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Mediators of Asthma Outcomes

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Abstract

Background—Patient adherence, the level of asthma self-management skills, exposure to stress, and depression can have considerable influence on a wide range of asthma outcomes, and thus are considered asthma outcome mediators.

Objective—National Institutes of Health (NIH) institutes and other federal agencies convened an expert group to recommend standardized measures for 7 domains of asthma clinical research outcomes measures. Although the review of mediators of these outcomes was not within the scope of any specific outcome topic, a brief summary is presented so that researchers might consider potential mediators.

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Methods—We prepared a summary of key mediators of asthma outcomes, based on expertise and knowledge of the literature.

Results—The rationale for including measures of adherence, self-management skills, and exposures to stress in asthma clinical research is presented, along with a brief review of instruments for collecting this information from clinical research participants.

Conclusions—Appropriate measurement of adherence, self-management skills, and exposures to stress will enhance characterization of study participants and provide information about the potential impact these factors can have on mediating the effects of treatment interventions.

Keywords

Adherence; self-management skills; asthma patient education; stress

INTRODUCTION

Asthma clinical research lacks adequate outcomes standardization. As a result, our ability to examine and compare outcomes across clinical trials and clinical studies, interpret evaluations of new and available therapeutic modalities for this disease at a scale larger than single trial, and pool data for observational studies (eg, genetics, genomics, pharmacoeconomics) is impaired.[1] Several National Institutes of Health (NIH) institutes that support asthma research (the National Heart, Lung, and Blood Institute; National Institute of Allergy and Infectious Diseases; National Institute of Environmental Health Sciences; and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development), as well as the Agency for Healthcare Research and Quality, have agreed to an effort for outcomes standardization. This effort aims at (1) establishing standard definitions and data collection methodologies for validated outcome measures in asthma clinical research with the goal of enabling comparisons across asthma research studies and clinical trials and (2) identifying promising outcome measures for asthma clinical research that require further development. In the context of this effort, 7 topic-specific expert subcommittees were established to propose and define outcomes: biomarkers, composite scores of asthma control, exacerbations, healthcare utilization and costs, pulmonary physiology, quality of life (QOL), and symptoms. The Quality of Life Subcommittee noted that patients' adherence, self-management skills, exposures to stress, and depression can have considerable impact on these outcomes and therefore merit consideration for characterizing patients' risk factors and for interpreting study findings on intervention effects. Hence, these factors may be considered mediators of asthma outcomes. Although not within the scope of any specific subcommittee topic, the Quality of Life Subcommittee offered to develop a brief summary of these mediators and identify key methods for measuring them in the context of asthma clinical research, hoping that future researchers will consider using them in their investigations.

MEASURING BEHAVIORAL AND PSYCHOSOCIAL MEDIATORS OF ASTHMA OUTCOMES

Asthma outcomes are directly and indirectly mediated by environmental, social, and individual factors. It is well recognized that patients' asthma self-management practices, including avoiding triggers, adherence to therapy, and use of an asthma action plan, are related to asthma outcomes. Social and psychological factors, including exposure to psychological stress (eg, negative life events, traumatic events such as violence, perceived stress, chronic strains such as financial difficulties, racism, discrimination) and psychological functioning (eg, depression), also have been found to mediate asthma morbidity. Appropriate measurement of these mediators can provide valuable information to investigators interested in more completely characterizing risk factors across different patient populations, as well as providing critical information on factors that may mediate treatment effectiveness, such as nonadherence. We briefly describe below key psychosocial and behavioral mediators that should be considered in a broad range of asthma clinical research studies. The decision about which mediators to measure would depend on the research questions and study design.

Asthma Self-Management

Self-management refers to the problem-solving behaviors that patients use to manage disease over time. For asthma, self-management involves a number of tasks in multiple areas to prevent and manage symptoms. For example, patients (or caregivers of children with asthma) must understand and take action to avoid known triggers, monitor their symptoms over time and detect declining physiologic function, communicate accurately with healthcare providers and access appropriate treatments, and take medications properly. The goal of self-management is to optimize physiologic status, improve symptoms, improve functioning, and achieve better overall QOL.

