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Tiotropium Compared to Long-Acting Beta2-Agonists in Improving Quality Outcomes in Patients with COPD

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Abstract

Chronic obstructive pulmonary disease (COPD) is a chronic and progressive disease that has been associated with high mortality rates and is now becoming an economic burden on public health (WHO, 2012). Tiotropium and long-acting beta2-agonists (LABA) are both utilized in managing patients with COPD. However, guidelines do not specify which medication is the drug of choice. To investigate the efficacy of LABA versus Tiotropium, a search of the current literature was undertaken. The database utilized was the Cochrane Library. Three systematic reviews were found and all included randomized control trials with similar methodology. Based on the analysis and synthesis of these reviews, no valid conclusions could be drawn with regard to the superiority of tiotropium or LABA in managing quality outcomes. Implications for clinical practice include possibly prescribing both tiotropium and a LABA for a trial period to allow the patient to decide which medication is better.

Keywords: COPD, tiotropium, LABA, treatment, prevention

Exact word count: 153

Background

Chronic obstructive pulmonary disease (COPD) is a respiratory disease that is characterized by chronic and progressive airflow obstruction, cough, shortness of breath and sputum production (GOLD, 2011). It affects more than 20% of adults over the age of 40 years with those aged greater than 65 years being four times more likely to have COPD compared to those aged 45-64 years (Stoller, 2012). Formerly a disease found only in men, the percentage of women who are being diagnosed with COPD rapidly increased from 2002 to 2012 (Stoller, 2012). In fact, the number of women who died from COPD in 2002 exceeded those in men (Stoller, 2012). According to the World Health Organization (WHO) (2012), it is estimated that more than sixty five million people are now living with moderate to severe COPD. In 2002, COPD was the fifth leading cause of death in the world but by 2030, it is projected to become the third leading cause of death worldwide (WHO, 2012).

COPD is comprised of two diseases: chronic bronchitis and emphysema (GOLD, 2011). Emphysema is a disease in which the air sacs of the lungs are gradually destroyed which leads to the surface area of the lungs being markedly reduced (Mayo Clinic, 2011). In addition, emphysema also causes narrowing of the terminal bronchioles by destroying the elastic fibers that enable the small airways to be kept open (Mayo Clinic, 2011). Bronchitis involves chronic swelling and inflammation of the mucous membranes of the bronchial tubes that lead into the lungs (Mayo Clinic, 2011). All these changes occur because of an insult of noxious particles or gases (Karner & Cates, 2012). Cigarette smoke is one of the major risk factors for COPD along with indoor or outdoor air pollution, occupational dusts and chemicals, and a hereditary alpha-1 antitrypsin deficiency (GOLD, 2011). There are additional other factors that may affect lung growth during the gestational period and in childhood (GOLD, 2011).

The signs and symptoms of COPD can vary depending on which of the diseases, emphysema or chronic bronchitis, is more prominent (Mayo Clinic, 2011). Breathlessness, wheezing, chest tightness, chronic cough, and mucus production are the clinical symptoms associated with COPD (Mayo Clinic, 2011). Due to its slow onset and under recognition, COPD is under diagnosed (GOLD, 2011). Spirometry is the most important lung function test to diagnose COPD (Mayo Clinic, 2011). It assesses the degree of airflow limitation and classifies COPD into four stages: mild, moderate, severe, and very severe (GOLD, 2011). A post-bronchodilator $FEV_1/FVC < 0.70$ (normal is 0.70-0.80) on spirometry confirms a diagnosis (GOLD, 2011). To date there is no cure for COPD, however, it is a preventable and treatable disease (GOLD, 2011). Management of COPD is multi-faceted and revolves around smoking cessation, education, pharmacological interventions, and pulmonary rehabilitation (Chong, Karner, & Poole, 2012).

Because of its chronic and progressive nature, COPD represents a substantial and mounting economic burden on public health. In the United States, COPD accounts for roughly 1.5 million emergency department visits, 726,000 hospitalizations, 119,000 deaths, and $32 billion in direct and indirect costs annually (Dalal, Shah, D'Souza & Mapel, 2011). Most of the cost of COPD is due in part to managing and preventing COPD exacerbations. Therefore, utilizing appropriate pharmacologic treatments in the management and prevention of COPD is prudent and are the primary goals of therapy (Karner & Cates, 2012).

