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Cost-Effectiveness of Aclidinium Bromide Compared with Tiotropium Bromide from the Perspective of Copd Patient Populations

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Abstract

Objective: To assess the cost-effectiveness of aclidinium vs. tiotropium in GOLD II, III, & IV COPD patients from the perspective of COPD patient populations. **Methods**: A cost-utility analysis was performed using the perspective of >65 year-old Medicare COPD patient populations. A Markov model decision tree was utilized to compare aclidinium and tiotropium in order to measure cost per quality-adjusted life year (QALY) gained for each treatment method. Sensitivity analyses were conducted for variables with uncertainty (e.g., exacerbations, recurrent exacerbations) in the aclidinium arm and patients' Medicare Part D plan costs. **Results**: Aclidinium yielded $60,817 and 13.49 QALYs over the treatment period and tiotropium yielded $36,963 and 13.12 QALYs, leading to a final incremental cost-effectiveness ratio (ICER) of $63,718/QALY for aclidinium vs. tiotropium in the base case analysis. Two-way sensitivity analyses related to annual drug costs suggested that as aclidinium cost falls below $2,400, it is preferred to tiotropium at any cost. Costs above $3,400 favor tiotropium therapy. For higher threshold willingness-to-pay (WTP) of $110, 840 (based on WTP for dialysis in the U.S.), aclidinium becomes preferable at a much higher cost (<$3,700). A higher exacerbation rate (40%) for aclidinium from the base case yields an ICER of $73,353/QALY. **Conclusions**: Based on the cost-utility analysis, aclidinium was found to be slightly more effective at a much larger incremental cost when compared to tiotropium. Large variability in patient costs based on the various Medicare Part D plans available resulted in a wide range of ICERs.

Keywords: COPD; aclidinium; tiotropium; cost-effectiveness; patient perspective, Medicare Part D.

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Background

Chronic Obstructive Pulmonary Disease (COPD) is a progressive disease that encompasses both chronic bronchitis and emphysema. The focus of COPD treatment is to control symptoms and to prevent acute exacerbations. COPD prevalence is extensive in the United States (U.S.), and the disease is a leading cause of morbidity and mortality. A 2012 CDC report showed that the prevalence of COPD was 6.3%, almost 15 million Americans.[1]In patients who are 65 years or older, the prevalence is closer to 12%.[1] Other reports have suggested that as many as 24 million U.S. patients have impaired lung function.[2]This indicates the potential for a large underestimation of current COPD prevalence. COPD is the fourth leading cause of death in the U.S., accounting for over 100,000 deaths per year.[3] Globally, COPD is the tenth most burdensome disease and the fifth leading cause of death.[4]By 2020, COPD is estimated to become the third leading cause of death.[4]

Due to exacerbations of symptoms, many patients seek a physician's care or require a hospital admission for COPD. In 2010, the CDC estimated that COPD led to approximately 715,000 U.S. hospital discharges.[5] The National Heart, Lung, and Blood Institute estimated that $49.9 billion of health care costs were attributed to COPD in 2010.[5]Astudy of U.S. Medicare patients with COPD demonstrated that they were more likely to utilize health care services and resulted in an average additional $20,500 in health care costs per patient.[6] Many patients suffering from COPD experience limitations of daily activities including working ability. In a national survey, 34% reported that they could not work due to their COPD.[7] Costs due to lost productivity were estimated to be $14.1 billion in 2002.[7]

COPD is a great financial burden in the U.S. and prevention of COPD exacerbations with medications can play a role in reducing costs. Managing symptoms and preventing exacerbations may reduce the number of doctor’s visits and hospitalizations and increase work productivity. In the U.S., treatment for COPD is based on the GOLD Guidelines, which stratify patients into four categories based on their forced expiratory volume (FEV1) and number of exacerbations per year. Bronchodilators, including long-acting beta-2 agonists and long-acting muscarinic antagonists (LAMAs) can be used for symptom relief.[8]

Until the recent FDA approval of aclidinium bromide (TudorzaPressair*[2]) in July 2012, tiotropium bromide (Spiriva Handi Haler**[3]) was the only LAMA available. The comparative effectiveness and economic literature available for tiotropium is heavily based on the payer perspective with a focus on international populations. Because aclidinium has been recently approved, there is a lack of economic literature comparing aclidinium to other treatments.

The patient perspective from a population level has gained new importance during the past decade since the publication of the Institute of Medicine's Report, *Crossing the Quality Chasm* in 2001. One of the six aims to improve quality of care was to include p*atient-centered* care "that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions".[9]Many efforts, such as the "Triple Aim"[10] have endeavored to include the patient's experience of care as part of improvements to achieve better health outcomes at lower costs. More recently, with the passage of the Affordable Care Act and the creation of the Patient Centered Outcomes Research Institute (PCORI), the patients' perspective are now included in a range of review activities related to evidence-based care in new ways.[11]Economic evaluations, however, have typically been conducted from payer and societal perspectives and not from the patients' perspective even though the patients' perspective is acknowledged. This analysis seeks to partly address this gap for COPD patients with its objective being to determine whether aclidinium is cost-effective relative to tiotropium in the treatment of patients with COPD in GOLD categories II, III, and IV from the perspective of COPD patient populations.

Methods

Target Audience, Perspective, Time Horizon, and Outcomes Evaluated

The target audience for our evaluation is COPD patients and decision-makers who are interested in patient perspectives from the population level. While the perspective of the evaluation will be from a population of patients, the overall evaluation will aid both providers and patients when making treatment decisions based on time and wages lost to COPD exacerbations and symptoms, as well as quality of life (QoL) measures.

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[2] *Tudorza and Pressair are trademarks of Almirall, S.A., Barcelona, Spain

[3] **Spiriva and HandiHaler are registered trademarks of BoehringerIngelheim International GmbH, Ridgefield, CT

Taken from the patients' perspective, the relevant clinical outcomes for COPD include exacerbations, exacerbations requiring hospitalizations, St. George's Respiratory Questionnaire (SGRQ), time lost to exacerbations, and all-cause mortality. Exacerbations and exacerbations requiring hospitalizations were used to calculate transitional rewards in cost during each cycle. The SGRQ is a common assessment in COPD trials that evaluates patients' quality of life. This scale can be converted to quality-adjusted life years (QALYs) to be used as another transitional reward. All-cause mortality was also incorporated into the economic evaluation.

