide as an Adjunct Therapy to Inhaled Corticosteroids in the Treatment of Adults With Chronic Asthma

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Abstract
Background: Asthma is a chronic respiratory disease effecting 24.6 million children and adults in the United States. Current treatment guidelines recommend the use of inhaled corticosteroids and both short and long acting beta agonists. Several systematic reviews have evaluated the use of anticholinergics with mixed results. Tiotropium bromide became available in the United States in 2004, yet there have been few studies utilizing this long acting anticholinergic for the treatment of asthma patients.

Purpose: This paper evaluates the current literature on the improvements in pulmonary function in asthmatics with the use of tiotropium in addition to an ICS. GRADE was used to rate the quality of evidence.

Method: An exhaustive search of the available literature using Medline, Pubmed, Web of Science, Cochrane Systematic Reviews and CINHAL. The keywords used included “tiotropium”, “asthma” and “adults” individually and in combination.

Results: Four articles were found to be relevant to the topic of this paper. Two randomized clinical trials showed statistically improved lung function with the addition of tiotropium to an ICS. One observational study showed that 33% of patients demonstrated a response of ≥ 15% improvement in FEV1 with the addition of tiotropium. A case report also demonstrated improvements in PEF and a decrease in oral steroid use in a chronic asthma patient.

Conclusion: Tiotropium bromide in conjunction with an ICS provides statistically significant improvement in lung function for adult patients with chronic asthma. This conclusion is based on a moderate grade of evidence using the GRADE analysis.
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Tiotropium Bromide as an Adjunct Therapy to Inhaled Corticosteroids in the Treatment of Adults With Chronic Asthma

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March, 2011

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Biography

[Redacted for privacy]

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To my family: Thank you for all of the support that you have provided over the years.

To Charles Bentz, MD: Thank you for encouraging me to follow my passion for healthcare and to apply to PA school.
ABSTRACT

Background: Asthma is a chronic respiratory disease effecting 24.6 million children and adults in the United States. Current treatment guidelines recommend the use of inhaled corticosteroids and both short and long acting beta agonists. Several systematic reviews have evaluated the use of anticholinergics with mixed results. Tiotropium bromide became available in the United States in 2004, yet there have been few studies utilizing this long acting anticholinergic for the treatment of asthma patients.

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Keywords: Tiotropium, inhaled corticosteroid, asthma, adult asthma.
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INTRODUCTION

Background

Asthma is a chronic respiratory disease affecting both children and adults with significant morbidity and mortality. It contributes to significantly personal, social and economic burdens. Asthma is characterized by recurring bronchial inflammation, airway obstruction and airway hyper-responsiveness. According to the Center for Disease Control (CDC), as of 2009, 24.6 million children and adults in the United States (8.2% of the population) currently have asthma. In 2008 there were 10.5 million missed school days and 14.2 million missed work-days due to asthma. For 2007 1.75 million asthmatics required emergency department visits and 456,000 required hospitalizations for exacerbations of their condition. Health statistics from 2007 determined that there were 3,447 deaths due to asthma in that year. The prevalence of asthma has increased by an average 1.2% annually between 2001 and 2009. (Akinbami, Moorman and Liu, 2011).

Current treatment guidelines published in 2007 by the National Asthma Education and Prevention Program (National Heart, Lung and Blood Institute, 2007) were developed to provide a best practices approach for clinicians to diagnose and treat patients with asthma. The guidelines provide a step-wise approach based on asthma severity to monitor and control patient symptoms. Patients with intermittent asthma are managed with short acting beta agonists (SABA), such as albuterol, on an as needed basis. As the severity increases the preferred treatment is a low dose inhaled corticosteroid (ICS). If the patient has
moderate to severe asthma the recommendation is to add a long acting beta agonist (LABA) to the ICS or to increase the dose of the ICS. However, the U.S. Food and Drug Administration (2010) now requires manufacturers to include a warning for LABAs due to potential increases in asthma exacerbations and deaths in asthma patients. This possible safety issue has lead researchers to study the use of long-acting anticholinergics such as tiotropium bromide in the treatment of moderate to severe asthmatics. (Peters, et al, 2010). Tiotropium is currently indicated for the treatment of Chronic Obstructive Pulmonary Disease (COPD), however it is not indicated for the treatment of asthma. The efficacy of tiotropium in COPD has been demonstrated in multiple randomized clinical trials including a long-term use trial by Tashkin, Celli, Kesten, Lystig and Decremer (2010). Based on recently published studies, tiotropium may prove to be an effective treatment option in conjunction with an ICS.

