Treatment Adherence Impact: The Systematic Assessment and Quantification of the Impact of Treatment Adherence on Pediatric Medical and Psychological Outcomes

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Objective Treatment adherence impact (TAI) is the quantification of the effects of adherence behaviors on medical or psychological outcomes using systematic assessment and analytic methods. The purpose of this review is to provide a framework for the measurement and analysis of TAI. Methods Specific studies were selected from the treatment adherence literature to illustrate methods to assess TAI. Results There are many methods available to investigators to evaluate TAI and, when possible, multiple impact outcomes should be included in adherence studies. The methods available to assess TAI and barriers to assessing TAI vary across illness group requiring illness-specific applications of the concepts presented. Conclusions Systematically examining TAI in adherence studies could advance the state of the art of treatment adherence science.

Key words treatment adherence; chronic illness; pediatric; assessment.

Introduction

It is estimated that 15–20% of children in the USA have a chronic health condition (e.g., asthma, diabetes, end stage renal disease; Judson, 2004; Perrin, 2004). The majority of these conditions require the child and his family to manage a medical treatment regimen, which may include tasks such as regular administration of medication, changes in diet, injection of medication, obtaining regular laboratory work, and going to clinic appointments. The complexity and time-consuming nature of these medical treatment regimens places substantial burden on families, making effective implementation of these regimens difficult at best. Indeed, difficulty following these regimens is reflected in rates of nonadherence. Nonadherence is prevalent with an estimated 50% of children with chronic illness not adequately adhering to their treatment regimens (Rapoff, 1999).

The prevalence of nonadherence is striking when one considers the potential impact. Nonadherence results in decreased exposure to a given medical treatment which can subsequently influence multiple medical and psychological outcomes. Medical outcomes linked to nonadherence include changes in key bioassay indicators [e.g., increased blood sugar levels (Duke et al., 2008; Iannotti et al., 2006) and viral loads (Van Dyke et al., 2002)], symptomatology (e.g., asthma exacerbation; Milgrom et al., 1996), and increased morbidity (e.g., infection) and mortality (Kennard et al., 2004). Adherence has also been linked to psychological functioning (Drotar et al., 2007) and changes in quality of life (QOL; Ekberg et al., 2007; Fredericks et al., 2008; Hommel, Davis, & Baldassano, 2008). As the degree of impact on these proximal medical and psychological effects of nonadherence increases, changes in distal outcomes including family functioning (Anderson, Ho, Brackett, & Laffel, 1999), healthcare utilization, and costs to medical institutions and society are more likely to result (Cloutier, Wakefield, Sangelo-Higgins, Delaronde, & Hall, 2006; Government Accountability Office, GAO, 2007; Lewis, Rachelefsky, Lewis, de la Sota, & Kaplan, 1984). Recognition of the prevalence and the adverse clinical outcomes associated with poor adherence have lead to an increased emphasis on research concerning factors influencing adherence and methods to improve adherence behaviors (Nichol, Venturini, & Sung, 1999).
Despite the burgeoning clinical and research interest in pediatric treatment adherence, assessing the impact of adherence/nonadherence on clinical and social outcomes is difficult at best. Indeed, many studies forgo the assessment of this critical link. To continue to advance the field of adherence research, critical questions regarding adherence–outcomes links will need to be routinely and systematically addressed including questions such as: “What level of nonadherence results in adverse medical outcomes?” “What level of adherence is necessary to achieve a clinical benefit on a selected outcome?” and “What is the threshold below which a medication or treatment has no effect on a chosen medical outcome?” Answers to these questions would provide an empirical foundation on which providers could base clinical decision-making and target interventions to those patients whose adherence is having the greatest impact on health and social outcomes.