The target patient population of this analysis was GOLD stage II, III and IV COPD patients over the age of 65. The analysis could not be subdivided into these specific patient groups, however, because of a lack of clinical data. In the clinical studies incorporated in this evaluation, patients were allowed to use other COPD medications including short-acting beta agonists, short-acting muscarinic antagonists, long-acting beta agonists and inhaled corticosteroids. Comorbidities were not reported in the trials or supplementary materials.[12,13] Other studies have suggested that patients with COPD suffer cardiovascular diseases at a rate of 2,256.3 per 10,000 patients and infections and infestations at almost 4,000 per 10,000 patients.[14] This prevalence data may not adequately describe our analysis's population because of the unavailability of trial data from UPLIFT and the ACCORD Extension Study. Nevertheless, patients age 65 and over typically take multiple medications and accrue high drug costs, while simultaneously having fixed income due to retirement.

The incremental unit of time used in this decision tree analysis was one year. Since these drugs are life-long therapies, a model with a time horizon of 35 one-year cycles reasonably captures the use of these drugs in the target population. An annual discount rate of 3% was applied to the model to account for a lower value for future events per the recommendation of the US Public Health Services' Panel on Cost-Effectiveness.[15]

The setting for this analysis was a U.S. population with cost data from Medicare Part D plans that are available in Boston, MA. Within the U.S., availability and prices can vary depending on region. Within the region studied, there were 27 prescription drug plans for patients to chose with a range of premiums and deductibles. Annual drug costs for tiotropium and aclidinium differ depending on Medicare Part D plans.

Drug costs were averaged based on these plans and ranged from $994 to $2,022 and $1,498 to $4,399 for tiotropium and aclidinium, respectively.[16] Twelve plans offer high deductible options and 12 plans carry $0 deductibles as shown in Table 1. Simple averages of annual drug cost were used for base case analysis but separate analyses were performed on the population of patients with a high deductible versus a low deductible. Another analysis was performed with those plans above the mean premium, $51.23, versus those below as shown in Table 2. Decision-makers interested in the patient perspective see value in how deductibles and premiums have an effect on annual drug costs and the associated ICER.

This model was formed as a cost-utility analysis due to the focus on the patient perspective. The results of an analysis with QALYs can be compared to results of other analyses done with QALYs in other disease states. This type of analysis takes into consideration the quality of life aspects of COPD treatment that are important to our patient population of interest.

The decision analysis tree is a Markov model created using TreeAge Pro 2013 Software. As depictedin Figure 1, each arm designates LAMA available for COPD therapy in a GOLD II-IV population. For each arm, a Markov model cycles patients through 35 one-year cycles. For each cycle, the patients either remain on stable COPD therapy or suffer death and move to the absorbing death state. If the patients continue on stable COPD treatment with the prescribed LAMA, they either suffer from an exacerbation or do not. For patients that suffer an exacerbation, a percentage of them will be hospitalized and the remainder treated in an urgent care setting. Following both of these outcomes, patients also then have a chance of having a recurrent exacerbation in the same year. Each arm will acquire transitional values based on the costs of each treatment and care. Both exacerbation arms are recycled back into the ‘Stable COPD’ arm. All treatment arms share the same outcomes but are associated with different rates and costs. Of note, TreeAge Pro calculates the ICER within the computer software using unrounded numbers but reports incremental cost and incremental effectiveness rounded to the hundredths place, potentially creating a discrepancy with manually calculated ICERs.

Data Sources for Populating the Model

Clinical Inputs (Table 3)

Mortality

Barr et al. estimated one year all-cause mortality for tiotropium users to be 1.7%.[17] Mortality was not an outcome in any current aclidinium trial and had to be assumed based on all-cause mortality with tiotropium. This assumption is a limitation that should be considered when interpreting the results.

Exacerbations

Exacerbation rates for tiotropium were estimated from the UPLIFT trial. The annual rate of exacerbation was 42%.[12] The rate of exacerbations that led to hospitalizations was calculated from the UPLIFT trial to be 37.9%.[12] Base case exacerbation rates for aclidinium were obtained from the ACCORD I Extension Trial where they reported an annual rate of 23.5%.[13] The ATTAIN trial reported an annual rate of 40%.[18] The ACCORD I study found an exacerbation rate of 7.4% over a duration of 12 weeks, resulting in a 29.6% annual rate of exacerbations.[19] Rate of exacerbations that led to hospitalizations for aclidinium were reported as 34% according to the ATTAIN trial.[18]

Recurrent exacerbations are assessed in the decision tree due to the high rate of occurrence in this population. The tiotropium recurrent exacerbation rate was 32% as noted in the INSPIRE trial.[20]Sinceaclidinium studies do not assess this factor, we conservatively assumed that the rate of recurrent exacerbation is similar to tiotropium and extrapolated this to aclidinium.

Quality of Life

All SGRQ scores were converted into Euro-QoL utilities using Equation 1from Starkie et al.[21] Euro-QoL is a more frequently assessed health related quality of life (HRQL) scale used in cost-effectiveness analyses. Baseline quality of life data were taken from the UPLIFT trial. The population average SGRQ score at baseline was 45.7.[12] Decline in population QoL averages were obtained from the UPLIFT and ACCORD I Extension Trial for tiotropium and aclidinium, respectively.[12,13]

SGRQ scores declined 5.5 points for tiotropium and 7.9 points for aclidinium at one year, yielding 0.7653 QALYs for tiotropium and 0.7871 QALYs for aclidinium.[12,13]

Equation 1:[21]

$$\text{EQ-5D utility} = 0.9617 - 0.0013\,(\text{SGRQ Total}) - 0.0001\,(\text{SGRQ Total})^2 + 0.0231\,(\text{Male})$$

Economic Model Inputs(Table 4)