Self-management is considered to be an important aspect of asthma care,[2] and a number of studies have evaluated the effectiveness of interventions focusing on enhancing self-management skills for individuals with asthma.[3] A recent Cochrane review concluded that education in asthma self-management that involves self-monitoring, regular medical review, and a written action plan can improve health outcomes, including QOL, for adults with asthma.[4] There also is evidence to support the effectiveness of self-management programs for children with asthma.[5–7] Thus it is pertinent to consider self-management as a potential mediator of asthma outcomes in clinical trials and epidemiologic studies.

Some measurement tools have been developed to assess patients' general knowledge and attitudes about asthma management.[8–11] For example, the Knowledge, Attitude, and Self-Efficacy Asthma Questionnaire (KASE-AQ) includes items measuring confidence in managing asthma and integrating asthma into daily life, as well as knowledge of medications, avoidance of triggers, and management of exacerbations.[9] In addition, a newly developed measure, the Asthma Self-Management Questionnaire (ASMQ), includes items that focus specifically on self-management activities, including knowledge of proper use of preventive strategies, peak flow meters, and inhalers, as well as understanding the

differences between quick-relief (short-acting β-agonist, or SABA) and long-term control medications.[12]

Fewer tools have been specifically designed to measure the extent to which self-management behaviors are used by an individual or family.[13, 14] These measures rely primarily on self-report of behaviors, rather than direct observation. However, it also is possible to directly monitor or measure self-management behaviors by conducting direct observations of patients and families (eg, observing administration technique using metered dose inhalers), by measuring biomarkers of environmental exposures such as cotinine, or by directly measuring exposures in the patient's environment (eg, air nicotine, allergen levels). These direct measurements require more resources in research, and consideration must be given to how these types of assessments might influence the behavior itself.

Adherence to Medications

Appropriate adherence to daily, long-term control medication is the cornerstone of effective asthma treatment. However, as with other chronic treatment regimens, nonadherence to asthma therapy is widespread and is a significant risk factor for asthma morbidity and mortality.[15–17] Conservative estimates indicate that almost half of the prescription medications dispensed yearly for asthma are not taken as prescribed. Multiple studies have confirmed that nonadherence is not only prevalent in clinical practice, it also is common in clinical trials.[18] Because patient adherence to asthma therapy is a fundamental mediator of asthma outcomes, measuring asthma therapy adherence should be considered key for a wide range of asthma studies. For example, in some genetic studies where it is critical to accurately phenotype patients' asthma severity, valid measures of patient adherence are essential to distinguish poor asthma control related to nonadherence from treatment-resistant asthma. In clinical trials examining the efficacy of new asthma treatments, accurate measures of patient adherence can clarify true-dose response relationships and confirm the internal validity of the study.[18, 19] And in behavioral or community asthma intervention studies, adherence measures can inform investigators of the degree to which nonadherence contributes to health disparities and poor outcomes, as well as clarify whether observed intervention outcomes are mediated by changing adherence behavior.

Adherence to asthma medication is most commonly measured in clinical research by (1) patient self-report or diary, (2) medication measurement, (3) electronic medication monitors, and/or (4) pharmacy refill data.[18, 19]

- Self-report or asthma diaries, the most widely used measures of adherence, are generally low-cost and simple to administer, useful for identifying patients who are candid non-adherers, as well assessing patient beliefs, attitudes, and barriers to adherence. However, because patients tend to over-report and exaggerate their adherence to therapy, this approach has been found in multiple studies to have limited validity for characterizing patients' adherence patterns and identifying nonadherence. Although all self-report adherence measures share these limitations, examples of measures of adherence with some level of published psychometric validation data include the Morisky Scale,[20–22] the ASK-20,[23] and others.[24–32] Recent methodological studies have suggested that electronic diaries may offer

improved validity over paper-and-pencil diaries. Self-report measures are best suited for studies where accurate adherence classification is not critical to characterizing patients[33–35] or understanding study outcomes. In clinical trials of asthma therapies, self-report and diary measures are best in combination with more objective and valid measures of adherence.