Treatment Adherence Impact
The term “treatment adherence impact” (TAI) will be used throughout this article to collectively refer to outcomes that attempt to answer questions such as those posed above. More specifically, TAI refers to the quantification of the effects of adherence behaviors on medical, psychological, or social outcomes. Examples of this quantification may include relationships between treatment adherence and concurrent or future relevant medical or psychological outcomes, or changes in treatment adherence (either poorer or better adherence) that result directly in changes in medical or psychological outcomes. An ideal operational definition of TAI would be “a clinical cutoff on an adherence measure for which scores above (or below depending on the directionality of the measure) indicate a level of nonadherence that results in change in medical or psychological outcomes (improvement or decline).” Akin to the term “clinical significance” used in the clinical psychology literature (Jacobson & Truax, 1991), TAI is a distinct construct in that (a) it refers specifically to the relationship between treatment adherence and medical and/or psychological outcomes, (b) TAI may describe effects that are not directly related to a distinct psychological or medical intervention, and (c) it does not necessarily imply a change from a clinical to a nonclinical status, rather enhanced psychological and/or medical health based on improved adherence behaviors (or negative changes that result from nonadherence).

The importance of understanding the impact of adherence on medical and psychological outcomes is clear. However, multiple barriers hinder the process of evaluating TAI including the multifactorial nature of adherence and health factors (e.g., genetic predisposition, illness severity, medication efficacy, medication metabolism). This may be related to the fact that adherence is only one of a number of outcomes that can affect the clinical outcomes of a chronic illness, thereby complicating the validation process. To overcome these barriers, a systematic approach to estimating the impact of treatment adherence on clinical outcomes will be needed. To address this need, the purpose of this article is to: (a) provide a systemic framework for conceptualizing TAI and (b) discuss methods to quantitatively evaluate TAI. Throughout, examples from previous research will be provided to illustrate the concept of TAI as well as discuss potential barriers to assessing TAI. Recognizing that chronic conditions and their treatment regimens vary widely, a broad range of illustrations are provided to highlight the generalizability of the construct TAI to various chronic conditions, to describe the state of the art in TAI, and to identify potential future directions for TAI research.

Framework for Conceptualizing and Methods to Incorporate TAI into Future Adherence Research
Inherently, approaches to assess adherence and TAI vary widely with regard to the clinical outcomes examined, the methods used to assess adherence and outcomes, and the methods to quantitatively assess the adherence–outcome relationships. Indeed, for each chronic condition there are likely to be multiple components to the adherence regimen (e.g., taking oral medications, clinic attendance, obtaining labs on a regular basis, changes in diet, etc.) and multiple ways to measure adherence to each treatment component (e.g., adherence to oral medication can be assessed via self-report, electronic monitoring, and, in some illness groups, via blood levels of a target medication). Moreover, adherence can potentially affect a range of medical and psychological outcomes. Finally, the sensitivity and specificity of assessment approaches that are available for examining TAI greatly differ between illness populations. To determine TAI from this complex set of measures and outcomes, a theoretically driven systematic approach for assessing TAI is needed.

In 2003, the World Health Organization (WHO) emphasized the importance of systems-based approaches for examining and addressing the problem of nonadherence (Sebate, 2003). Consistent with the conclusions of the WHO the following outlines a framework, grounded
in systems theory, for quantitatively evaluating TAI. When using a systemic approach to examine TAI, investigators should consider two primary design factors: (a) types of outcomes and the methods to assess these outcomes (e.g., self-report, bioassay) and (b) methods of analysis (e.g., normative ranges, clinical cutoffs). The proposed framework provides a generalizable, systematic approach for examining TAI. However, the methods to apply this framework will be illness-specific and, as such, inherently vary across conditions.