Since the patient population is Medicare eligible, costs of drugs, admissions and ER visits came from their respective Medicare benefits programs. Hospital exacerbation costs were obtained from Medicare A. The patient has no insurance premium but has a $1,184 deductible per year in 2013.[22] To calculate the cost of our patient's time lost due to exacerbations, we assumed a median monthly pension earning of $2,533or $81.71/day.[23]This is the maximum social security benefit for a full time worker at retirement age. Since these patients are assumed to be post-retirement age and are not losing work time, the weekly earning is pre-tax. We inflated 2008 cost inputs to February 2013 based off the medical consumer price index (CPI) available using the Bureau of Labor Statistics website.[24]Each hospital exacerbation was associated with a three-day hospital admission[12] and emergency room visits were assumed to take oneday. Emergency room visits from 2008 costing $647 were inflated to current 2013 prices, $697.67.[25]Assuming that all patients are enrolled in Medicare Part B and paying a 20% co-payment,[26] a patient pays $139.53 per visit.[25,26]These costs are current for 2013.Medicare Part B premiums and deductibles are omitted because they would be similar for each arm. Annual drug costs for each drug were taken from the simple average of 27 Medicare Part D plans available in Boston, MA for the base case (Table 1).[16] Data were not available on preferences for plans so a weighted average could not be obtained. Deductible and premium data are available in Table 1 and 2.

Sensitivity Analysis

Due to uncertainties in certain clinical parameters in the available literature, one-way sensitivity analyses were performed for exacerbations, recurrent exacerbations, mortality, and hospitalization rate associated with aclidinium.

A two-way sensitivity analysis was run on the annual drug costs of tiotropium and aclidinium. A separate analysis of high deductible plans versus low deductibles plans was also performed to capture any differences.

The annual exacerbation rate related to aclidinium for the base case, obtained from the ACCORD I Extension Trial was 23.5%.[13] This is the longest duration trial of aclidinium to date. The ATTAIN study had an annual exacerbation rate of 40%.[18] This was a 24 week study and annual rates were then assumed by the authors of ATTAIN. In the ACCORD I trial, 12-week exacerbation rates for aclidinium were 7.4%.[19]This equates to a 29.4% annual rate. Since there is a lack of long-term data on exacerbations with aclidinium, a one-way sensitivity analysis was performed assuming a range of 23.5% to 40%.

Recurrent exacerbation rates for tiotropium were obtained from the INSPIRE trial.[20] While this information is not currently available for aclidinium, we believe it is reasonable to assume that it may be similar. To account for any changes, a one-way sensitivity analysis was performed for recurrent exacerbation rates related to aclidinium from 0% to 100%.

Rates of hospitalization were available from the ATTAIN trial at 34% of exacerbations.[18] This was similar to the 37.9% rate of hospitalization while receiving tiotropium.[12]Due to the limitations of using data from the 24-week ATTAIN trial, a one-way sensitivity analysis was performed for rates of hospitalization related to aclidinium from 24% to 44%.

Similar to other clinical inputs, long-term mortality data are not yet available for aclidinium. The base case uses the same mortality rate seen with tiotropium, 1.7%.[17] In light of the absence of mortality data, it is reasonable for a one-way sensitivity analysis to be performed from 0 – 3.4%. This will account for mortality with aclidinium that is double that of tiotropium.

Annual drug costs for tiotropium and aclidinium differ depending on Medicare Part D plans. In Boston, MA there are 27 available plans for seniors. Drug costs were averaged based on these plans but large ranges exist for both drugs. A two-way sensitivity analysis was performed for tiotropium annual costs ($994-$2,022) and aclidinium annual costs ($1,498 - $4,399).[16]Ranges were derived from the lowest and highest priced plans.

A separate analysis was performed comparing a population with high deductibles ($325) to a population with low deductibles ($0). The three plans with intermediate deductibles were excluded from this analysis. A similar analysis was done for those plans higher than the mean premium, $51.23, versus those lower (9 vs. 18 plans; see Table 2). For each population's plans, a simple average was taken of their annual drug costs and input into the model.

The maximum social security benefit was used in the base case but thought was given as to whether wage data for this age group would be a more appropriate measure of lost revenue. The median weekly income was $770.[29] We inflated this value to $778.62 per week, or $111.23 per day, to reflect February 2013 earnings using the Bureau of Labor Statistics website.[24] This value was then used to assess the associated incremental cost.

Results

The final cost results of each treatment regimen are representative of the discounted drug costs accrued over the 35, 1-year cycles run in the model. Aclidinium cost $60,817 with 13.49 QALYs and tiotropium cost $36,963 with 13.12 QALYs over the treatment period. The incremental effectiveness was marginal at 0.37 QALYs over 35 cycles. The final ICER was $63,718/QALY.

Sensitivity Analyses

Over a variable exacerbation range of almost 17% (0.235-0.40), aclidinium exhibits a minimal change in incremental cost effectiveness. Essentially, evaluating the cost-effectiveness over this broad range of exacerbation rates yields an ICER of $63,718/QALY to $73,353/QALY.

Due to the variations in the costs of aclidinium and tiotropium depending on which Medicare drug plan is selected, a two-way sensitivity analysis was conducted with two different values for willingness-to-pay per QALY. The annual cost of aclidinium ranges from $1,498 to $4,399 and the annual cost of tiotropium ranges from $994 to $2,022 based on various Medicare Part D plans in the Boston area.[16]

For a willingness-to-pay of $50,000 (Figure 2), as the annual cost of aclidinium falls below approximately $2,400, aclidinium is superior to all costs of tiotropium. When the cost of aclidinium is between $2,400 and $3,400, cost-effectiveness is dependent on tiotropium costs; however, when the annual cost of aclidinium rises above approximately $3,400, tiotropium is the superior choice.

Figure 3 shows the preferred agent when the willingness-to-pay threshold is $110,814 instead of the typically used $50,000 threshold. This alternative willingness-to-pay threshold is associated with an analysis of the value of a life-year based on dialysis versus no dialysis in 2003 conducted by Lee et al (2009).[30] As the annual cost of aclidinium falls below approximately $3,700, aclidinium is superior than all costs of tiotropium. When the cost of aclidinium is between $3,700 and $4,399, cost-effectiveness is dependent on tiotropium costs.

One-way sensitivity analyses were performed to see how cost changed as patients experienced a range in the rate of recurrent exacerbation (Figure 4)and hospitalizations. Evaluating the cost-effectiveness over the range of recurrent exacerbation rates yields an ICER of $60,391/QALY to $70,787/QALY. The one-way sensitivity analysis with hospitalization rates yields similar findings with ICERs ranging from $61,089/QALY to $66,347/QALY.