Current guidelines recommend the use of either a long-acting anticholinergic, such as tiotroprium or a LABA as first line therapy for persistent or worsening breathlessness (GOLD, 2011). Tiotropium is an anticholinergic that works by blocking the action of acetylcholine which results bronchodilation (Karner & Cates, 2012). LABA's works by activating beta2-receptors

within the smooth muscles of the airway leading to a cascade of events that ultimately causes bronchodilation (Karner & Cates, 2012). Over the years, tiotropium has gained widespread acceptance for being a once daily maintenance therapy for people with stable COPD (Karner & Cates, 2012). However, the guidelines do not specify if tiotropium is superior to an LABA or in conjunction with an LABA in stabilizing COPD (Barr, Bourbeau, & Camargo, 2008; Chong, Karner, & Poole, 2012; Karner & Cates, 2012). The topic of this paper is to evaluate the evidence on the utility of tiotropium alone, LABA alone, or in conjunction with a LABA on quality of life, exacerbations, symptoms, lung function and serious adverse events in patients with COPD.

Analysis

Karner & Cates (2012) investigated the long-term effects of tiotropium when used in combination with a LABA compared to using either a LABA or tiotropium alone. The authors did an extensive database search of respiratory journals, clinicaltrials.gov, manufacturers' websites, and the Cochrane Airways Group Specialized Register of trials (CAGR). CAGR is a database that is derived from systematic searches of databases from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PyschINFO.

Five randomized, parallel group, placebo-controlled trials were included in this systematic review. Four of the trials were double-blinded with only one trial being partially blinded. The length of the studies ranged from 12 weeks to one year of treatment and all were multi-center studies; three were conducted in several different countries, one was conducted in 27 Canadian medical centers, and another was conducted in 35 centers across the United States.

The sample consisted of 3,473 participants with a mean age varying between 63 and 68 years. Gender distribution also varied between 54% and 79% being males. All five studies included participants who had moderate to severe COPD with the mean baseline lung function varying between 38% and 52% (Karner & Cates, 2012).

For the intervention, all five studies used 18 μg of tiotropium, one inhalation daily. The LABA choice varied amongst the studies: salmeterol 25 μg/puff, two puffs twice daily, indacaterol 150 μg once daily, formoterol 12 μg twice daily and 10 μg twice daily. Regardless of the interventions, the studies did allow other co-treatments to be utilized which included salbutamol, inhaled corticosteroids, oxygen, antileukotrienes and methylxanthines (Karner & Cates, 2012).

The outcomes measures that Karner and Cates (2012) looked at were divided between primary outcomes and secondary outcomes. Quality of life, hospital admissions, mortality and disease specific mortality all constituted the primary outcomes. The secondary outcomes looked at FEV_1, exacerbations, symptoms, serious adverse events, disease specific adverse events, and withdrawals. Dichotomous data variables (i.e. mortality and withdrawals), were analyzed using odds ratios and were combined using Mantel-Haenzsel odds ratios with a 95% confidence intervals, with a fixed-effect model. If the events were rare, Peto odds ratio was employed. Generic Inverse Variance model was utilized in cases where treatments of effects were reported (Karner and Cates, 2012).

In the treatment group LABA plus tiotropium compared to tiotropium alone, Karner and Cates (2012) found a slightly larger improvement in the mean quality of life when both medications were used concurrently (95% CI -2.93 to -0.29). However, in the other two primary

outcomes, hospital admissions and mortality, no significant differences were found. For secondary outcomes, the authors noted a statistically significant improvement in the pre-bronchodilator FEV_1 with LABA plus tiotropium (95% CI 0.05 to 0.09) with none of the other secondary outcomes showing any significant differences. In the LABA plus tiotropium versus LABA group, formoterol was used and Karner and Cates (2012) found no real significant differences with any of the outcomes. Furthermore, a one year study by Karner and Cates (2012) also looked at the cost effectiveness of tiotropium within a Canadian healthcare system and based on 2006 prices, found tiotropium to be more cost effective compared to tiotropium plus LABA.

Barr, Bourbeau and Camargo (2008) also wanted to look at the efficacy of tiotropium when compared to a placebo, ipratropium bromide, and to LABA in patients with stable COPD. An extensive search of CAGR, respiratory journals, and LILACS was performed by the authors with the searches being current as of October 2004. Nine studies met the author's inclusion criteria. Of these nine studies, seven compared tiotropium to placebo, one compared tiotropium to ipratropium, and one compared tiotropium to a placebo as well as to salmeterol.

