Asthma Outcome Measures

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Abstract and Introduction

Abstract

Asthma is a common chronic disease with underlying inflammation of the airway. Advances in science have led to increased understanding of the heterogeneous nature of asthma and its complex mechanisms. Traditionally, asthma-practice guidelines have focused on optimizing lung function and the US FDA has required increases in lung function and reduction of exacerbation as primary outcomes in clinical trials of new asthma therapeutics. Improved lung function is a critical indicator of bronchodilator therapy, but the importance of long-term asthma control while maintained on controller medication is increasingly emphasized. The NIH asthma guidelines suggest the use of patient-reported outcomes, including health-related quality-of-life measures, to assess asthma control. Clinical practices and research studies concerning asthma can benefit from harmonizing the major outcome measures so that comparisons across studies can be made. In this article, we review common asthma outcome measures with a focus on recent efforts to harmonize outcomes for therapeutic clinical trials in asthma.

Introduction

Asthma is a common chronic disease with underlying inflammation of the airway that affects more than 300 million people worldwide and 25 million people in the USA.[101] Advances in science have increased understanding of the heterogeneous nature of asthma and its complex mechanisms. Asthma comprises asthma symptoms, variable airflow obstruction, airway hyper-responsiveness (AHR) and underlying inflammation.[1,102] The goals of asthma treatment are not only controlling the patient's current symptoms, but also preventing recurrent asthma exacerbations (AEs). As noted by the US FDA, bronchodilators may control symptoms and lung function in the short term, but use of long-acting bronchodilators without the concurrent use of an inhaled corticosteroid is dangerous because bronchodilators do not reduce airway inflammation or AHR. Asthma management needs to optimize the patient's current clinical state and prevent adverse outcomes, including AEs and side effects of the therapeutics.

Identifying relevant short-term and long-term outcome measures is critical for the management of asthma and evaluating the efficacy and effectiveness of therapeutic interventions. The criteria used to assess asthma outcomes have varied widely from study to study. When asthma is poorly controlled, the patient's activities tend to be restricted, their role function is limited and their work productivity is reduced. In addition, they may require unscheduled, urgent use of healthcare. Hence, patient-reported outcomes, including health-related quality of life (HRQOL), are important indicators of asthma control.

Clinical practices and research studies in asthma can benefit from harmonizing the major outcomes so that comparison across studies can be made and meta-analyses performed, thereby contributing to comparative effectiveness research. In this article, we review asthma outcome measures with a focus on recent efforts to standardize outcomes for therapeutic clinical trials in asthma and with attention to HRQOL.

Asthma Exacerbation

Leading international asthma guidelines have consistently described the goals of asthma treatment as not only controlling current symptoms, but also preventing recurrent AEs. These guidelines include the Global Initiative for Asthma and the National Heart, Lung and Blood Institute/National Asthma Education and Prevention Program: Expert Panel Report 3.[1,102] Experts have argued that AEs may be the most important clinical outcome because they constitute a great risk, cause distress to patients and their families and generate substantial healthcare system costs. AE episodes vary considerably in speed of onset and time to resolution, ranging from a few minutes to several weeks. While severe AEs are more common in patients with poorly controlled asthma, they may also occur in patients with well-controlled asthma. For example, an airway infection can overwhelm the asthma control achieved previously by use of combination therapeutics. AEs are defined by use of healthcare, systemic corticosteroids and rescue medicine.

The recently published American Thoracic Society (ATS)/European Respiratory Society (ERS) Statement: Asthma Control and Exacerbations (joint ATS/ERS statement), provides a comprehensive review of the definitions of AE, asthma control and severity.[2] The joint ATS/ERS statement defined AEs as events characterized by a change from the patient's previous status and it stratified AEs by severity. In the clinical setting, the severity of AEs varies considerably. AEs can be identified by changes in symptoms, rescue medication use or lung function that differ from the patient's usual day-to-day variation. Severe AEs are events that include at least one of the following: requirement for systemic corticosteroids; an increase from a maintenance dose of daily medicine for at least 3 days; or a hospitalization or emergency department (ED) visit requiring systemic corticosteroids. Moderate asthma exacerbations are defined by temporary changes in treatment and include one or more of the following: deterioration in symptoms; deterioration in lung function; or increased rescue bronchodilator use lasting for 2 days or more, but requiring neither a hospitalization or ED visit, nor systemic corticosteroids.