Mortality rates were varied for aclidinium to assess this factor's influence on the cost-effectiveness ratio. As expected, as the mortality rate decreases down to 0%, the ICER becomes smaller and falls below traditional willingness-to-pay cut-offs, favoring aclidinium. As mortality increases, however, the ICER becomes negative, meaning that aclidinium becomes less effective and more expensive, thus being dominated by tiotropium.

When the population's prescription drug plans are divided into high deductible ($325) versus low deductible ($0), there is a non-substantial difference in ICER, $62,982/QALY and $59,140/QALY, respectively. The annual cost of both medications decreases from the base case in the high deductible group and increases in the no deductible group. In both plan populations, however, the associated incremental cost is decreased from the base case, resulting in a lower ICER.When prescription drug plans are divided into those plans above the mean premium, $51.23, and those below, there is larger difference in ICER.

Higher premium plans are associated with an ICER of $71,384; however, lower premium plans are associated with an ICER of $59,884/QALY.

When using median wage data obtained from the Bureau of Labor Statistics website instead of Social Security monthly payments, the ICER decreases slightly to $62,763/QALY from the base case. Either of these inputs may be appropriate from this perspective, and is reassuring that there are no striking differences in the results.

One-way sensitivity analyses were conducted over ranges in annual drug costs, probability of exacerbations, probability of recurrent exacerbations, and probability of hospitalizations with aclidinium in a tornado diagram (Figure 5). As the diagram suggests, the ICER changes little when exacerbation rates and hospitalization rates of aclidinium change. The largest variable in ICER is annual drug costs, second to the wide variety of Medicare Part D plans available. Based on the base case analysis using average costs, aclidinium is more expensive, but if a patient were to enroll in a plan where the annual cost was only $1,498, it may prove to be less expensive than tiotropium. Because of a lower rate of exacerbations and higher associated quality of life, aclidinium would be less costly and more effective, thus dominating tiotropium. This becomes a plan-specific issue depending on the patient population's region, concomitant medications, co-insurance plans and personal preferences.

A Monte Carlo simulation (Figure 6) was implemented with 10,000 runs. Using a willingness-to-pay threshold of $110,814, 87.93% of ICERs fell below this threshold and 12.07% were higher.

Discussion

In our base case analysis, tiotropium was found to be cost effective compared with aclidinium with an associated ICER of $63,718/QALY. Current therapy dictates that at their COPD stage, these patients receive a LAMA for medication therapy. Until recently, tiotropium has been the only LAMA available for therapy. No other cost analyses have looked at the implications that this treatment provides especially inthe patient perspective from a population level. Treatment with aclidinium was associated with a higher ICER than historical willingness-to-pay cut-offs but lower than re-calculated cut-offs, $50,000/QALY and $110,814/QALY respectively.

There is, however, wide variability in ICERs after sensitivity analyses were performed. When rates of exacerbations were lowered, the price per QALY decreased but not to a significant extent. The largest variability with the inputs was in annual drug cost. In the base case, simple averages of the 27 Medicare Part D plans were assumed as annual drug costs. Each average was associated with a wide range depending on the patients' plan. If a group of patients selects the lowest price plan for aclidinium, it may be associated with a more favorable cost-effectiveness ratio; whereas, if a group of patients selects the highest priced plan for aclidinium, it will have a less favorable cost-effectiveness ratio. When considering deductible amount, the model suggests that those populations with higher deductibles have lower drug costs but a higher associated ICER than those populations with no deductible. On average those plans with high deductibles have a lower premium, $33.74/month, versus those with lower deductibles, $69.48/month. Of all prescription plans available, the average premium is $51.23. As seen in Table 1, only one plan (8.3%) with a high deductible has a premium over this mean, as opposed to the low deductible plans, where seven plans (58.3%) are above this average premium. When stratified by the cost of the drug premium, nine plans lie above the premium mean while the remaining 18 are below. The ICER for the higher premium plans is $11,500 more per QALY versus the lower premium plans. The incremental cost is greater than the base case with the higher premium plans while less than the base case with the lower premium plans. Due to variability with the economic inputs, it is difficult to concisely say that one agent is universally preferred for this patient population over another. Depending on the patients' plan, either drug could be viewed as favorable.

The Monte Carlo analysis shows that most of the points lay to the right of the graph suggesting that over the range of values, the majority of ICERs are below a $110,814/QALY willingness-to-pay. The wide variability in ICERs can be explained by the results of the one-way analysis on annual drug costs. Large ranges in cost have resulted in a wide range of available ICERs.

Because of the patient perspective and advent of a new COPD agent where options are limited, this information is valuable to patients and providers. When deciding on step-up therapy, efficacy and cost should be discussed so that patients can make the right choices for themselves. An over-65-year-old population can use the information compiled to make more informed healthcare decisions. This information is applicable to the Medicare population with stable COPD and the providers that manage their COPD.

Although cost data are from Medicare, because of the wide range of annual drug costs depending on drug plan, patients with different insurance coverage might be able to use this information as well.

When longer-term data are available for aclidinium, it would be beneficial to update the mortality and exacerbation rates. It would also be beneficial to stratify patients based on GOLD classes, but due to the lack of data in this area, many assumptions would need to be made on the population.

Due to the recent approval of aclidinium, there are few analyses comparing aclidinium to other treatments options. During an economic literature review, six published economic evaluations of tiotropium were identified. The analyses involving tiotropium were performed in Belgium,[31] Greece,[32] United Kingdom,[33] Italy,[34] the United States,[35] and Spain.[36]The six evaluations reviewed had inconsistent findings regarding tiotropium. The studies done in Belgium and the U.S. concluded tiotropium had a favorable cost-effectiveness ratio, while those in Italy, Greece, Spain, and the United Kingdom found a less favorable cost-effectiveness ratio for tiotropium. This may be due to differences in the methods use, variation of QALYs based on population and different comparators for each study. The data gaps contribute to the difficulties in interpreting these various analyses. The addition of the patient perspective within this study will help decision-makers consider the implications of the various economic analyses. Incorporating the patients' perspective via PCORI activities in the U.S. also will likely help decision-makers gain insights into the tradeoffs that patients value.

