Economic and health effect of full adherence to controller therapy in adults with uncontrolled asthma: A simulation study

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Background: Adherence to evidence-based controller treatments for asthma is disappointingly low in many jurisdictions. Quantifying the burden associated with suboptimal adherence in patients with uncontrolled asthma will help establish the priorities for policymakers.

Objective: We sought to quantify the benefits in the United States of improving adherence to controller therapies in adults with uncontrolled asthma in terms of health care costs and quality-adjusted life years (QALYs).

Methods: A Markov model of asthma was created to simulate the effect of treatment with controller medications on asthma control and exacerbations over a 10-year time horizon. Health care costs and QALYs associated with the current level of adherence *(status quo)* were compared with a hypothetical scenario in which each patient with uncontrolled asthma at baseline will be fully adherent to an evidence-based controller therapy (the full-adherence scenario). We also evaluated the cost-effectiveness of adherence interventions as a function of their costs and improvement in the adherence.

Results: The *status quo* level of asthma management was associated with $2,786 costs and 7.55 QALYs over 10 years, whereas the corresponding values for the full-adherence scenario were $5,973 and 7.68, respectively. Consequently, the incremental cost-effectiveness ratio of the full-adherence versus the *status quo* was $24,515/QALY. To be cost-effective, a program that improves adherence by 50% should cost less than $130 ($450) per person annually at a willingness-to-pay value of $50,000/QALY ($100,000/QALY). Inclusion of productivity loss in the analysis resulted in the full-adherence scenario being cost-saving.

Conclusion: Considering the extent of suboptimal adherence, our study shows that attempts in improving adherence to evidence-based therapies in patients with uncontrolled asthma can be associated with significant return on investment.

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Key words: *Asthma, cost-effectiveness analysis, decision analysis, evidence-based treatment, adherence*

Asthma is an episodic chronic inflammatory disease of the lower respiratory tract affecting persons of all ages and, because of its high prevalence, results in a tremendous economic and health burden for the patient and society.[1] The current and future public health burden of asthma is a complex function of several factors, including the patient's characteristics, the current level of asthma control, and the innate level of disease activity, as well as practice patterns, the availability of health care resources, and changes in the population (eg, population growth and aging).

The main objective of asthma management is to achieve clinical control and prevent future risk of exacerbations.[2] Compared with controlled asthma, uncontrolled asthma is associated with higher medical costs, productivity loss, future risk of exacerbations, and reductions in quality of life.[3] Despite the availability of effective treatments in achieving asthma control,[4] in practice, there remains a high prevalence of poorly controlled asthma caused by suboptimal treatment.[5,6] This signifies a care gap and potential for improvements in asthma control and reduction in disease burden.

The objective of this study was to quantify the effect of narrowing such a care gap by improving adherence to controller therapies in patients with uncontrolled asthma. We hypothesized that asthma-related outcomes at the population level can be improved substantially and asthma-related costs can be decreased by improving adherence to already existing controller therapies in the US population.

METHODS

A decision analytic model of asthma was created to estimate the outcomes associated with 2 contrasting scenarios with regard to asthma management in the United States: the *status quo* scenario, which represents the current state of asthma controller therapy, and a full-adherence scenario based on providing regular controller treatment to all adults (≥19 years of age) with uncontrolled asthma at baseline. Although modern guidelines recommend controller therapy for all but the mildest asthma, regardless of current control status, we thought potential programs in improving adherence would most likely start with patients with uncontrolled asthma. Indeed, patients whose asthma

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Abbreviations used
CEAC: Cost-effectiveness acceptability curve
GOAL: Gaining Optimal Asthma Control
ICER: Incremental cost-effectiveness ratio
ICS: Inhaled corticosteroid
PDC: Proportion of days covered
QALY: Quality-adjusted life year
RCT: Randomized controlled trial
RR: Relative risk
WTP: Willingness to pay

symptoms are controlled but receive suboptimal treatment will eventually experience uncontrolled asthma; hence such a program will ultimately result in full controller therapy in all asthmatic patients. The outcomes associated with such a full-adherence scenario can be seen as an upper limit of the return on investment of programs that improve adherence. We also used the same analytic framework to perform a scenario analysis in which the cost-effectiveness of a hypothetical intervention as a function of its operational cost and the resulting change in adherence was quantified.

The outcomes of the model were the direct asthma-related medical costs, quality-adjusted life years (QALYs), and number of exacerbations, all measured in the next 10 years among the cohort of prevalent uncontrolled asthma cases in the United States. The figure of merit in this analysis was the incremental cost-effectiveness ratio (ICER), with QALY as the effectiveness outcome, for the full-adherence scenario relative to the *status quo* scenario and for the hypothetical intervention relative to the *status quo* scenario. Cost-effectiveness was assessed by using willingness-to-pay (WTP) thresholds of $50,000/QALY and $100,000/QALY.

