Issues in Clinical Child Psychology

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Adherence to Pediatric Medical Regimens

Third Edition

Springer

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Series Editor

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Michael A. Rapoff, Ph.D.

To my wife, Kim, who I always love, therefore I always need.

To our children, Lindsey and Nathan, and Grandchildren, Harrison and Elliott, our hope for the future and the joys of our lives.

In loving memory of my mother, Shirley Rapoff, for making all her six children feel special.

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Preface

Medications don't always work like they should, transplanted organs are rejected, bacteria develop resistance to previously effective antibiotics, and physicians are hampered in their ability to judge the efficacy of treatments they have prescribed. What factors could account for these alarming trends in medicine? One significant factor is that patients and their families don't always adhere to prescribed treatments. Why this is the case and what can be done about it is the subject of this book.

Before proceeding with the discussion of medical adherence in pediatrics, several caveats are in order:

1. *It is incumbent on medical providers that they are asking patients to adhere to regimens with demonstrated efficacy*. Providers need to remind themselves of the Hippocratic Oath: "I will follow that system of regimen which, according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous" (as cited in Cassell, 1991, p. 145).

   Providers need to be adherent to established treatment guidelines. For example, interventions have been tested that targeted improvements in adherence to asthma treatment guidelines by providers (Okelo et al., 2013)
2. *Providers need to abandon the "blame and shame" approach to dealing with medical adherence problems*. It is tempting to blame patients for adherence failures and shame them into changing their behavior. Providers need to share the blame (or better yet omit blame) and look at their own attitudes and behaviors which impact adherence. For example, failing to simplify regimens or minimize negative side-effects can adversely impact patient adherence.
3. *Patients and their families are no longer (or maybe were never) satisfied with a passive role in their health care*. In fact, the term "compliance" lost favor in the literature because it implied for some an authoritarian approach to health care that required unquestioned obedience by patients to provider recommendations (Dimatteo & DiNicola, 1982; Vrijens et al., 2012). Comprehensive and effective health care requires a cooperative relationship between providers and patients and their families. It also acknowledges the following realities, particularly for treating persons with chronic illness:

> Doctors do not treat chronic illnesses. The chronically ill treat themselves with the help of their physicians; the physician is part of the treatment. Patients oversee themselves. They determine their food, activity, medications, visits to their doctors – most of the details of their own treatment. (Cassell, 1991, p. 124)

4. *Finally, children are not little adults*. Pediatric adherence issues are arguably more complex than with adults because of the influences of family members and peers. There are also developmental processes and constraints that uniquely affect adherence for children and adolescents. Caution is in order when extrapolating from theoretical and empirical work with adults and applying this information to pediatric patients.

This volume is intended to give primary and allied healthcare providers, researchers, and students an overview of the topic of medical adherence in pediatrics. Chapter 1 reviews definitions of adherence, types of adherence problems, and adherence rates to regimens for chronic diseases. Chapter 2 is a review of the consequences of nonadherence and correlates of adherence. Chapter 3 reviews and critiques adherence theories, such as self-efficacy theory, and the clinical implications of these theories. Chapter 4 reviews developmental factors related to assessing and improving adherence (a new chapter for this edition). Chapter 5 describes and critiques different measures of adherence such as assays, electronic monitoring, and self-reports. Chapter 6 reviews measures of disease and health status measures, such as quality of life (this chapter has been separated from the chapter on adherence measures from the previous edition, as this is a growing topic and deserves a chapter of its own). Chapter 7 summarizes and critiques adherence intervention studies for chronic pediatric diseases including meta-analyses of pediatric adherence intervention studies. Chapter 8 is a review of educational, organizational, and behavioral strategies for improving adherence. Chapter 9 review ways to improve pediatric medical adherence research, such as using single-subject designs, minimizing attrition, and calculating effect sizes and documenting clinical significance/social validity (a new chapter for this edition). Chapter 10 concludes the book with a review of cultural, ethical, and legal issues related to adherence clinical and research activities (also a new chapter for this edition).

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Contents

Chapter 1
Definitions of Adherence, Types of Adherence Problems, and Adherence Rates

The Problem of Adherence

A 10-year-old boy with asthma presents in the emergency room looking pale, is having extreme problems in breathing, and is admitted to the intensive care unit. After several days, his asthma is stabilized and he is sent home. This pattern has been repeated several times over the past several years for this boy. The boy and his mother report that he "usually" takes all his prescribed inhaled and oral medications to treat his asthma and rarely misses a dose. His pulmonary function test results, his frequent visits to the emergency room, and his repeated hospitalizations would suggest otherwise.

Health professionals are all too familiar with the above scenario. There is now over five decades of research documenting that nonadherence to medical regimens is common and persistent problem (averaging around 50% with regimens for chronic diseases). Medical nonadherence can compromise the effectiveness of healthcare treatments, as well as the overall health and quality of life of youth with chronic health conditions (DiMatteo, 2004; DiMatteo et al., 2002; Fredericks et al., 2008; Kvarnström et al., 2018; McGrady & Hommel, 2013). Medication nonadherence is further associated with increased healthcare utilization and substantially higher healthcare costs (Hommel et al., 2017; Sokol et al., 2005). This chapter will review how adherence has been defined, the types of adherence problems young people experience, and the studies reporting on adherence rates to regimens for chronic diseases.