Categories of TAI Outcomes

Adapted from multiple systems models including ecological systems theory (Brofenfrenner, 1979), outcomes that reflect TAI can be conceptualized as falling into categories that range on a continuum from those that are most proximal to the patient such as bioassays to distal outcomes such as healthcare utilization. The category levels are (a) the Patient (e.g., bioassays, Kennard et al., 2004; symptoms and complications, White et al., 2001; psychological outcomes; Hommel et al., 2008), (b) the Micro level—family (e.g., family functioning, effectiveness of patient monitoring), (c) the Meso level—the clinic, institution, community, and transplant center (e.g., transplant success rates, Magee, Krishnan, Benfield, Hsu, & Shneider, 2008), and (d) the Macro level—healthcare utilization and policy (e.g., costs to Medicare, GAO, 2007; healthcare utilization, Cloutier et al., 2006, Lewis et al., 1984) (Fig. 1). Each category describes the impact that patient adherence has on the patient and/or aspects of the system surrounding the patient. Although patient-level outcomes are likely to be most immediately relevant, a broader model is needed to fully conceptualize the potential impact of treatment nonadherence. To illustrate, the impact of nonadherence may initially be expressed only at the patient level (e.g. elevated blood glucose in diabetes) with little or no effect on micro-, meso-, or macro-level outcomes. However, persistent and/or severe changes in patient-level outcomes may eventually impact the more distal outcomes resulting in increased family conflict surrounding the treatment regimen, poor school attendance due to increased symptomatology, missed work for parents, more hospitalizations, and increased healthcare costs. See Figure 1 for examples of outcomes at each of these levels. Where available we will provide examples of TAI from the literature for each of these levels.

Patient-Level Outcomes

Patient-level outcomes are used most often to assess TAI and may include serum medication levels (e.g., trough

![Figure 1. Multi-level measurement framework for assessing TAI. In potential statistical methods column, where available, citations of studies that illustrate the use of a particular analytical technique are provided in the parentheses.](image-url)
levels of tacrolimus in renal transplant patients, 6-mercaptopurine (6-MP) metabolites in acute lymphoblastic leukemia (ALL) patients), serum levels of disease activity (e.g., viral load), and serum levels of physiologic functioning (e.g., HbA1c in diabetes, creatinine as a measure of renal function). Other patient-level outcomes that reflect TAI include symptomology, morbidity, and mortality. For example, in patients with pediatric asthma the median adherence rate was 13.7% for those patients who experienced exacerbations and 68.2% for those who did not experience exacerbations (Milgrom et al., 1996).

A notable example of innovative work to develop a patient-level outcome measure is by Bucuvalas and colleagues (2005) in pediatric liver transplant. They developed a web-based tool to track patient calcineurin inhibitor blood levels (CNI, an immunosuppressant medication) as a function of time. Instead of looking at a single CNI blood value, the mean and ± 1 and ± 2 SD were also calculated for the patient’s most recent 20 CNI blood levels. Although the original intent of this method was purely for therapeutic drug monitoring, Shemesh and colleagues (2000, 2004) validated this method as an adherence assessment tool by correlating the standard deviations of immunosuppressant blood levels with physician and parent reports of adherence. They convincingly demonstrated that patients with larger standard deviations of immunosuppressant blood levels had poorer adherence. The validation of standard deviations of immunosuppressant concentration levels in the blood was further refined by the identification of clinical cutoffs that are associated with biopsy proven rejection (Stuber et al., 2008).

**Micro-Level Outcomes**

Most proximal to the patient-level outcomes are the micro-level outcomes. Micro-level outcomes include individuals and systems that the patient regularly has direct contact with including family members. A number of family functioning variables have consistently been associated with adherence. Although family functioning has not been explicitly examined with regard to TAI, the relationships between poor treatment adherence, increased illness-specific family conflict, and metabolic control are closely linked and most likely reciprocal in nature (Anderson & Laffel, 1997). Furthermore, the impact of adherence enhancing interventions on illness-specific family functioning will be important to examine (Anderson et al., 1999).

**Meso-Level Outcomes**

Meso-level outcomes include institutional and community outcomes such as transplant success rates, decreased academic or work productivity, and increased school resources to provide academic services during illness exacerbations (Magee, Krishnan, Benfield, Hsu, & Shneider, 2008). Very few studies have examined the impact of adherence on meso-level outcomes. However, there are preliminary data to suggest the value of examining meso-level outcomes. For instance, one study noted that patients with a history of nonadherence had higher school-dropout rates than patients without a history of adherence (Lurie et al., 2000). Others have suggested that nonadherence may lead to healthcare providers having fewer appointments and less time available for other patients (Bender & Rand, 2004). Other meso-level outcomes could include missed days at work and lost wages due to illness exacerbations resulting from nonadherence.