Previous systematic reviews have evaluated the use of anticholinergics in the treatment of asthma with mixed results. A systematic review by Westby, Benson and Gibson (2004) did not find enough adequate data at the time to determine the specific role that long-acting anticholinergics have in the treatment of chronic asthma. In the review by Flynn, Glynn and Kennedy (2009), the authors concluded that there was not enough current data to support the use of anticholinergics in chronic asthma. The review by Donahue (2004) found that anticholinergic agents provide more benefit to patients with COPD than patients with asthma. However, he concluded that some asthmatics, especially the
elderly patients with a history of smoking or with concurrent beta-blocker use might benefit from the addition of an anticholinergic.

Most studies of anticholinergic use in asthma patients in the past have evaluated the effects of ipratropium on the improvement of lung function in both acute and chronic asthma. Ipratropium is a short acting anticholinergic that requires dosing every 6 hours. In 2004, tiotropium became available in the United states as a once-daily anticholinergic agent for the treatment of patients with COPD. Recently, there has been interest to continue to evaluate the use of anticholinergics in asthma patients with the availability of the longer acting tiotropium.

Purpose of the Study
The purpose of this paper is to perform a systematic review of the literature on the use of tiotropium bromide as an adjunct to inhaled corticosteroids for patients suffering from moderate to severe asthma using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group.

METHODS
An extensive literature search was performed using Medline, Pubmed, Web of Science, Cochrane Systematic Reviews and CINHAL. These databases were accessed through the Pacific University Library system. The keywords searched included “tiotropium”, “asthma” and “adults” individually and in combination. The search was limited to human subjects and the English
language. The initial results included 37 articles. Articles older than January 2000 and duplicates were excluded. Articles with COPD as the main topic were also excluded. Four articles were chosen for this review based on their relevance to the topic.

RESULTS

The first study reviewed was conducted by Peters et al. (2010) and was funded by the National Heart, Blood and Lung Institute who published their results in an article entitled *Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC) Study*. The study was a randomized, double-blind, triple crossover study that compared the outcomes of the addition of tiotropium, salmeterol or increased dose of beclamethasone (Qvar) in patients that were not controlled with a lower dose of ICS. Patients were enrolled in the study if they were over the age of 18, had a history of asthma, a forced expiratory volume greater than 40%, and less than a 10 pack year history of smoking.

Each participant was subjected to a common four week run-in period that included treatment with 80 µg beclamethasone meter dosed inhaler (Qvar) twice daily. Patients that at the end of the four week run-in period had less than 70% predicted FEV1 and no contraindication for tiotropium were then randomized into one of three treatment arms. One arm consisted of 160 µg beclamethasone twice daily and placebo for tiotropium and salmeterol. The second arm was treated with 80 µg beclamethasone twice daily and 18 µg tiotropium bromide once daily and placebo in place of salmeterol. The third arm was treated with 80 µg of
beclamethasone twice daily, salmeterol xinafoate 50 µg inhaler (Serevent) twice daily and a tiotropium placebo. Each arm was treated for 14 weeks and then washed-out for two weeks on just 80 µg beclamethasone inhaler twice daily. They were then crossed over to another treatment arm for an additional 14 weeks. This was followed by an additional two week wash-out period and another crossover in treatment arms. The primary outcome in the study was the difference in the morning peak expiratory flow (PEF) compared to baseline. Secondary outcomes included; evening PEF, albuterol rescue inhaler use, mean daily symptom score, proportion of asthma-control days, prebronchodilator FEV1, Asthma Symptom Utility Index Score, Asthma-Control Questionnaire score, Asthma Quality-Of-Life Questionnaire score and forced expiratory volume in one second (FEV1) after four puffs of albuterol. The mean difference in change from baseline of the morning PEF for the tiotropium versus double-dose beclamethasone was 25.8L per minute, 95% confidence interval (14.4 – 37.1), p-value < 0.001. The tiotropium versus double-dose beclamethasone analysis had a mean difference change from baseline for the evening PEF of 35.3L per minute, 95% CI (24.6 – 46.0), p-value < 0.001. The tiotropium versus salmeterol analysis had a mean difference change from baseline for morning and evening PEF of 6.4L per minute, 95% CI (-4.8 – 17.5), p-value 0.26 and 10.6L per minute, 95% CI (-0.1 – 21.3), p-value 0.05, respectively. The salmeterol versus double-dose beclamethasone analysis had morning and evening PEF differences of 19.4L per minute, 95% CI (9.4 - 29.4), p-value <0.001 and 24.7L per minute, 95% CI (15.2 – 34.3), p-value <0.001, respectively. The authors determined that
tiotropium in addition to an ICS provided statistically better PEF when compared to twice the dose of ICS. They also reported that the addition of tiotropium to an ICS was not inferior to the use of salmeterol and an ICS.