- Medical measurement, including dose counting, pill counting, and canister weighing, provides a more objective and valid measure of adherence, yet remains relatively simple and low-cost to implement in clinical trials. For these reasons, medication measurement is generally considered the gold standard for assessing adherence in most clinical trials. However, research has shown that medication "dumping" is common in clinical trials (up to 20% of participants in 1 study).[18]
- Investigators may want to consider using electronic medication monitoring to more precisely measure participants' patterns of medication use. Medication monitors can add substantial cost and complexity to the conduct of a clinical trial, and device failure has plagued a number of studies using electronic monitors. However, the technology of medication monitoring has improved in recent years, as well as the reliability of devices, and as a result their use in asthma clinical research is increasingly common. Further, the precision and detail of the adherence data provided by this measurement strategy can enrich analyses of dose-response relationships and individual responses. Electronic metered-dose inhaler (MDI) monitors, including the DOSER™, the Medilog™, and the Smartinhaler™ devices, have been commercially available for a number of years and have been frequently used to measure MDI adherence use in asthma clinical trials.[36] The Medication Event Monitoring System (MEMS) electronic pill bottle cap has been used in hundreds of studies to measure pill adherence across a range of chronic illnesses, including asthma. Newer devices are now becoming available to measure dry powder inhaler adherence. However, to date they have been used in very few published clinical studies.
- In recent years, electronic pharmacy and medical records have provided a wealth of data on asthma patients' patterns of adherence with thorough examination of refill data. Although pharmacy records cannot provide information about daily patterns of use, this data source is extremely valuable for characterizing broad adherence categories of both individual study patients as well as overall study populations.[37] Collecting pharmacy refill data as a study measure is increasingly feasible for patients enrolled in managed care or pharmacy benefits plans. The growing use of e-prescribing will further expand this option. Individual pharmacies also can provide refill data with patients' informed consent. Investigators should consider collecting pharmacy refill data in epidemiological studies that expect to collect medical record data, in behavioral intervention studies where adherence is either an important mediator or study outcome, and in all comparative effectiveness research conducted within healthcare delivery settings that collect these data. Strategies for developing and using pharmacy data in clinical research have been described in detail by Steiner et al.[38]

Psychological Stress

Studies link psychological stress to asthma severity and exacerbations in both children and adults.[39–45] The multidirectional pathways linking stress and related psychological correlates to asthma exacerbations and outcomes are briefly outlined here and have been more extensively reviewed elsewhere.[46, 47] In this context, the model of Lazarus and Folkman provides a useful framework conceptualizing stress as a multidimensional construct differentiating between stress-provoking factors, which may elicit a stress reaction (eg, trauma and other negative life events, financial strain, racism, discrimination); stress-mediating or moderating factors, which may interact with or modify the effect of stress-provoking factors on the stress response (eg, coping, social support); and stress-resulting factors, which reflect the resulting psychological sequelae (eg, depression).[48] These factors, in turn, may affect such asthma outcomes as physiological measures (eg, lung function, immunophenotypes), symptoms, exacerbations, response to medications, QOL, and choices regarding whether and where to seek medical care.

High-stress states may directly influence symptoms due to increased inflammation (eg, may increase airway narrowing or responsiveness). Stress also may affect airway physiology through non-inflammatory mechanisms (disrupted neuroendocrine and/or autonomic nervous system functioning), resulting in changes in lung function. Notably, studies have found that 20–40% of people who have asthma have significant changes in lung function induced by emotional stimuli.[49] The efficacy of asthma medications may be altered in subjects under chronic stress.[50–52] Stress and related psychological correlates (eg, depression) may influence morbidity indirectly as well, for example, by affecting how children and adults perceive and manage their asthma. Subjects with poor psychological adjustment may have difficulty accurately appraising asthma symptoms and detecting deterioration.[53] Moreover, an individual's perceptions, expectations, and interpretations of health may be altered by stress, thus affecting other subjective outcome measures (ie, asthma-related QOL).[54] Additionally, stress may affect adherence to medications and self-management strategies, resulting in worsened asthma control. For example, studies document the contribution of caregiver mental health (specifically caregiver depression) to pediatric asthma morbidity and self-management.[55, 56] Stress also may lead to adverse health behaviors that increase an individual's exposure to known asthma triggers (eg, smoking)[57]; and stress may modify or potentiate the effects of physical environmental exposures that contribute to asthma exacerbations and/or response to therapy.[58, 59] Thus stress may be an important factor to consider in a trial examining the effectiveness of an environmental intervention on asthma outcomes (eg, reducing residential exposure to allergens and/or pollutants).