The model

We created a Markov model of asthma with weekly cycles in which asthmatic patients transition between 3 levels of control (controlled, partially controlled, and uncontrolled), as defined by the Global Initiative for Asthma,[7] and separate states representing asthma exacerbation and death over a 10-year time horizon. Fig 1 provides an illustration of the asthma model. The model was created with the statistical programming environment R version 2.15.2.[8]

Subgroups

The cost-effectiveness of treatment strategies can be varied across different subgroups in a population. Modeling the natural history of the disease and the effect of treatment within subgroups increases the accuracy of a decision analysis. In addition, if such subgroups can be determined at the time treatment is provided, then the overall efficiency of the program can be improved through a targeted implementation of subgroup-specific cost-effective strategies. In this context age at baseline and baseline level of controller therapy are 2 important variables that could conceivably affect the outcomes, which could also be easily ascertained at the implementation stage.

To model the effect of age at baseline, we stratified the population into 3 age groups (18-35, 36-64, and >64 years).[9] In addition, patients with uncontrolled asthma at baseline can receive different intensities of controller therapies. The course of asthma and responsiveness to controller therapy is presumably different between a patient with uncontrolled asthma despite high doses of controller therapy versus a patient with uncontrolled asthma who is not receiving any controller medication. To recognize the variation in the baseline level of controller therapy, we classified patients at baseline into 3 strata in accordance with the definition used in the landmark Gaining Optimal Asthma Control (GOAL) study[4]: stratum I consisted of patients with uncontrolled asthma who were not using any controller medications; stratum II consisted of patients with uncontrolled asthma who received low-dose controller therapy (beclomethasone-equivalent daily dose of up to 500 μg); and stratum III consisted of patients with uncontrolled asthma despite receiving medium or high doses of controller therapy (beclomethasone-equivalent daily dose of 500-1000 μg). The proportion of patients who do not receive any controller medication despite having uncontrolled asthma (stratum I) in the United States is reported to be 40%.[9] The relative proportion of patients in strata II and III was inferred from another study that reported adherence rates to inhaled corticosteroids (ICSs) in patients with uncontrolled asthma. Details are provided in the Appendix E1 in this article's Online Repository at www.jacionline.org.[10]

Consistent with the step-up approach in asthma therapy as recommended by the Global Initiative for Asthma guideline,[7] for patients in strata I and II, the controller therapy was chosen to be higher ICS doses, whereas for patients in stratum III who are already receiving high-dose ICSs, the combination of ICSs and long-acting β-agonists was chosen as treatment.

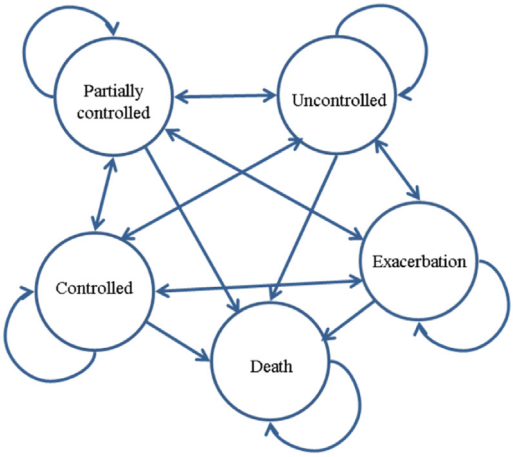

FIG 1. Schematic illustration of the asthma Markov model.

Model parameters

Table I[9-16] presents the parameters used to populate the model. Some model parameters were estimated through combining sources of evidence and performing model calibration, details of which can be found in Appendix E1 and E2 this article's Online Repository at www.jacionline.org.

Transition probabilities. A critical set of model parameters is the transition probabilities across the model states for a given level of adherence to controller medications. For the full-adherence scenario, we used the stratum-specific weekly transition probabilities from the corresponding arm of the GOAL study.[17] Because GOAL did not include a placebo arm, it does not provide evidence on the transition probabilities when patients do not take controller medications or take them irregularly. Unfortunately and to the best of our knowledge, no placebo-based randomized controlled trial (RCT) has reported transition between levels of asthma control. In general, asthma control as defined by modern guidelines has rarely been an outcome of previous RCTs. Nevertheless, many placebo-controlled RCTs have reported on asthma exacerbation rates that are related to the level of control.[10,18-23] We used the reported association between rate of exacerbation and control status, as well as the relation between adherence to controlled medication (quantified as the proportion of days covered [PDC] with the controller medication) and exacerbation rates, to indirectly estimate the transition probabilities.[10,18-23] Details are provided in Appendix E2 in this article's Online Repository.

Model costs. Details on the cost parameters are provided in Table I. Costs in the base case analysis included the cost of controller treatment itself, costs incurred while experiencing exacerbation, and the maintenance costs of asthma management within each level of control (not including the controller treatment costs). In the main analysis we followed the recommendation of the US Panel on Cost-Effectiveness in Health and Medicine[24] and excluded productivity costs from the reference case analysis. All the costs were adjusted to 2011 US dollars.