Other recommendations proposed by expert workgroups and researchers differed in part from the joint ATS/ERS statement. However, there may be difficulty in distinguishing moderate AEs from worsening of symptom control. Defining AEs by systemic corticosteroid use, ED use or hospitalizations is consistent with the joint ARS/ERS statement's definition of severe AE, without including the less severe moderate AE category.

Measures of asthma-specific healthcare use are often applied as indirect indicators of intervention efficacy and asthma control. These measures, whether made prospectively or retrospectively, may include outpatient care, pharmacy-dispensing data, ED visits and hospitalization. Measures of asthma-specific events can be obtained from survey data, administrative claims or health services encounter data.

Each type of data source has limitations. Administrative data are rich in details on duration, diagnosis and treatment, but errors and bias may occur owing to coding and billing issues. Survey data collection relies on self-reports and is affected by recall bias.[3] Unscheduled outpatient visits could indicate AEs or worsening of asthma control. Asthma-specific systemic corticosteroid use for at least 3 days (higher than maintenance dose) or ED visits or hospitalization or both, indicate loss of asthma-symptom control and severe AE. Consistent methods and reporting of these outcomes allow comparability across studies. When measuring counts of asthma healthcare events, study duration is an important consideration; adverse outcomes such as hospitalizations are relatively rare – events may fluctuate owing to seasonal factors and may be under- or over-represented in studies of less than 12 months duration.

Asthma Control

With the growing recognition of the importance of the patient's perspective,[4–6] current leading asthma guidelines, including the Global Initiative for Asthma and Expert Panel Report 3, have consistently identified asthma control as the focal concept for asthma. Asthma-practice guidelines traditionally focused on optimizing lung function, minimizing symptoms and preventing exacerbations. Lung function was regarded as the primary end point in earlier guidelines,[7,8] until recent findings on the poor correlation between lung function, inflammation and symptoms.[9,10] Both clinical

practices and clinical trials have focused increasingly on assessing asthma control. Asthma control incorporates the global assessment of symptoms, use of rescue or reliever medicine or both, lung function and patient-reported functioning and activity limitations.

Asthma control can be defined as the extent to which manifestations of asthma are reduced by treatment. The concept that asthma control ought to encompass not only a patient's current or recent clinical state, but also future risk of exacerbation and side effects from therapeutic interventions, is increasingly recognized. Because asthma control is a multidimensional construct without universally recognized criterion standards, the criteria used to assess asthma control have varied widely from study to study. Therefore, harmonizing the measures of asthma control is important for assessing the efficacy of therapeutic interventions in patients with asthma.

Survey Measurement Instruments

The Asthma Control Questionnaire includes lung function tests and has been extensively evaluated.[11] The Asthma Control Test consists of five survey items and does not include lung function tests: shortness of breath, night-time symptoms, use of rescue medications, daily functioning and overall perceptions of asthma control. A simple sum of the items is used to create a score that indicates 'poor' to 'complete' asthma control.

Asthma Severity

Asthma severity is a key concept in asthma control. Previously, severity was defined before treatment began. More recently, severity has been measured based on the intensity of treatment required to achieve good asthma control.[6] Asthma severity is influenced by the underlying disease activity as well as by the patient's phenotype and responsiveness to treatment. Patients' pathological and physiological markers may help characterize asthma severity and act as surrogate measures of future risk.

Asthma Symptoms

In primary care settings, where most asthma is managed, the diagnosis of asthma is often based on symptoms (wheezing, coughing, shortness of breath and chest tightness) despite the fact that these symptoms are often nonspecific to asthma. Revicki *et al.* recommended the Asthma Symptom Utility Index as a core measure for asthma therapeutic studies.[12]

As asthma symptoms vary over time, retrospective surveys are limited by patient recall. In addition, it has been noted that self-reports of symptoms may underestimate severity compared with measures of airway obstruction from a medical exam.[13] Thus, some have argued that clinical measures more accurately assess the level of asthma control achieved.[14] Patients can also use daily symptom diaries, as summarized in the following section.