**Macro-Level Outcomes**

Macro-level outcomes are most distal from the patient and are conceptualized as reflecting the societal impact of treatment nonadherence. The impact of adherence on macro-level outcomes is rarely examined directly. However, there is evidence that the costs of nonadherence to the community and society are significant and thus important to consider. For instance, DiMatteo’s meta-analysis (2004) examined the prevalence of nonadherence in adult and pediatric populations and estimated the excess cost associated with nonadherence to be as high as US$300 billion a year. Studies estimating the costs of nonadherence in adults also suggest that macro-level outcomes are important to consider. One study estimated that the economic burden of hospitalization attributable to nonadherence to be US$1.6 billion (Iskedjian et al., 2002), whereas another estimated that cost of medication that is wasted or discarded due to illness exacerbations resulting from nonadherence to be US$1 billion per year.

**Key Considerations when Choosing TAI Outcomes**

Notably, the choice of outcomes will be largely driven by available measures and the state of the art in adherence research (e.g., if a biomarker is available) in a particular illness group. Therefore, assessing a range of available outcomes or potential new markers for a particular illness group is recommended. Notably, a comprehensive review of the methods to assess adherence will not be discussed here as there are several excellent reviews on this topic (e.g., Kenna et al., 2005; Quittner, Espelage, Levers-Landis, & Drotar, 2000; Quittner et al., 2008). Although a broader model is needed to conceptualize the full range
of the impact on treatment nonadherence with respect to clinical relevance, it is likely that patient-level outcomes will be the most sensitive indicators of TAI. Therefore, investigators might wish to incorporate at least one patient-level outcome that is as proximal to the adherence behavior as possible. For example, biomarkers such as serum medication levels, a more proximal outcome, are more likely to be affected by nonadherence than symptoms, which are influenced by other factors such as environment (i.e., exposure to allergens in asthma) and baseline disease severity. In absence of sensitive biomarkers, investigators must carefully consider the variability in their outcomes that may be due to factors unrelated to adherence and incorporate alternative indicators of TAI in order to clarify the impact of adherence on clinical outcomes.

Notably, the issues of assessment, measurement, and validity are closely linked. As such, novel methods of combining multiple adherence assessments with multiple outcomes will be an important component of advancing the quantification of TAI. Specifically, modeling techniques to combine and minimize error from each adherence measurement source should be examined in studies when possible (McGullaugh & Nelder, 1989; Quittner et al., 2008). The advantages of exploring methods to combine multiple adherence measures are nicely illustrated in a study of inner-city children with asthma (Bauman et al., 2002). This study used two methods to measure adherence (“admitted” nonadherence and a “risk for nonadherence” measure), and each indicator exerted independent effects on the variance on all but one of nine morbidity outcomes (i.e., hospitalization for asthma). Subsequently, a typology was developed combining information from both adherence indicators resulting in significantly improved prediction of asthma morbidity. Thus, to effectively examine the multifactorial nature of adherence and the subsequent health outcomes, advanced measurement approaches that utilize information from multiple sources and integrate these data to optimize prediction are needed.

Quantitatively Evaluating TAI

A number of empirical approaches can be used to estimate TAI. The specific analytical methods used to quantify TAI will be driven by the measurement tools available (i.e., is a bioassay available), the state of adherence research in a particular illness group, and the question being asked. Novel analytic approaches will be needed to characterize TAI, including the use of advanced statistical techniques such as cluster analyses and area under the curve. The use of such analytic techniques could facilitate the identification of novel links between adherence and medical outcomes as well as the increase in the specificity of TAI measurement.

The following reviews some of the methods most frequently used to quantitatively evaluate TAI (i.e., effect sizes and odds ratios) as well as some potential analytical tools that could be more effectively utilized in the future.

Methods Frequently Used to Quantify TAI

Effect Sizes

Effect sizes including correlations (Cohen, 1992, 1998; Wilkinson & APA Task Force on Statistical Inference, 1999) are the most frequently used statistical methods to evaluate TAI. Effect sizes are useful because they provide consistent, stable, and reproducible means of communicating the potential TAI of study findings. For example, correlations have been used to examine relationships between adherence and serum levels of medication levels (Pai, Drotar, & Kodish, 2008), adherence and medical symptoms (Milgrom et al., 1996), adherence and viral loads (i.e., the amount of virus in the blood as in HIV, Van Dyke et al., 2002). However, effect sizes alone are not sufficient to demonstrate TAI and are best used in conjunction with other statistical methods.