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Definitions

The term "adherence" is preferred over compliance because it better reflects a more active role for patients and their families in consenting to and following prescribed medical regimens and treatments (Lutfey & Wishner, 1999; Vrijens et al., 2012). Adherence has been defined as "...the extent to which a person's behavior (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice" (Haynes et al., 1979, pp. 1–2). This is historically the most widely quoted definition in the literature and retains its usefulness because it specifies several important elements related to adherence:

- *Specific behaviors are required of a prescribed medical regimen*. Patients are asked to do specific tasks, e.g., take medications and follow diets.
- *Adherence is not a dichotomous, all-or-nothing phenomenon*. There are qualitative and quantitative differences in adherence. For example, nonadherence to medications can take many forms, such as never filling the prescription, omitting doses, doubling up on missed doses, and even overdosing.
- *There can be concordance or lack of concordance between what patients are asked to do and what they actually do* (if their behavior "coincides" with advice they are given). This implies that there is a standard for judging whether adherence is acceptable or not.

While the "standard" for nonadherence has been somewhat arbitrary across the literature and varies widely between different chronic disease groups (e.g., Dracup & Meleis, 1982; Osterberg & Blaschke, 2005), a taxonomy approach with standard definitions has been proposed by Vrijens et al. (2012). This taxonomy for patient medication adherence relies on two key elements:

- *Adherence to medications* is the process by which patients take their medications as prescribed. Adherence to medication is comprised of three phases, including initiation, implementation, and discontinuation of medications:
  - *Initiation* occurs when the patient takes the first dose of a prescribed medication.
  - *Implementation* is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until discontinuation.
  - *Discontinuation* occurs when the patient stops taking the prescribed medication.
- *Management of adherence* is the process of monitoring and supporting patients' adherence to medications by healthcare systems, providers, patients, and their social networks.

In 2003, the World Health Organization updated the previous definition of adherence (Haynes et al., 1979) to incorporate the importance of the patient-provider relationship. The adherence literature identifies the *quality* of the treatment relationship between the patient and healthcare provider as an important determinant of

adherence (e.g., Rand, 1993). Effective patient-provider treatment relationships are characterized by an atmosphere in which alternative therapeutic options are discussed and the medical regimen is negotiated and agreed upon. Thus, the World Health Organization agreed upon the following definition of adherence: "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (World Health Organization, 2003, pp. 3–4). This definition was further updated in 2005 by the National Coordinating Centre for NHS to define *Intentional* and *Unintentional* nonadherence (Horne et al., 2005). These definitions of nonadherence focus on the concept that agreement to follow a prescribed medical regimen has been secured from the patient. In pediatrics, the agreement to follow a prescribed regimen must also be obtained from caregivers, particularly for younger children.

The World Health Organization (2003) definition of adherence is consistent with a more patient- and family-centered approach to adherence that acknowledges that patients and their families make an initial decision to follow a prescribed regimen and make the decision to sustain adherence over time. The three-phase taxonomy proposed by Vrijens et al. (2012) defines the initiation of medication as *primary adherence*. The second and third phases of medication adherence (implementation and discontinuation) are defined as *secondary adherence*. Secondary nonadherence has been the focus of most research studies and is used frequently as a quality measure for clinical trials and pharmacy reimbursement. In contrast, primary medication nonadherence (e.g., not filling prescription) has been highlighted as a gap in the medication adherence literature (Adams et al., 2004; Cheen et al., 2019).

The World Health Organization (2003) definition of adherence further places the responsibility on healthcare providers to explain treatment options and to negotiate with patients and families on what they are willing to do (Adams et al., 2004). However, how much healthcare providers can negotiate with patients and families without compromising the standard of care is an ethical and potentially legal dilemma. If they compromise care by agreeing to a less intense regimen and the child has a bad outcome, the healthcare provider may open themselves to a lawsuit. Also, while adolescents can and should take part in negotiations, there is uncertainty regarding how much younger children can be involved. Children up to 11 years of age do not always understand the value of preventive medications and find it difficult to understand why someone should take medications when they are not feeling sick (Sanz, 2003). For example, they may not understand why inhaled steroids should be taken to control inflammation for asthma especially when they are not experiencing any breathing problems.

When reading this book, a clear definition of chronic disease (versus acute illness) must also first be established. This book adopts the following definition of chronic disease: a disease that is permanent; has long-term consequences; causes some level of disability; is caused by nonreversible pathological alteration; requires special training of the patient for treatment and/or rehabilitation; or may require a long period of supervision, observation, or care (World Health Organization, 2003).