Limitations

Several limitations should be taken into account when interpreting this analysis. Aclidinium has been on the market for a relatively short period of time and, therefore lacks long-term effectiveness data. Recently published, the ACCORD COPD Extension Study is a 52-week extension looking at safety and efficacy of aclidinium. While the incorporation of this new information strengthens the results of this analysis, the relatively short market history with the medication should be considered a limitation. It is important to note that the assumption has been made in some cases, especially in mortality and recurrent exacerbations, that aclidinium is just as effective and safe as tiotropium.

Until further data are available, these assumptions, however, are inevitable and should be kept in mind when interpreting the results. Table 5 shows the positives and negatives of each agent.[37,38]

The patient population used in this analysis reflected those in the ACCORD I COPD Extension, ATTAIN and UPLIFT trials. These trials allowed patients to use other concomitant medications as part of their therapies, creating a uniform and more realistic population base to use in a Markov model. Unfortunately, the co-morbidities and medications are not represented in these studies and therefore it is difficult to define our population further. The prevalence of COPD comorbidities in the general COPD population is known but it would be inappropriate to assume that the patients in these randomized control trials had similar prevalence. The analysis does not compare the cost-effectiveness of COPD treatment to other co-morbid therapies, which could provide valuable information to a patient with a fixed budget and many co-medications. The UPLIFT trial was conducted in centers around the world, possibly making the data difficult to transfer to a solely American population. The inability for this analysis to stratify patients based on GOLD category is an added limitation of this analysis. While this information has not been reported for aclidinium yet, the individualization of COPD severity has the potential for dramatic impacts on cost and effectiveness of a particular agent. The growing use of microsimulation modeling methods[39] will help mitigate some of the limitations of traditional analyses based on Markov models.

The use of QALYs is intended for use for population level analyses for use by economists and clinicians to translate this material to a population of patients. QALY data were based on SGRQ scores, which are known to accurately reflect patients' quality of life, and, therefore, better represent real life patient scenarios; however, QALYs have been suggested to be an inappropriate measure on which to base health care decisions. As identified by Kind et al, two of the downfalls to using QALYs are the disconnect between the literature and daily practice by clinicians and their inability to take into consideration patient specific measures during calculation.[40]For societal use, an intervention whose cost-effectiveness is well above current respected thresholds may still be paid for because of our health care systems inherent desire to save lives.[41]

The medication costs for this analysis were taken from Boston Medicare Part D plans, making results of this analysis relative to those particular plans that were selected; however, the wide variety of plans analyzed in this trial increases the range of applicability. Other drug plans throughout the U.S. are likely to have similar ranges to Medicare costs. When applying this information individually, however, a specific Medicare D plan should be evaluated and chosen based on patient-specific criteria.

Uninsured patients were not included in the patient population used in this analysis. Although the advent of the health insurance mandate reduces the uninsured population dramatically, those who are uninsured should still be considered. When looking at the direct out-of-pocket cost of a 30 day supply, tiotropium and aclidinium cost $312.17 and $261.00, respectively.[27,28] Based on the results of this analysis, aclidinium also had slightly better efficacy, potentially making aclidinium a favorable option in this specific population. A separate analysis should be performed to capture a more accurate payment structure for this group of individuals. For those without insurance and on a fixed income, there are prescription assistance programs that are offered, but not in direct affiliation with the drug manufacturers. Available for both medications, these programs are income driven and depend on the number of medications that a patient takes. These plans could be an option for those without insurance with a limited income.

Conclusion

Based on this economic evaluation, the ICER associated with aclidinium was $63,718/QALY, which falls between typically recognized willingness-to-pay thresholds. Since annual drug costs in the Medicare population are highly variable, there are circumstances in which either drug could provide value at a favorable cost. In conclusion, aclidinium was found to be slightly more effective at a larger incremental cost when compared to tiotropium based on an average across Medicare Part D plans.

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Figure 1: Decision Tree Structure

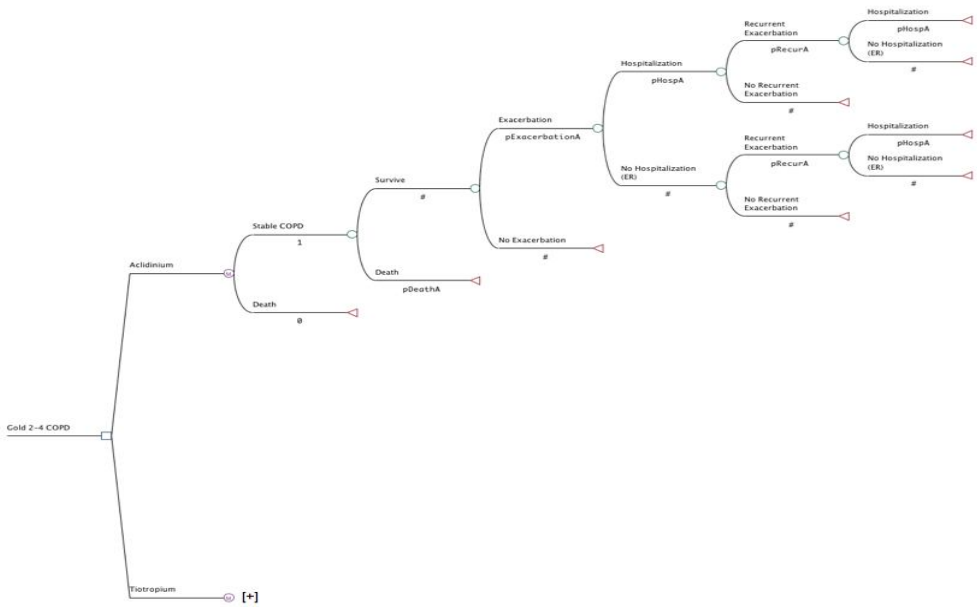

Figure 2: Two-Way CE Sensitivity Analysis of the Cost Associated with Aclidinium&Tiotropium (WTP=$50,000)