Categorical Analytic Strategies

Categorical analytic strategies include a variety of statistical tests including Chi-square, odds ratios, Fisher’s exact test, as well as many others (Agresti, 2002). Odds ratios are commonly used to evaluate TAI in studies, where the odds of a particular medical outcome are determined based on an adherence score or group assignment (e.g., Bauman et al., 2002). However, when odds ratios are used as a statistical approach, arbitrary cutoffs may be frequently used to either classify patients as adherent or not. This method may be useful in studies that have data to support the use of cutoffs. Otherwise, the use of arbitrary cutoffs to assess the relationship between adherence measures and medical or psychological outcomes is misleading and should be avoided. For example, Kennard and colleagues (2004) acknowledged they chose an arbitrary cutoff to categorize patients as nonadherent in their study. No detailed rationale was given for how they chose the cutoff or data describing the sensitivity and specificity of this cutoff. This practice has serious implications for the field as key relationships could be missed through misclassification of patients. The continued use of arbitrary cutoffs will limit the degree to which data are available to answer critical questions such as, “What is the threshold below which a medication has no effect?” or “What level of
nonadherence results in adverse medical outcomes?”. Alternatively, the rates of adherence can be compared between patients that experience a particular medical outcome (e.g., complications) and those that do not (e.g., Milgrom et al., 1996). The objective medical classification avoids the drawbacks of arbitrary cutoffs on adherence measures.

**Currently Underutilized Methods to Evaluate TAI**

Advanced data analytic methods can be used to quantify TAI in future adherence research. A few examples of potential techniques are presented below, and where available examples from the adherence literature are provided.

**Cluster Analysis**

The development of validated clinical thresholds is critically needed. Such a threshold would indicate either the absence of or level of a drug that is below a therapeutic dose. Cluster analysis may be one approach that could be useful in describing and establishing clinical thresholds with medications that have multiple metabolites (Aldenderfer & Blashfield, 1984; Everitt, Sabine, & Morven, 2001). An example in adherence research is a study which identified adolescent ALL patients that may be at risk for nonadherence by examining serum levels of two metabolites of the chemotherapy drug, 6-MP (Traore et al., 2008). Using cluster analysis, thresholds for two 6-MP metabolites indicative of nonadherence in adolescents with ALL were identified. Essentially, patients that had low levels of both 6-MP metabolites were identified as at-risk for nonadherence (Traore et al., 2006). The patient clusters were then validated against self-report data of adherence (Pai et al., 2008). Genetic polymorphisms must be considered when assessing 6-MP adherence in ALL patients (Lennard, Welch, & Lilleyman, 1997; Zimm et al., 1983). Thus, for this population, using self-report in conjunction with blood assays is critical. With further validation and development, these two measures (i.e., self-report and 6-MP bioassays), could be combined to create a powerful clinical tool to assess adherence and eventually tie levels of adherence to clinical outcomes.

**Area Under the Curve**

To our knowledge, only one study has used area under the curve (AUC) to examine the TAI of adherence. AUC or response operator characteristics are viable analytic tools for establishing validated cutoffs. Briefly, AUC refers to the probability that a score (on an ordinal or continuous measure) drawn at random from one sample (e.g., adolescents who are adherent) is higher than that drawn at random from a second sample (e.g., adolescents who are nonadherent). Or in the case of a randomized clinical trial, AUC is the probability that a patient in the treatment group has an outcome preferable to the patient in the control group. If AUC = 0.50 the patient outcome is not likely to be better for the treatment versus the control patient. An AUC = 1.0 means that every treatment patient has an outcome better than that for every control patient. For a complete description of AUC, see Kraemer and Kupfer (2006); McFall and Treat (1999); Zweig and Campbell (1993). A recent article by Stuber and colleagues (2008) illustrates how this analytic strategy can be used to establish a validated clinical cutoff to determine what level of nonadherence on a particular measure would likely result in adverse clinical outcomes. Specifically, this study established that patients with a standard deviation value of ≥2.5 for their immunosuppressant levels had approximately eight times higher chances of experiencing a rejection episode.