Diaries

Diaries can be useful for minimizing recall bias and documenting symptoms while patients are using medications in their day-to-day life.[15,16] 'Symptom-free days' is a useful diary variable, but it is not responsive to change among those at the extremes with either very frequent or infrequent symptoms. In addition to symptoms, ambulatory peak expiratory flow (PEF) measurements can be recorded in dairies. PEF provides an objective measure of airway obstruction and is one of the most commonly reported asthma outcomes. However, PEF is inferior to the forced expiratory volume (FEV) in 1 s (FEV_1) as a measure of airways obstruction because PEF underestimates airway obstruction in patients with airway remodeling. Diaries can also be used to record inhaler use for prophylactic or rescue use.

Health-related Quality of Life

The National Asthma Education and Prevention Program recommends using patient-reported outcomes such as HRQOL measures to assess asthma control. HRQOL includes physical functioning, role limitations, emotional wellbeing, social functioning and a variety of symptoms such as pain and energy or fatigue levels, along with disease-targeted symptoms.[17] HRQOL measures provide an important indication of the effects of asthma on daily functioning and wellbeing.[18] Generic HRQOL instruments such as the Short Form (SF)-36 provide a means to compare the effects of asthma with those of other conditions such as cancer.[19]

Role functioning and work-related productivity are among the most important aspects of HRQOL for asthma. Health-related work productivity losses may occur through either absenteeism (time missed from the workplace) or presenteeism (reduced productivity while at the workplace).[20] Mattke *et al.* conducted a systematic review of methods to measure and monetize health-related work productivity loss.[21] Support for the reliability and validity of several of these methods has been published.[22,23] The Work Limitations Questionnaire[24] and the nonproprietary WHO Health and Work Performance Questionnaire[25,26] are perhaps the two most highly regarded measures of health-related work productivity loss.[27] However, the survey instrument most often used in research is the nonproprietary Work Productivity Assessment Instrument.[28] Using these tools to measure health-related work productivity losses provides information on the ways in which asthma impacts on the ability of adults to work and participate fully when at work.

Asthma-targeted instruments such as the Asthma Quality of Life Questionnaire[15] and Asthma Quality of Life Questionnaire (Marks')[29,30] provide in-depth information about the effects of asthma on functioning and wellbeing. Meads *et al.* developed the Asthma Life Impact Scale to go beyond the earlier focus on symptoms, functioning and environmental triggers.[31] For example, the Asthma Life Impact Scale includes items to assess emotional issues not represented in other instruments. Turner-Bowker *et al.* developed an online computerized adapting test (ASTHMA-CAT) that assesses HRQOL with minimal respondent burden.[32]

Preference-based measures integrate across domains to produce a single summary score for each health state anchored relative to 'dead' (score of 0) and 'perfect' or 'full' health (score of 1). Some of the most widely used preference-based measures include the Quality of Wellbeing scale,[33] the Health Utilities Indexes Mark 2 and Mark 3,[34] the EuroQol-5D[35] and the SF-6D.[36] However, these measures are not interchangeable. For example, Kaplan *et al.* administered the five preference-based measures to a sample of 457 cataract patients before and after surgery and found statistically significant improvements in HRQOL 1 month after surgery for all indexes except the SF-6D.[37] The mean differences in HRQOL ranged from 0.00 (for the SF-6D) to 0.06 (for the Health Utilities Indexes Mark 3).

Preference-based measures are especially important for cost–effectiveness analyses used to evaluate different interventions. Quality-adjusted life years (QALYs) combine preference-based measures and life expectancy to yield a single measure of the morbidity and mortality effects. QALYs were recommended by the Institute of Medicine's Committee to Evaluate Measures of Health Benefits for Environmental, Health and Safety regulation.[38] Two alternatives similar to QALYs for measuring disease burden are healthy-year equivalents and disability-adjusted life years. Healthy-year equivalents measure the number of years in optimal health that yield the same level of utility as a particular lifetime health profile that reflects all health states experienced over one's lifetime. Disability-adjusted life years represent the number of healthy years of life lost owing to death or disability and are estimated by assigning disability scores to diseases.