Although a comprehensive discussion of the challenges involved in the assessment of stress in asthma clinical research was beyond the scope of the Asthma Outcomes workshop, we present a brief discussion of questionnaire and interview instruments that have been extensively used and which may be suitable for use in asthma clinical trials. The self-report measures listed here are relatively brief, can be self-administered as well as conducted through interview, and do not have to be administered by trained clinicians. For a more

extensive discussion on the strengths and weaknesses of instruments to measure stress, we refer the reader to recent reviews on the topic.[60, 61]

Measuring stress—Stress can be assessed subjectively using standardized self-report life event checklists, if attention is given to ensuring the adequacy of the measure to capture the relevant and prevalent life events in the population being studied. For example, the Crisis in Family Systems (CRISYS) survey[62, 63] was specifically developed for low-income, ethnically diverse populations. This measure also is validated in Hispanic populations.[64] The CRISYS assesses life events experienced across 9 domains: financial, legal, career, relationships, community and home violence, medical problems, other home issues, discrimination or prejudice, and difficulty with authority. Subjects endorse which events they have experienced in the past 6 months and rate each as positive, negative, or neutral. A sum of the number of events endorsed can be used as an index of the level of stress in their lives. Other life event checklists, which may be better suited to other populations, have been reviewed elsewhere.[65] Another common approach to characterizing stress is through the administration of a brief and well-validated measure of global stress appraisal, for example, the 4- or 10-item Perceived Stress Scale (PSS).[66, 67] The PSS is a brief self-report questionnaire that measures an individual's subjective perception of how stressful he or she finds his or her life to be, compared with the preceding month. This includes the individual's appraisal of whether the events he or she encounters are threatening, taxing, or potentially overwhelming to his or her existing coping resources. The measure may tap into the extent of current environmental demands on the individual and reveal differences in how study subjects evaluate events in the world or their ability to cope. A 1-time measure may represent contemporaneous stress, but it may be necessary to administer repeated assessments on the PSS over the course of a study to capture dynamic changes in stress appraisal or to better characterize chronic stress. That is, perceived stress cannot be assumed to be stable over time, particularly if the individual's environment is not stable (ie, stressors and life events are likely dynamic) or the individual's approach to stress appraisal changes depending on the challenges being faced. Both repeated assessments of stress appraisal over time and more comprehensive measurements of life events that individuals and families experience within the study period will index chronic stress. However, the latter, comprehensive approach may be preferred because environmental demands that result in stress may be experienced across a number of life domains and social structures (eg, household/family, work, community), and knowing more about the sources of stress leading to adverse effects will better inform both the development and the evaluation of intervention strategies.

Measuring depression—Depression is among the most prevalent psychiatric illnesses. It is estimated that approximately 30–50% of individuals who have asthma experience depression, and mental health symptoms are common in caregivers of children with asthma. Because depressive symptoms have been found to significantly influence asthma outcomes,[56, 68, 69] assessing study participants for depression is an important measure to consider in clinical trials. Standardized self-reported questionnaire measures of depression typically assess severity of symptoms (rather than being used to establish a diagnosis of depression). The 21-item Beck Depression Inventory (BDI)[70, 71] and the 10- and 20-item

versions of the Center for Epidemiologic Studies Depression Scale (CES-D)[72] are commonly used. Screening measures also have been developed to be more specific to life periods (eg, pregnancy and the postpartum period). The 10-item Edinburgh Postnatal Depression Scale (EPDS)[73–75] is the only measure of depressive symptoms that has been validated for use during pregnancy and postpartum. The EPDS avoids the loss of specificity of many commonly used self-report depression scales by focusing on the cognitive and affective symptoms of depression and avoiding the somatic complaints (eg, fatigue, appetite changes), which may be biased in pregnant women or the postpartum period. In general, it is preferable to select an assessment survey that is validated against more well-established structured and semi-structured diagnostic interviews, such as the Structured Clinical Interview for DSM-IV (SCID)[76] or the Composite International Diagnostic Interview (CIDI).[77] Cutoff criteria to categorize clinically significant symptoms of depression also have been established for these scales and can be used in analyses when appropriate.

While we have briefly introduced self-report measures that may be appropriate for inclusion in asthma clinical trials, the decision about which to include will depend on the specific research questions and study design being considered. Because parent and child perceptions of symptoms are not precisely correlated, it is important to note that studies including pediatric subjects may need to assess stress experiences, perceptions, and psychological characteristics of both the caregiver and child, when age appropriate.

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Abbreviations

MDI	Metered-dose inhaler
NIH	National Institutes of Health
QOL	Quality of life

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