All nine studies were randomized, parallel, double-blinded RCT's. The combined sample consisted of 6,584 adult participants. All participants had stable COPD with those who had other lung disease such as asthma, cystic fibrosis, and bronchiectasis being excluded. The participants were aged greater than 35 years with the mean age varying between 61 and 68 years. Gender distribution varied between 57% and 99% being males. The length of studies varied from one month to 12 months with a weighted mean duration of 6.3 months. All were multi-center studies with the mentioned settings consisting of the United States, US Veterans' Administration Medical Center, Belgium, and Netherlands. Two of the studies did not cite specific countries

where the research was performed but noted one was conducted in 18 countries while the other was conducted in 12 countries (Barr, Bourbeau & Camargo, 2008).

Tiotropium 18 μg one inhalation daily was utilized as the intervention in all nine RCT's. One study employed salmeterol 50 μg twice daily while the dosage of choice for ipratropium was 40 μg four times a day in another study. In addition, all the studies allowed the use of short-acting β_2-agonists and inhaled corticosteroids as co-treatments (Barr et al., 2008).

Barr et al. (2008) analyzed the data using the Cochrane Review Manager RevMan 4.2. All nine studies were grouped together to yield weighted mean differences (WMD) or odds ratios. Reporting was done employing a 95% confidence interval. The authors found that tiotropium did reduce COPD exacerbations compared to placebo (OR 0.75; 95% CI 0.66 to 0.85) as well as when compared to ipratropium (OR 0.64; 95% CI 0.44 to 0.92). However, there was not a statistically significant difference (OR 0.88; 95% CI 0.65 to 1.17) between the tiotropium and salmeterol groups.

Hospitalizations for COPD exacerbations were reduced within the tiotropium group when compared to a placebo (OR 0.65; 95% CI 0.50 to 0.85); however, there was no real statistically significant difference in the ipratropium (OR 0.59; 95% CI 0.32 to 1.09) and salmeterol (OR 0.59; 95% CI 0.29 to 1.23) groups. Additionally, all nine RCT's did not find any statistically significant differences among all three groups when looking at mortality (OR 0.73; 95% CI 0.35 to 1.49). Furthermore, the confidence interval was wide which was attributed to small numbers (Barr et al., 2008).

Based on the secondary outcomes, the use of tiotropium showed a statistically significant improvement in the St. George's Respiratory Questionnaire (SGRQ) and in the transitional

dyspnea index (TDI) when compared to placebo (WMD -3.3; 95% CI -4.6 to -0.8 and OR 1.96; 95% CI 1.58 to 2.44) and ipratropium (WMD -3.3; 95% CI -3.2 to -1.0 and OR 2.01; 95% CI 1.26 to 3.20). When comparing tiotropium to salmeterol, there was a slight improvement in SGRQ and TDI but it was not statistically significant (WMD -3.3; 95% CI -4.7 to -2.2 and OR 1.08; 95% CI 0.80 to 1.46). Improvements in spirometric indices from baseline were greater and more statistically significant with tiotropium compared to placebo and ipratropium whereas there was a smaller but still statistically significant improvement when compared to salmeterol. Finally, dry mouth was the only adverse event that was reported with sufficient consistency and was greatest in the tiotropium group (Barr et al., 2008).

In the third systematic review, Chong, Karner, and Poole (2012) compared tiotropium bromide alone to LABA alone against measures of quality of life, exacerbations, lung function, and serious adverse events in people with COPD. In addition, these authors also looked at the cost benefit of using tiotropium alone compared to a LABA. The authors extensively searched CACR, respiratory journals, meeting abstracts, clinicaltrials.gov, and manufacturers' websites for research studies as well as NHS EED and HEED for economic evaluations.

Seven clinical studies were included in this review but only six were used in the pool analysis of data. All studies compared tiotropium to a LABA: four studies used salmeterol, one study employed formoterol, and another study utilized indacaterol. The sample size consisted of 12, 223 participants with COPD. The mean age ranged between 60 and 65 years with males constituting the majority of the participants. All the studies used tiotropium 18 μg once daily and were double-blinded in design except for two studies where a placebo form of tiotropium was not available. The studies that evaluated tiotropium with salmeterol utilized salmeterol 50 μg with the length of the studies varying from 12 weeks to one year. Formeterol 10 μg was used

over a six month period whereas indacaterol 150 µg and 300 µg were used over a period of 26 weeks (Chong, Karner & Poole, 2012).

Data was analyzed using the Cochrane Review Manager (RevMAN 5.1) software. As previously mentioned in the Karner and Cates (2012) review, Chong et al. (2012) also analyzed dichotomous data variables with Mantel-Haenzsel odds ratios using a fixed-effect model with a 95% confidence interval. Peto odds ratio was utilized in cases where events were rare. A fixed-effect mean difference with a 95% confidence interval was used in cases where continuous data needed to be analyzed (Chong et al., 2012).