**Longitudinal Analysis Methods**

Due to the lack of longitudinal data in adherence research, longitudinal analyses are rarely used. However, there are a variety of analytic approaches that could be utilized with longitudinal data that would be especially helpful in evaluating TAI, including survival analyses and growth curve modeling (Bryk & Raudenbush, 1987; Muthén, et al., 2002; Singer & Willett, 2003; Willett & Sayer, 1994). Survival analysis may be especially helpful in populations in which there are distinct health events that may occur due to poor adherence such as cancer (time to relapse), epilepsy (time to seizure), or transplant (time to rejection) (Hosmer & Lemeshow, 1999). The study by Kennard and colleagues (2004) provides an excellent example of using survival analysis to estimate the TAI on more distal outcomes such as time to relapse and death. To identify the impact of adherence on rates of graft loss in pediatric kidney transplant patients Jarzembowski and colleagues (2004) employed survival analyses and concluded that nonadherence accounted for 71% of cases of late graft loss.

**Summary and Critiques of the Current Literature**

To advance the state of adherence science a theoretically grounded, systemic approach to determine TAI is needed. Preliminary evidence for TAI has been documented in a number of conditions including cancer, solid organ transplant, diabetes, and asthma. However, there are multiple
pediatric populations for which there is little to no evidence including gastrointestinal diseases (e.g., inflammatory bowel disease, celiac disease), epilepsy, and obesity.

One clear determinant of the ability to document TAI and the current evidence available in any particular illness group is the availability of a biomarker to assess adherence and/or assess adherence impact. In terms of adherence assessment, the availability of medication serum assays that are validated to assess adherence provide researchers with a relatively objective indicator of adherence. Biomarkers that are more proximal indicators of disease control such as blood glucose in diabetes and viral load in HIV are also invaluable in that they are often detectable before symptoms or other disease outcomes.

One of the most apparent gaps in adherence research is the lack of studies demonstrating the TAI of other types of treatment regimens such as diet and exercise. This is likely due to the fact that many of the relationships between adherence to diet and exercise are inherently illness-specific and need to be established empirically for each condition. There is certainly evidence in some pediatric groups demonstrating the importance of adherence to diet and exercise regimens (Mehta et al., 2008). A better understanding of the effects of these behaviors is critical given that they are frequently cited as the most difficult types of regimens to adhere (DiMatteo, 2004).

Knowledge regarding the impact of treatment adherence on psychological outcomes is also limited. For instance, the directionality of the adherence–QOL relationship is not well understood. Understanding the emotional, social, and behavioral impacts of adherence will be essential for informing the development of medical regimens and interventions to improve adherence. This will also be an important area in the future as patient-reported outcomes are increasingly required to support drug trials.

**Clinical Applications**

Currently, adherence is not routinely assessed in clinical practice. In many conditions, clinicians may suspect non-adherence based on patient symptoms or medication assays. However, neither of these approaches is necessarily sensitive, specific, and reliable methods to identify adherence problems. If objective measures of adherence could be validated against clinical outcomes in accord with the framework presented then clinicians and scientists could have the data on which to target interventions to those patients whose adherence is having the greatest impact on their health outcomes. In a unique example of applying TAI assessment techniques to practice Shemesh and colleagues (2008) assessed adherence using the standard deviation of immunosuppressant levels developed in research (Bucuvalas et al., 2005; Shemesh et al., 2000; Shemesh et al., 2004) and used this information to identify patients to target with an adherence-enhancing intervention. Patients with immunosuppresant standard deviations >3 received an intervention that increased clinic visits, increased monitoring of medication blood levels, provided education about the importance of adherence, and problem-solved the best methods to execute medical regimens.