Lung Function Tests

Symptoms and lung function tests are not strongly correlated with one another. Both symptoms and lung function should be monitored by clinicians who assess asthma control in clinical practice and analyzed separately in clinical trials. For example, improvement in symptoms can be achieved by using long-acting β-agonist therapy, which may occur without any change in FEV_1 before bronchodilator (BD) use (pre-BD FEV_1).[39]

Spirometry is one of the fundamental measures of asthma control; it provides an objective measure of airflow limitation caused by smooth-muscle contraction or structural changes. The measures relevant to asthma are: FEV_1, forced vital capacity (as vital capacity or FEV_6), FEV_1 to forced vital capacity ratio, BD responsiveness (change in FEV_1 after inhaled BD) and post-BD spirometric results. Pre-BD FEV_1 has been used as the primary end point of lung function in most of the asthma clinical trials over the last three decades, based on the early focus on airway obstruction as the primary characteristic of asthma. Low FEV_1 measures (pre-BD, on treatment or random) are independent predictors of subsequent AEs.[40–42] BD reversibility is also an independent predictor of death due to asthma.[41] BD responsiveness is only weakly associated with measures of AHR and airway inflammation, but is an independent predictor of response to inhaled corticosteroid therapy.[43]

Studies have found that pre-BD FEV_1 is associated with most other measures of asthma control[44–46] but it correlates weakly with symptoms[47] and with disease-targeted HRQOL.[48,49] Changes in FEV_1 over time are associated with changes in most other asthma outcome measures,[50] but such associations are generally poor (including airway inflammation indexes).[51] Taken together, these findings indicate that lung-function measurements provide complementary information to that provided by other measures.[52]

Airway Hyper-responsiveness

Airway hyper-responsiveness is a measure of variable airflow limitation and is one of the defining features of asthma. AHR reflects the increased sensitivity of the airways to inhaled stimuli, even when spirometric results are normal. AHR is commonly measured by using direct or indirect challenge tests (referring to the mode of action of the agents in relation to smooth-muscle contraction; methacholine is commonly used as a direct smooth-muscle stimuli). AHR is a crucial outcome measure in studies focusing on modifying underlying disease activity. Direct challenge agents can be considered for assessing mid- and long-term disease modification, while indirect challenge agents are relatively more responsive when investigating short-term responses to anti-inflammatory interventions.

Airway hyper-responsiveness is only weakly associated with symptoms, lung function and markers of airway inflammation,[53] but provides independent and complementary information.[54] Studies performed with direct-challenge agents have demonstrated that AHR is strongly related to the clinical course of asthma. Increased AHR is an important risk factor: it predicts loss of control of asthma[55,56] and development of irreversible loss of lung function.[57,58] Increased AHR is a significant risk factor for the subsequent development of physician-diagnosed asthma and chronic obstructive pulmonary disorder in the general population.[59]

Airway hyper-responsiveness is considered an integrative disease marker reflecting multiple pathophysiological mechanisms and should be included in asthma therapeutic trials. In treatment, AHR-guided therapy has shown promise in preventing lung-function decline[60,61] by targeting bronchial hyper-responsiveness.[62]

Biomarkers

Phenotypical or pathophysiological biomarkers can be useful in providing relevant information in guiding treatment decisions. Several pathological and physiological biomarkers have been shown to predict risk of exacerbations.[63] However, no single biomarker has been recommended to assess asthma among all patients for all medications. Biomarkers of airway inflammation are becoming more widely available in clinical settings and can be considered when the differential diagnosis of asthma is difficult. They also provide objective measurements for asthma clinical trials. Characterization of patients' phenotype will probably become increasingly important in developing targeted therapies. For example, in treatments based on sputum eosinophils, measurements of exhaled nitric oxide have shown benefit in terms of fewer exacerbations or reduced medication requirements.[64,65] Clinical studies may collect biomarkers such as IgE,

cortisol, urinary leukotrienes, exhaled nitric oxide and sputum esoinophils for supplementary information.