For quality of life, the authors did not pool that data together due to a high level of heterogeneity. In the authors' review, two of the studies found indacaterol to be more statistically significant in improving SGRQ results over tiotropium. On the other hand, two other studies found a non-statistical difference with salmeterol or formoterol compared to tiotropium. COPD exacerbations were shown to be lower within the tiotropium group (OR 0.86; 95% CI 0.79 to 0.93) however, one of the largest studies included in the review did show significant difference. Hospital admissions related to COPD exacerbations were found to have no statistical difference within three of the studies (OR 0.93; 95% CI 0.57 to 1.54) whereas four of the studies revealed a significant lower rate of hospital admissions in the tiotropium group (OR 0.87; 95% CI 0.77 to 0.99). There were no significant difference in FEV_1 (MD 10.53; 95% CI -11.47 to 32.51) and TDI score (MD -0.22; 95% CI -0.63 to 0.19) between tiotropium and LABA. Serious adverse events and withdrawal rates were lower in the tiotropium group (Chong et al., (2012).

Chong et al. (2012) also looked at six economic evaluations that assessed the cost and cost-effectiveness of tiotroprium 18 µg daily compared to salmeterol 50 µg twice daily. The

studies were based either on Markov model, an economic model, or on empirical analysis of data obtained from RTC's. The settings of these studies took place in a primary or secondary care in Greece, UK, Netherlands, Spain, and the United States. All studies looked at the maintenance costs and costs of exacerbation which included respiratory medications, laboratory visits, physician visits, visits to the emergency department, and hospitalizations. Tiotropium was found to be linked with lower annual total costs compared to salmeterol in three of the studies. In another study, tiotropium was associated with a higher cost but also with the highest expected net benefit within acceptable values for the willingness to pay value. Notwithstanding, two studies did not compare tiotropium directly to salmeterol but instead drew conclusions regarding costs indirectly by comparing tiotropium to a no treatment group. Overall, uncertainty does surround these results based on the sensitivity analysis of the findings found in the various studies.

In this literature review, three similar systematic reviews were able to be utilized. All three reviews had similar purposes in evaluating the efficacy of tiotropium either alone or in conjunction with LABA in patients with COPD (Barr, Bourbeau, & Camargo, 2008; Chong, Karner, & Poole, 2012; Karner & Cates, 2012). All studies were conducted in multiple centers across numerous countries which allowed the samples to be well represented with a diverse population. However, none of the reviews fully depicted what percentages of ethnicities were involved or what socioeconomic classes were included. In addition, all the studies had roughly identical designs with regard to inclusion and exclusion criteria surrounding disease severity, age, smoking history, and baseline lung function all of which supports the quality of evidence found in these reviews. It is important to note that some of the studies were referenced in more than one systematic review (Barr, Bourbeau, & Camargo, 2008; Chong, Karner, & Poole, 2012; Karner & Cates, 2012).

All studies had participants with COPD take different medications (tiotropium, salmeterol, ipratropium, formoterol, indacaterol). Since these medications were already approved for use in COPD patients and co-treatments were allowed as well as all participants were randomly assigned to the different treatment groups; this created a low risk, high risk benefit ratio and the studies were deemed safe (Barr, Bourbeau, & Camargo, 2008; Chong, Karner, & Poole, 2012; Karner & Cates, 2012). All studies were RCT's with most having a double-blind design. Unfortunately there were a few studies that were partially blinded due to tiotropium not being available in a blinded format. Chong et al. (2012) and Karner and Cates (2012) did address this issue in their review.

Two of the systematic reviews found no statistical significance in reducing COPD exacerbations with tiotropium over other LABA's (Chong, Karner, & Poole, 2012; Karner & Cates, 2012). The study by Barr et al. (2008) did show statistical significant with tiotropium over placebo and ipratropium but no significant difference with comparing tiotropium to salmeterol. All three reviews found no statistical variation in any of the treatment groups regarding hospitalizations and mortality (Barr, Bourbeau, & Camargo, 2008; Chong, Karner, & Poole, 2012; Karner & Cates, 2012). In Karner and Cates (2012), the authors found no statistical significance for adverse events in either of its treatment groups; however, Chong et al. (2012) did find a small but statistical difference in rate of adverse events within the tiotropium group over the LABA group. Furthermore, Barr et al. (2008) also showed statistical difference in the tiotropium group.