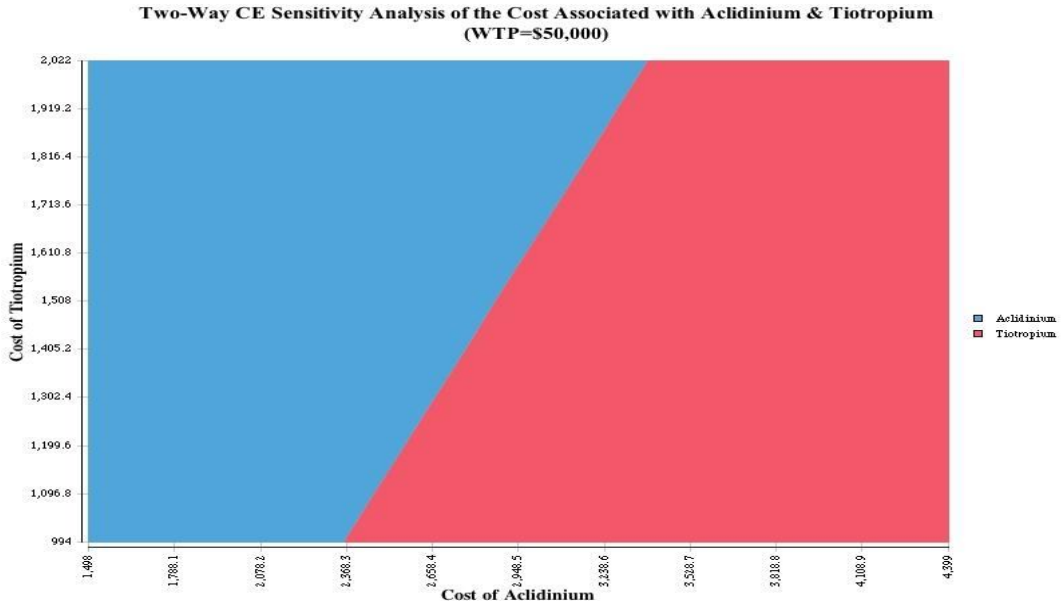

Figure 3: Two-Way CE Sensitivity Analysis of the Cost Associated with Aclidinium&Tiotropium (WTP=$110,814)

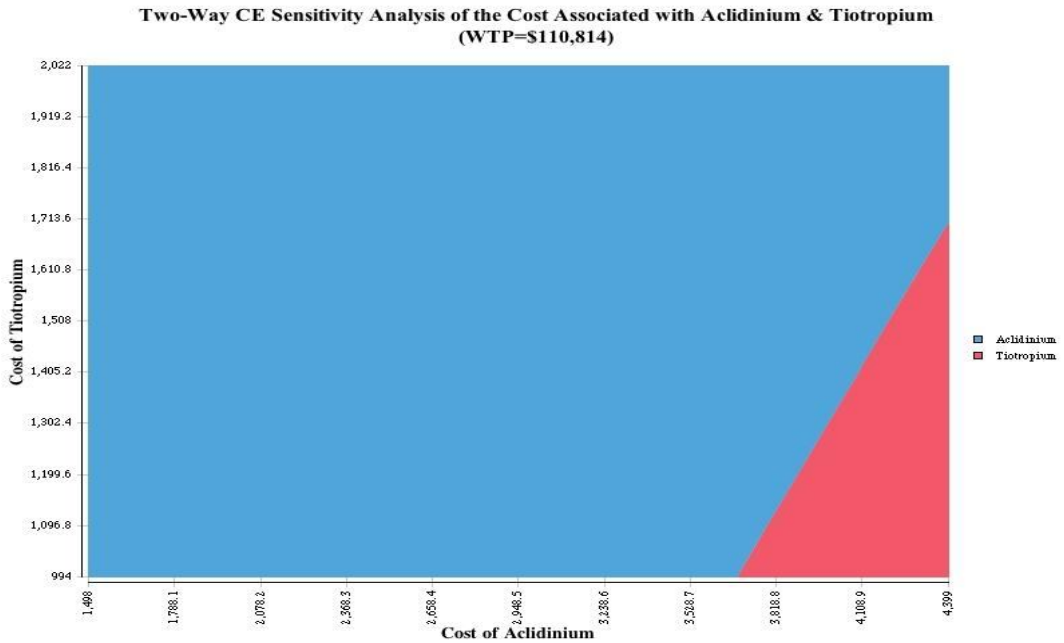

Figure 4: One-Way CE Sensitivity Analysis of Recurrent Exacerbation Associated with Aclidinium&Tiotropium

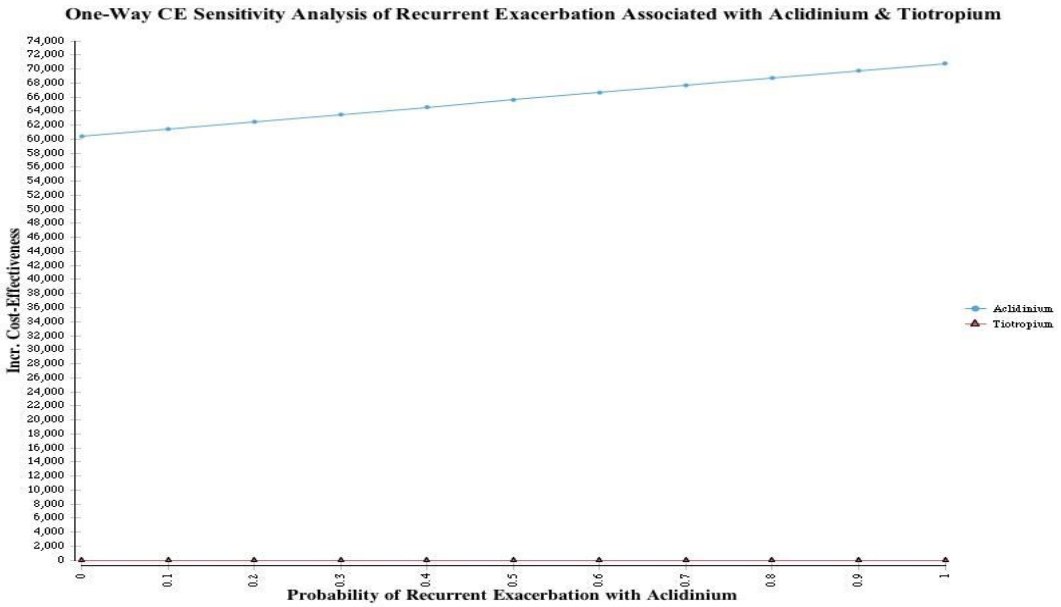

Figure 5: Tornado Analysis (ICER)