The most difficult challenge will be translating the tools that we use to assess TAI in research into tools that can be used in the fast-paced and demanding world of clinical practice. There are many barriers to the routine assessment of adherence including the high costs of routine bioassay testing and time to score adherence measures (Quittner et al., 2000; Quittner et al., 2008). Moreover, once poor adherence is identified, there are relatively few empirically supported interventions to promote adherence and many of these interventions, in their current form are not feasible to implement in the context of clinical practice (Kahana, Droter, & Frazier, 2008). Clinicians not only need more standardized methods to routinely assess adherence but they also need empirically supported interventions to address adherence problems once they are identified. The framework for quantitatively assessing TAI could facilitate the assessment of the effectiveness and efficacy of new adherence promoting interventions in the future.

**Limitations**

The conclusions drawn from this review should be considered in light of several limitations. First, it should be noted that this review also does not comprehensively review all pediatric adherence literature. We explicitly chose to highlight a few key studies in order to illustrate the concepts of TAI. In addition, the studies that were reviewed were heavily focused on oral medication adherence. Unfortunately, this is a direct reflection of the current state of adherence literature. Finally, explicit criteria for determining whether an investigator has effectively demonstrated TAI for specific illness groups were not provided.

**Recommendations for Evaluating TAI**

The multifactorial nature of adherence behaviors and medical outcomes requires a multifactorial measurement
and analysis approach. The decision on which methods to use to assess TAI should consider the level of the outcomes (patient, micro-, meso-, and macro-levels), the methods of assessment available at each level (e.g., self-report, bioassay, etc.), and the specific statistical methods available to evaluate (e.g., sensitivity/specificity analysis) each pediatric illness group. This multi-method approach will facilitate the development of valid cutoffs in the adherence literature. Despite their drawbacks (Filler, Bendrick-Peart, & Christians, 2008; Gregoor et al., 1999), bioassays should be incorporated in designs when possible as they provide a relatively objective and proximal measure of adherence or an intermediate measure of adherence impact. Consistently documenting distal TAI outcomes in adherence research, such as macro-level outcomes (e.g., healthcare utilization and cost effectiveness of the methods to assess and enhance adherence), will also be important as the field progresses. Providers will ultimately have to justify the resources needed to monitor and promote adherence if best practice guidelines potentially borne from the proposed lines of research are to be sustainable. In order to obtain sufficient quality data, healthcare utilization/cost effectiveness variables will have to be regularly incorporated into study designs (e.g., Lee, Balu, Cobden, Joshi, & Pashos, 2006). Increasing collaborations with experts in epidemiology, healthcare economy, and public health could facilitate these efforts.

Between patient and within patient differences in responses to treatments (e.g., differences in medication metabolism) are often overlooked in the development of medical treatments or in clinical practice. Therefore, adherence investigators are often missing a piece of the puzzle when trying to understand the relationship between adherence and medical outcomes. In instances in which there are weak or nonexistent relationships between adherence measures and medical outcomes, factors that are unrelated to adherence behaviors should be considered. For instance, individual difference factors can influence the metabolism of 6-MP (a chemotherapy medication used to treat leukemia, rheumatoid arthritis, and inflammatory bowel disease) including variability in function of the intestine and liver (Lennard, Keen, & Lilleyman, 1986; Lennard & Lilleyman, 1989; Zimm, Collins, O’Neill, Chabner, & Poplack, 1983) and genetic polymorphisms. Thus, to develop a better understanding for the role adherence plays in medical outcomes, interdisciplinary research (e.g., psychologists, pharmacologists, physicians, etc.) that integrates adherence, pharmacological, and relevant genetic influences will be essential to form a more complete picture of TAI.

In terms of study design, more longitudinal and intervention studies are needed. Intervention studies including studies of clinical effectiveness provide an important opportunity for demonstrating the impact of adherence, especially if studies are adequately powered to detect changes in adherence and the relevant outcomes that are expected to be affected by improved adherence. Information from such studies could ultimately inform clinical practice and how clinical practices impact patient outcomes. With advancements in measurement methods (e.g., bioassays, electronic monitoring capabilities) future studies will be better equipped to examine the question, “What level of nonadherence results in adverse clinical outcomes?” for pediatric populations.

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