Asthma Self-management

Leading asthma treatment guidelines emphasize that asthma self-management education should be integrated into all aspects of asthma care and reinforced over time.[1,66,102] Asthma self-management refers to the problem-solving behaviors that patients use to manage asthma over time and involves several tasks in multiple areas. Patients must learn to implement behaviors that enable them to understand their illness and take action to avoid known triggers, monitor their symptoms over time, detect declining physiological function, communicate accurately with healthcare providers, access appropriate treatments and take medications properly. The goal of self-management is to optimize physiological status, improve symptoms and improve functioning and wellbeing. Asthma self-management practices, including therapeutic adherence and use of an asthma action plan, are associated with asthma outcomes.

Appropriate consideration of patients' asthma self-management practices can further characterize patient risk and factors that mediate treatment effectiveness. A Cochrane review indicates that self-adjustment with the aid of a written action plan is equally as beneficial as regular review by a physician.[67] Several measurement tools have been developed for patient asthma self-management. Notably, the Asthma Self-Management Questionnaire, includes items that focus specifically on self-management activities.[68] These activities include knowledge of proper use of preventive strategies, proper use of inhalers, understanding the differences between rescue and maintenance medications and use of peak flow meters. Therapeutic adherence is discussed in more detail in the next section.

Therapeutic Adherence

Adherence with controller therapy is the cornerstone of long-term asthma treatment. Multiple studies have reported that nonadherence is common not only in clinical practice but also in clinical trials. Because patient adherence to therapeutics is a fundamental factor in determining asthma outcomes, patient adherence measures are essential to differentiate poor asthma control owing to nonadherence from treatment-resistant asthma. In clinical studies, accurate measures of patient adherence demonstrate the degree to which nonadherence contributes to therapeutic failure. Asthma adherence is most commonly measured in clinical research by a self report survey or diary, medication measurement (dose or pill counting), electronic medication monitors or pharmacy refill data. In clinical trials, self-reports should be used in combination with more valid measures of adherence. Electronic pharmacy records can yield a wealth of data on asthma patients' patterns of adherence based on refill data and can be useful in characterizing patients individually or as a group.

Expert Commentary & Five-year View

Traditionally, asthma-practice guidelines have focused on optimizing lung function and the FDA requires increases in lung function to be the primary outcome in clinical trials of new asthma therapy. Improved lung function has been an important measure of BD therapy, but long-term asthma control when maintained on controller therapy has been increasingly emphasized and is arguably an even more important outcome. Asthma guidelines have consistently described the goals of asthma treatment as encompassing not only the control of the patients' short-term symptoms, but also risk prevention – preventing recurrent AEs. Protection from side effects of therapeutic interventions and long-term protection from adverse outcomes such as airway remodeling and fixed-airway obstruction should also be considered in the guidelines.

The clinical usefulness of these asthma outcome measures is also affected by the rapidity of symptom changes over time in response to treatment. Symptoms and lung function may change quickly from day to day or even hour to hour and can respond rapidly to initiation of treatment, whereas airway responsiveness tends to change slowly with therapeutic interventions. How patients with asthma should be assessed and how therapeutic outcomes should be evaluated are important and challenging issues. Outcome measures to evaluate therapeutic asthma interventions are now increasingly

available. Harmonizing major clinical outcomes to allow comparison across studies can benefit asthma treatment in clinical practices and research. This article highlights the major issues in measuring asthma outcomes. Comprehensive understanding of the effects of therapeutic agents on asthma requires assessment of standard clinical indicators of lung function and AHR, multidimensional indicators of asthma control such as symptoms and their severity and the effect on day-to-day functioning and wellbeing. Finally, evaluating asthma self-management and adherence to therapeutic recommendations is critical.

Sidebar

Key Issues

- Asthma outcome assessment needs to capture asthma control, prevention of adverse events, symptoms and health-related quality of life, as well as lung function.
- The Asthma Control Questionnaire is recommended for clinical research.
- The Asthma Symptom Utility Index is recommended as a core measure of asthma outcomes.
- The Asthma Quality of Life Questionnaire can be used to supplement generic health-related quality of life measures to provide a deep understanding of the effect of asthma on functioning and wellbeing.

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respiratory care quality performance measures. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

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