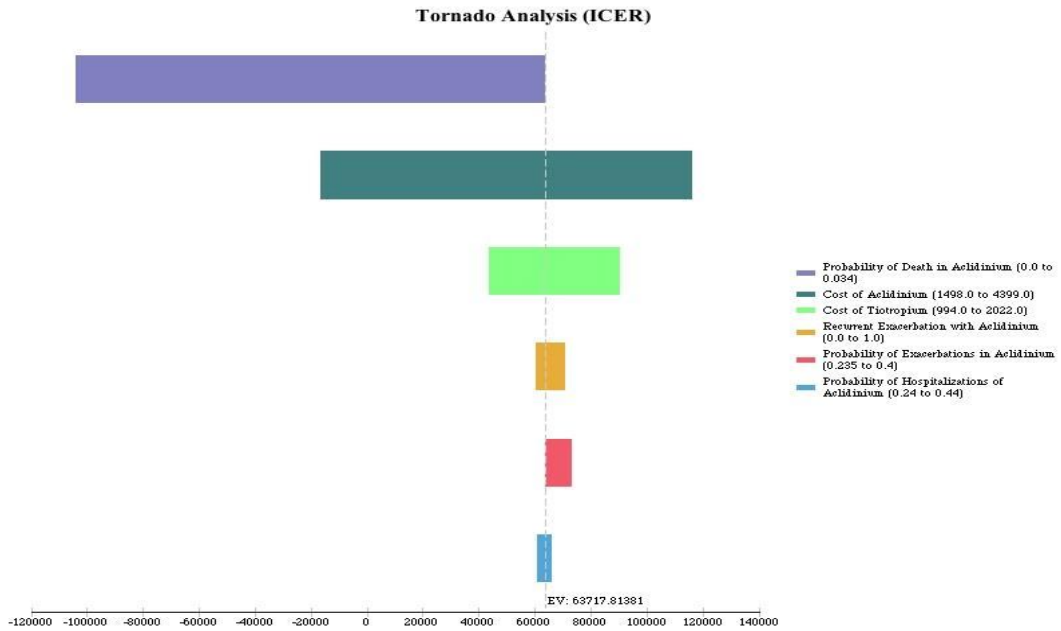

Figure 6: Monte Carlo Simulation

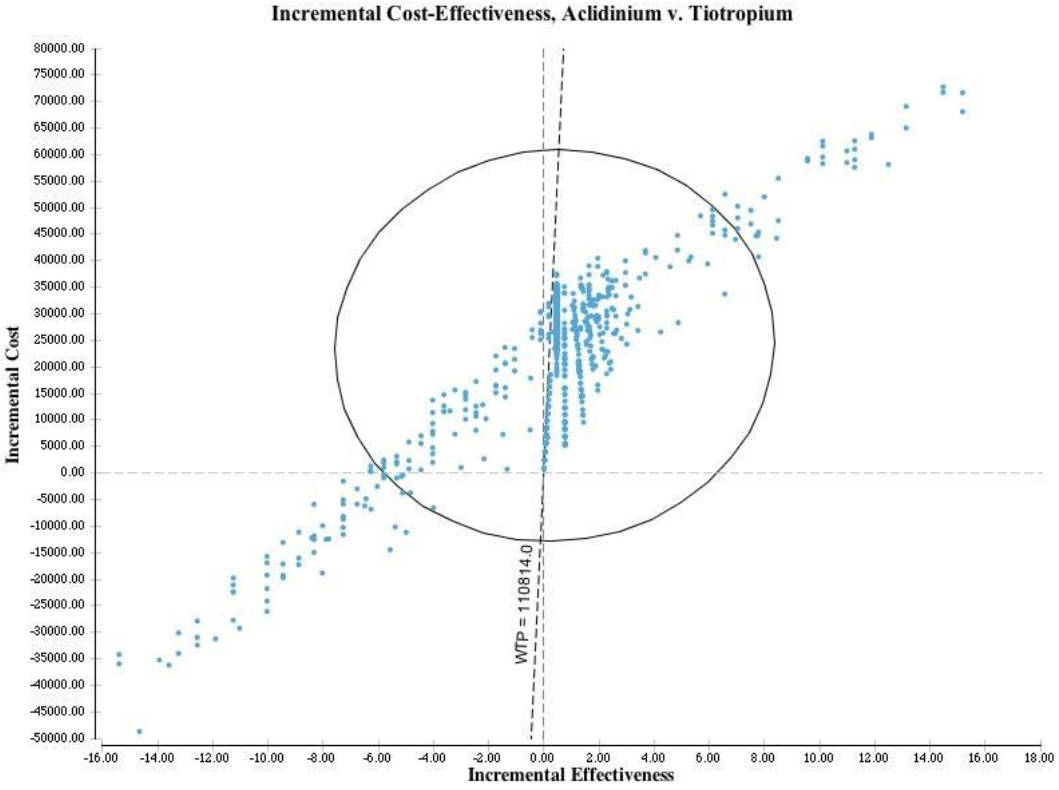

Table 1: Prescription Drug Plans by Deductibles16

Plan Name	Monthly Premium	Deductible	Tiotropium Annual Drug Costs (Includes premium)	Aclidinium Annual Drug Costs (includes premium)
Rewards Standard	$52.50	$325.00	$2,022.00	$2,022.00
Express Scripts	$47.80	$325.00	$1,691.00	$3,587.00
HealthSpring	$37.70	$325.00	$1,652.00	$3,478.00
First Health Value Plus	$34.90	$325.00	$1,635.00	$1,822.00
Cigna	$34.00	$325.00	$1,221.00	$3,425.00
United Select	$33.70	$325.00	$1,816.00	$3,424.00
Readers Digest	$33.60	$325.00	$1,333.00	$3,435.00
EnvisionRX	$33.20	$325.00	$1,566.00	$3,430.00
Smart D Saver	$32.40	$325.00	$1,398.00	$3,420.00
Aetna	$31.60	$325.00	$1,297.00	$3,393.00
Humana Walmart	$18.50	$325.00	$1,443.00	$3,253.00
AARP Saver Plus	$15.00	$325.00	$994.00	$3,197.00
Averages	**$33.74**		**$1,505.67**	**$3,157.17**
Blue	$39.20	$250.00	$1,329.00	$3,484.00
Envision Gold	$54.00	$150.00	$1,742.00	$3,679.00
United	$51.20	$140.00	$1,331.00	$3,634.00
Humana Complete	$114.00	$0.00	$2,021.00	$4,399.00
Aetna Premier	$109.60	$0.00	$1,953.00	$4,329.00
Blue MedicareRX	$100.70	$0.00	$1,679.00	$4,222.00
First Health Premier	$92.40	$0.00	$2,081.00	$2,294.00
AARP Enhanced	$90.00	$0.00	$1,714.00	$4,097.00
Cigna Plan Two	$76.50	$0.00	$1,551.00	$3,935.00
Smart D Plus	$69.00	$0.00	$1,558.00	$3,859.00
Humana Enhanced	$43.10	$0.00	$1,236.00	$3,549.00
WellCare Extra	$39.00	$0.00	$2,118.00	$1,858.00
AARP Preferred	$37.70	$0.00	$1,087.00	$3,469.00
First Health	$31.00	$0.00	$1,644.00	$1,512.00
WellCare	$30.80	$0.00	$1,568.00	$1,498.00
Averages	**$69.48**		**$1,684.17**	**$3,251.75**
Average Premium	**$51.23**	**Average Annual Drug Cost**	**$1,580.74**	**$3,248.30**

Table 2: Prescription Drug Plans by Premium[16]

Plan Name	Monthly Premium	Deductible	Tiotropium Annual Drug Costs (Includes premium)	Aclidinium Annual Drug Costs (includes premium)
Humana Complete	$114.00	$0.00	$2,021.00	$4,399.00
Aetna Premier	$109.60	$0.00	$1,953.00	$4,329.00
Blue MedicareRX	$100.70	$0.00	$1,679.00	$4,222.00
First Health Premier	$92.40	$0.00	$2,081.00	$2,294.00
AARP Enhanced	$90.00	$0.00	$1,714.00	$4,097.00
Cigna Plan Two	$76.50	$0.00	$1,551.00	$3,935.00
Smart D Plus	$69.00	$0.00	$1,558.00	$3,859.00
Envision Gold	$54.00	$150.00	$1,742.00	$3,679.00
Rewards Standard	$52.50	$325.00	$2,022.00	$2,022.00
Averages	**$84.30**	**$52.78**	**$1,813.44**	**$3,648.44**
United	$51.20	$140.00	$1,331.00	$3,634.00
Express Scripts	$47.80	$325.00	$1,691.00	$3,587.00
Humana Enhanced	$43.10	$0.00	$1,236.00	$3,549.00
Blue	$39.20	$250.00	$1,329.00	$3,484.00