Two studies looked at withdrawal rates with Karner and Cates (2012) finding no real significant difference whereas Chong et al. (2012) showed a slightly lower withdrawal rate in the tiotropium group. Comparing the two reviews that looked at TDI scores, Chong et al. (2012)

found no statistical difference but Barr et al. (2008) did find statistical differences with tiotropium over placebo, ipratropium and salmeterol. All three reviews found varied results pertaining to which medication improved quality of life for COPD patients: Barr et al. (2008) found statistical significance with tiotropium compared to placebo and ipratropium; Karner and Cates (2012) revealed a significant difference when tiotropium was used in conjunction with a LABA, and Chong et al. (2012) found no real difference overall in their review. Lastly, spirometric indices were found to be significantly improved in the tiotropium group in two of the reviews.

These statistics are clinically relevant as the reviews demonstrated that in general, tiotropium is not a superior drug compared to LABA's. No real patterns emerged from these reviews as each one found different results. Because of a lack of consistency among the three reviews, a strong argument cannot be made to recommend tiotropium as the first drug of choice to be utilized in COPD patients. Overall, the reviews had strong methodology by incorporating large sample sizes, similar designs, similar evaluation tools, and biases were addressed.

Synthesis

Based on the examination of these three systematic reviews all results were related to the variable of interest in terms of discovering whether tiotriopium, LABA, or a combination of both were more of a benefit for patients with COPD (Barr, Bourbeau, & Camargo, 2008; Chong, Karner, & Poole, 2012; Karner & Cates, 2012). Unfortunately, the results were not consistent across the reviews therefore making it difficult to state with authority that one drug is more beneficial to these patients over others. Barr et al. (2008) and Chong et al. (2012) did show COPD exacerbations to be reduced in the tiotropium group; however, results were not found to

be statistically significant. A majority of the findings were of no statistical difference except for Barr et al. (2008) saw a statistical difference in SGRG with the combination tiotropium and LABA. In addition, Chong et al. (2012) saw a statistical significant improvement in spirometric indices with tiotropium compared to placebo, ipratropium, and salmeterol.

From a social justice perspective, the results from these studies were based on patients who had moderate to severe COPD (Barr, Bourbeau, & Camargo, 2008; Chong, Karner, & Poole, 2012; Karner & Cates, 2012). Since patients with mild or very severe COPD were not included, this can lead to unequal treatment for patients who are at different stages of the disease. In some cases, patients with mild COPD may be asymptomatic, however, may in the long run benefit from these medications if they were initialized at an early stage of the disease. When treating these patients, it is essential for providers to take into consideration the severity of the disease, the different medications such as tiotropium or a LABA and to compare the benefit to harm ratio. Providing education to patients will not only make the patient feel more in control of their disease but will also allow the provider to give holistic care. In addition, the cost of these medications will affect patients who are in the lower socioeconomic class or are uninsured.

Overall, the studies had different levels of statistical differences with regards to each outcome but they all showed efficacy of utilizing any one of the medications that were reviewed. Depending on what the patient or provider is looking at to control, these results will aid them in their decision making process.

Summary of Recommendations

Based on this literature review, no one drug drastically produced statistically significant results across all three studies (Barr, Bourbeau, & Camargo, 2008; Chong, Karner, & Poole,

2012; Karner & Cates, 2012). Certain drugs were shown to be more beneficial to specific quality outcomes. Therefore, advance nurse practitioners may want to reflect on the findings to understand which medication may be more suitable for achieving a specific outcome. Because tiotropium was not shown to be superior to LABA's in controlling COPD symptoms, advance nurse practitioners could reasonably perform a medication trial for their COPD patients allowing them to use one or the other, tiotropium or LABA, each for 1 week to help decide which medication is more appropriate and convenient for them.

Tiotropium was found to be more cost effective when compared to salmeterol, however, this result is not truly well represented due to location of study and size of sample (Chong et al, 2012). As a result, advance nurse practitioners need to be aware of which medications are less expensive, especially when it comes to caring for patients with financial constraints. Properly educating patients about COPD and medication treatments is essential in providing the highest quality of care. Patient education contributes to patient empowerment in controlling their disease and may ultimately lead to improved health care outcomes.

Since all three studies were conducted on patients with moderate to severe COPD, further research is indicated to assess the role these medications play in patients who have mild and severe forms of COPD. In addition, longer studies are needed to study the benefits and long-term effects. Chong et al (2012) suggest further research should be conducted at comparing various dosages of the same drug in order to assess efficacy. Furthermore, more trials are needed to compare these drugs alone or in combination with inhaled corticosteroids.

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