The next study reviewed was conducted by Park et al. (2009) and evaluated the response of severe asthmatics to the addition of tiotropium to high-dose ICS and an inhaled LABA. They enrolled 160 patients diagnosed with severe persistent asthma determined by lung function testing and medication usage records. The patients also had to have a 10 pack year history of smoking, a change in FEV1 of less than 5% over eight consecutive weeks prior to study enrollment, and no abnormalities detected on chest radiograph. The patients in this study were being treated with a high-dose corticosteroid (equivalent dose to 800-1600 µg of budesonide inhaler) and a LABA. Tiotropium bromide 18 µg inhaler was added to their treatment regimen for 12 weeks and they were evaluated with spirometry every four weeks. The patients were then categorized as responders or non-responders to tiotropium based on a finding of 15% improvement in FEV1 for at least 8 consecutive weeks. Of the 160 patients, 138 (86%) enrollees completed the study. Reasons for drop-out were five exacerbations, 11 patients noncompliant with treatment, and withdrawal of six patients from enrollment. Out of the 138 patients that completed the study, 46 (33.3%) were categorized as responders to tiotropium. Of the remaining nonresponders, 15 had improvements in FEV1 but did not maintain that improvement for the full 8 week period. The authors of this study concluded that
Tiotropium provided benefit to 33% of severe asthmatic patients with decreased lung function on standard therapy.

The next article reviewed was authored by Kapoor et al. (2009) and is a case report on a 43-year old man with severe asthma requiring 20mg of oral prednisone, 500µg inhaled fluticasone and 50mg salmeterol as the Advair discus formulation, montelukast 10 mg daily and salbutemol rescue inhaler used several times a week. His initial pulmonary function tests demonstrated his severe airflow restriction that was reversible with salbutemol. Tiotropium 18µg daily was added to his treatment regimen for one year. Initially, he had a PEF of 450L per minute. After 3 months on tiotropium his oral prednisone was decreased to 15mg daily and he had a PEF of 490L per minute. Between 6 months and a year the patient’s oral prednisone dose was decreased to 2mg daily and he was able to maintain a PEF between 520 - 740L per minute. The patient also reported improvements in his quality of life and exercise capacity. The conclusion of this case report was that tiotropium may provide patients a “steroid sparing” benefit on high doses of oral glucocorticosteroids.

The final study reviewed was conducted by Fardon, Haggart, Lee and Lipworth (2007) and was a randomized, double blind, placebo controlled, crossover study evaluating the benefit of halving the dose of ICS and adding either salmeterol and placebo or salmeterol and tiotropium. Patients were included in the trial if they were over 18 years of age, with no history of an upper respiratory tract infection or use of oral corticosteroids in the past 3 months and they had an FEV1 • 65% and FVC of less than 80% of the predictive values for
both respectively. 26 patients were enrolled in the trial. The patients stopped all first and second line asthma treatments and were treated with 1000 µg fluticasone inhaler dosed as 250 µg two puffs twice daily for a four week run-in period. The patients were then reevaluated using FEV1 and forced vital capacity (FVC) measurements as a baseline after the run-in period. They were then randomly assigned to receive a total of 500 µg fluticasone and 100 µg salmeterol (125 µg fluticasone and 25 µg salmeterol 2 puffs twice daily) daily plus placebo tiotropium or the 500/100 dosing plus 18 µg tiotropium bromide inhaler. Each study arm was treated for 4 weeks with cross-over after 4 weeks of treatment. The improvements from baseline (1000 µg fluticasone) as measured by morning PEF were 41.6L per minute, 95% CI (14.4-68.6), p-value < 0.01 and 55.3l per minute, 95% CI (31.97-78.7), p-value < 0.01 for the fluticasone, salmeterol, placebo (F,S,P) group and the fluticasone, salmeterol and tiotropium (F,S,T) group respectively. The change from baseline for the evening PEF was 37L per minute, 95% CI (12-63), p-value < 0.01 for the F,S,P group and 44L per minute, 95% CI (26-62), p-value <0.01 for the F,S,T group. The authors concluded that the addition of salmeterol and tiotropium to half the dose of fluticasone provided patients with a small amount of improvement in lung function compared with twice the dose of fluticasone.