WellCare Extra	$39.00	$0.00	$2,118.00	$1,858.00
HealthSpring	$37.70	$325.00	$1,652.00	$3,478.00
AARP Preferred	$37.70	$0.00	$1,087.00	$3,469.00
First Health Value Plus	$34.90	$325.00	$1,635.00	$1,822.00
Cigna	$34.00	$325.00	$1,221.00	$3,425.00
United Select	$33.70	$325.00	$1,816.00	$3,424.00
Readers Digest	$33.60	$325.00	$1,333.00	$3,435.00
EnvisionRX	$33.20	$325.00	$1,566.00	$3,430.00
Smart D Saver	$32.40	$325.00	$1,398.00	$3,420.00
Aetna	$31.60	$325.00	$1,297.00	$3,393.00
First Health	$31.00	$0.00	$1,644.00	$1,512.00
WellCare	$30.80	$0.00	$1,568.00	$1,498.00
Humana Walmart	$18.50	$325.00	$1,443.00	$3,253.00
AARP Saver Plus	$15.00	$325.00	$994.00	$3,197.00
	$34.69	**$220.28**	**$1,464.39**	**$3,048.22**
Average Premium	**$51.23**	**Average Annual Drug Cost**	**$1,580.74**	**$3,248.30**

Table 3: Clinical Inputs

Treatment	Mortality[17]	Exacerbations[12,13]	Exacerbations leading to hospitalization[12, 18]	Recurrent Exacerbations[20]	Baseline SGRQ[12]	Decline in SGRQ[12,13]	Associated QALYs
Aclidinium	0.017	0.235	0.34	0.32	45.7	7.9	0.7871
Tiotropium	0.017	0.42	0.379	0.32	45.7	5.5	0.7653

Table 4: Economic Inputs

Resource	Estimated Use	Unit Cost	Source
Hospital Exacerbation	1 admission	$1,184 deductible/year	Medicare Part A Website[22]
ER Exacerbation	1 visit	$139.53/visit	Dalal et al[21] Medicare Part B Website[26]
Lost Wages (Hospitalization)	3.1 days	$81.71/day	UPLIFT[12] Social Security Fact Sheet[23]
Lost Wages (ER visit)	1 day*	$81.71/day	Social Security Fact Sheet[23] *assumed
Annual Drug Costs (tiotropium) fr	12 months of daily drug therapy	$1,580.74	Lexicomp: Spiriva[27] Medicare Part D Website[16]
Annual Drug Costs (aclidinium) fr	12 months of daily drug therapy	$3,248.30	Lexicomp: Tudorza[28] Medicare Part D Website[16]

±Taken from the patient perspective, costs important to patients include costs related to their exacerbations as well as time lost while suffering from their exacerbation. Lost wages secondary to hospitalization or ER visit is intended to capture that lost time.

Table 5: Pros/Cons of Each Medication

Drug	Pros	Cons
Tiotropium[37]	Once-daily dosing	1 dose/time, loaded into device as individual capsules
	Minimum flow rate less than aclidinium	Steady state achieved in 2-3 weeks
	Extensive long-term clinical efficacy and safety data	
Aclidinium[37, 38]	Inhaler device preferred and associated with higher overall inhaler success rate compared to other dry powder inhalers	Twice-daily dosing
	Significantly higher percentage of patients very satisfied with inhaler	Lack of long-term clinical efficacy and safety data
	Steady state achieved in 2 days	