**DISCUSSION**

All four articles included in this review reported significant improvements in pulmonary function with the use of tiotropium in those with moderate to severe asthma. The articles by Peters et al. (2010) and Fardon et al, (2006)
demonstrated the improvement in both PEF and FEV1. The study conducted by Park et al. (2010) only reported the improvement in FEV1. The case report by Kapoor et al. (2009) evaluated the improvements in lung function by PEF.

The improvements noted in PEF and FEV1 by Fardon et al. (2006) were small but still statistically significant. A limitation of their study is the small study population of 26 patients with only 18 (69%) completing the study. An additional limitation to this crossover study was that there was no apparent wash out period between study arms. The measurements of PEF and FEV1 were conducted during the study visits before and after the crossover with no wash-out period to return to the baseline line comparator of double-dose fluticasone. Each segment of the trial was only four weeks in length. This may have had an effect on the results of the crossover. The patients in the first half of the study were stepped down to half the dose of fluticasone. At the time of the crossover, the patients had already been on half the dose of fluticasone for four weeks. Additionally, in the article by Park et al. (2010), they determined in a preliminary study that a treatment of eight weeks was necessary to note improvements in the FEV1 with tiotropium. The short treatment length of each arm could lead to an underestimation of the true effect of tiotropium on lung function.

The study by Peters et al. (2010) demonstrated a significant improvement in both morning PEF and FEV1 in patients that were given tiotropium in addition to an ICS. This was compared to doubling the dose of the ICS. They also found that the addition of tiotropium to an ICS was not inferior to the use of an ICS and salmeterol. This study provided a longer treatment arm of 14 weeks and a
four-week washout period between crossovers. The potential limitations of this study include the moderate sized population of 210 patients and the reported compliance with treatment. As part of the study oversight, treatment compliance was monitored. Compliance percentages were reported as “84.1%±16.2%, 92.6%±12.3%, and 93.0%±12.2%” (p.1719) for beclamethasone, salmeterol and tiotropium, respectively. The difference in treatment compliance between beclamethasone and salmeterol or tiotropium may have an effect on the pulmonary function measurements in this study.

The article by Park, et al. (2009) demonstrates the response that severe asthmatic patients have with the addition of tiotropium. Responders to tiotropium did have significant improvements in their FEV1 showing an improvement in one measure of their lung function. However, there are several limitations to this article. The primary weakness of this study is that it was an observational study with no comparator group. Nor did the authors mention the time of day that the pulmonary function testing was completed. This is significant since patients with asthma may have considerable differences in their FEV1 depending on the time of day. It is not disclosed in the paper whether the patients were given the doses of tiotropium in the morning or the evening. Without this information it is difficult to evaluate the true effect of tiotropium on lung function. Timing of medication dosing can add several confounders to the analysis. Patients can have a lower pre-dose trough FEV1 than a post-dose FEV1. The time of day is also important in asthmatic patients with significant atopy. The authors noted that the responders to tiotropium had higher rates of atopy determined by skin prick. This
can effect the lung function results based on exposure to potential allergens. An additional limitation to the results is that only 86% of the patients completed the study. Patients were dropped from the study due to exacerbations of their asthma, noncompliance or because they withdrew from enrollment. This can provide a significant variation in the data in a study with 138 patients at the beginning of enrollment.

According to the guidelines, oral corticosteroids should be considered in patients who are still unable to control their asthma symptoms despite the use of a high dose ICS and LABA. The case report by Kapoor et al. (2010) demonstrates the benefit to lung function that tiotropium conferred on a patient still symptomatic despite using a high dose ICS, LABA, leukotriene modifier and oral corticosteroids. Over a one-year period the patient had significant improvements in his PEF while slowly reducing his oral steroid dose from 20mg prednisone to 2mg daily. This article has many limitations however. First, it is a case report which means that the information is anecdotal instead of statistically relevant. This patient also had a 15 pack-year smoking history. This is a significant confounder because the worsening of symptoms since his first diagnosis at age 26 could be partially due to a COPD component of his airway disease. The authors did note that the patient maintained some fixed airflow obstruction after bronchodilator use when measuring his initial FEV1.

The evidence supporting the improvements in pulmonary function with tiotropium as an adjunct therapy to inhaled corticosteroids for adult patients with asthma we be evaluated using the Grading of Recommendations Assessment,
Development and Evaluation (GRADE) approach. (Guyatt et al. 2008). The GRADE approach was developed to evaluate the quality of clinical evidence in regards to patient management. Levels of evidence include very low, low, moderate, and high. The GRADE working group defines these levels of evidence as:

*High Quality* – Further research is very unlikely to change our confidence in the estimate of effect

*Moderate quality* – Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate

*Low quality* – Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimates

*Very low quality* – Any estimate of effect is very uncertain (Guyatt et al. 2008, p. 926)

The outcomes evaluated in this review are the improvement in lung function, improvement in PEF and improvement in FEV1. The evidence for these outcomes is listed in the GRADE table in the appendix.

The two randomized clinical trials provided a moderate level of evidence to support the use of tiotropium to improve pulmonary function, PEF and FEV1. Their GRADE begins as a high level of evidence because they are RCTs. Both studies did provide consistent evidence that tiotropium did improve pulmonary function, PEF and FEV1. The overall evidence that they provide is decreased however because they are indirect comparisons of tiotropium. Peters et al.
(2010) and Fardon et al. (2006) had different treatment arms in their clinical trials and cannot be directly compared. Overall, the two RCTs provided a moderate level of evidence.

The case report article by Kapoor et al. (2010) demonstrated the improvements in pulmonary function and PEF. This level of evidence begins as low quality due to it being a case report of a single patient. It gains strength to a moderate level because of the significant dose response seen with the addition of tiotropium as measured by the PEF and the decrease in use of oral glucosteroids OGS. The authors were primarily reporting on the decrease in OGS versus the use of tiotropium with an ICS. This causes this article to have the greatest indirectness with the other articles in terms of the authors outcomes but the improvements in PEF were directly related to the outcomes in this review.

The study by Park et al. (2009) also showed improvements in pulmonary function and FEV1 with the use of tiotropium. Because it is an observational study the initial level of evidence is low. The dose-response noted in this study increases its strength. However, the obvious confounders mentioned above decrease the strength of the evidence. This study provided a low quality of evidence for the outcomes evaluated in this review.

The four articles reviewed here provide an overall moderate level of evidence of the improvement of pulmonary function, PEF and FEV1 seen with the use of tiotropium along with an ICS in the treatment of adults with asthma.

Based on the GRADE assessment of the evidence, tiotropium appears to provide benefit to adult patients with asthma. Further large-scale RCTs need to
be conducted in order to recommend tiotropium be added to the asthma treatment guidelines. Longer studies could adequately evaluate other outcomes such as decreases in exacerbations, decreases in rescue inhaler use, and improvements in quality of life. Longer studies can also evaluate potential risks of long term use of tiotropium in asthma patients.

In conclusion, the available data to date demonstrates that tiotropium in conjunction with an ICS provides statistically improved lung function in patients with moderate to severe asthma. Tiotropium should be considered as a treatment option when patients are not well controlled on the currently recommended treatment regimens.
REFERENCES


Fardon, T., Haggart, K., Lee, D. & Lipworth, B. (2007). A proof of concept study to evaluate stepping down the dose of fluticasone in the combination with salmeterol and tiotropium in severe persistent asthma. Respiratory Medicine, 101, 1218-1228.


### APPENDIX A

#### Table 1: GRADE Table

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Quantity and type of evidence</th>
<th>Findings</th>
<th>Decrease GRADE</th>
<th>Increase GRADE</th>
<th>Grade of Evidence by article type</th>
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<tr>
<td>Tiotropium vs increased doses of Inhaled Corticosteroids in asthma</td>
<td>Pulmonary Function (based on all measurement types)</td>
<td>2 RCT</td>
<td>Improved pulmonary function</td>
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<td>Mod</td>
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<td>Peak Expiratory Flow</td>
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<tr>
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<td>1 Case Report</td>
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<tr>
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