Types of Adherence Problems

There are qualitative as well as quantitative differences in adherence. For medications, families may not even fill a prescription given to them by a healthcare provider (primary nonadherence), or they may not refill it in a timely fashion or never refill (secondary nonadherence). Patients may miss or delay doses in a variety of ways. For example, if patients do not take any medications for 3 or more consecutive days, this has been labeled a "drug holiday" or "treatment intermission" (Tibble et al., 2020; Urquhart & De Klerk, 1998). The possible consequence of taking treatment intermissions is that there is a decline in drug concentrations and actions, and if the delay is long enough, the actions can completely fade away. For example, in an animal model of epilepsy, a 2-week period of nonadherence to carbamazepine was associated with significant reductions in seizure control; however, these effects were reversible with restarting the medication (Thomson et al., 2017). In adolescent renal transplant patients, treatment intermission occurred in 28.6–45.5% of patients, with nonadherence leading to kidney rejection in some cases.

Another commonly described phenomenon is "white-coat adherence." This is when patients increase their adherence to medications just prior to a scheduled clinic visit, due to the social desirability effects of wanting to look adherent to their medication regimen (Driscoll et al., 2016; Modi et al., 2012; Urquhart, 1994). If drug assays are obtained at a clinic visit, it may appear that the patient has been adherent consistently because most drugs have plasma half-lives that are less than 16 hours, when in fact the measured plasma level only reflects dosing in the prior 48 hours or less, the peak time period for white-coat adherence (Urquhart, 1994; Urquhart & De Klerk, 1998). With the increased availability of electronic medication monitoring (see Chap. 5), recent studies have begun investigating treatment intermissions and white-coat adherence patterns among youth with chronic diseases.

White-coat adherence has been documented in pediatric patients with asthma (Keemink et al., 2015), type 1 diabetes (Driscoll et al., 2011, 2016, 2017; McConville et al., 2020), and epilepsy (Modi et al., 2012). In one study examining white-coat adherence in youth with asthma, a subgroup of patients (15.4%) were documented to increase their adherence to inhaled corticosteroids in the month following a clinic visit. Several studies have noted white-coat adherence in type 1 diabetes. Both younger children and adolescents with type 1 diabetes tend to engage in increased frequency of blood glucose monitoring, carbohydrate counting, and delivery of insulin boluses for the 1- to 2-week period before a clinic visit compared to prior weeks (Driscoll et al., 2011, 2016, 2017; McConville et al., 2020). In pediatric patients with epilepsy, Modi et al.' (2008) pilot study of 35 pediatric patients found that children did not demonstrate white-coat adherence during the first month of treatment. However, in Modi et al. (2012) larger longitudinal study examining medication adherence over a 13-month period in 120 children with newly diagnosed

epilepsy, children demonstrated increased white-coat adherence during the 3 days preceding their neurology clinic visits over time. Children with epilepsy further demonstrated increased variability in their medication adherence over time. These studies emphasize that medication adherence is variable among pediatric patients and their parents, tends to change over time, and is not a static outcome.

Another qualitative distinction in the literature is whether nonadherence is intentional or unintentional nonadherence (Horne et al., 2005). Examples of unintentional nonadherence include forgetting to take medications, missed dosages due to changes in family routines, low income and lack of resources to obtain or refill medication, and misunderstanding how to carry out a specific regimen (Adams et al., 2004; Klok et al., 2015; Lehane & McCarthy, 2007; Wu et al., 2018). Even in pediatric leukemia treatment where motivation is high, unintentional nonadherence is not uncommon (Mancini et al., 2012). It is also possible that nonadherence to prescribed regimens may be strategic, rational, and adaptive in certain cases (Deaton, 1985). This type of nonadherence has been described as "intentional," "volitional," "educated," and "adaptive" nonadherence (Adams et al., 2004). Intentional barriers to adherence are common and are often driven by patient or family perceptions of the child's illness, beliefs about medications, avoidance of medication side effects, and/or a deliberate choice not to follow the provider's medical recommendations (Klok et al., 2015; Mancini et al., 2012). Intentional nonadherence is common in youth with chronic medical conditions (e.g., Hodges et al., 2020; Morton et al., 2014; Schober et al., 2011) and is driven by a variety of reasons. For example, in a study of youth with diabetes, youth reported intentional insulin overdosing due to wanting to engage in binge eating, intentional self-harm accompanying stress or suicidal ideation, attempt to gain attention from parents, and wanting to feel high with hypoglycemia episode (Schober et al., 2011). Youth reported insulin underdosing or omission due to patient denial of diabetes in situations with peers, fear of a severe hypoglycemia episode, and intentional weight reduction.

The historical "culture of medical practice" rests on the assumption that patients or their parents seek medical advice and will follow this advice with reasonable fidelity (Vandereycken & Meermann, 1988). Yet medical treatments sometimes have serious side effects or do not produce anticipated outcomes, or patients find more acceptable substitutes. Studies in both youth and adult patients with HIV (Heath et al., 2002), epilepsy (Brodtkorb et al., 2016; Tang et al., 2013), sickle cell disease (Fogarty et al., 2022; Hodges et al., 2020), and other chronic diseases (Konstantinou et al., 2020) document intentional nonadherence due to negative medication side effects or fear of negative medication side effects, such as severe physical symptoms (e.g., loss of hair, pain, fatigue, jaundice) and feelings of depression on the medication. Other reasons why patients or families may intentionally not adhere are that their treatment goals are different from their provider and the prescribed treatment does not fit into their lifestyle (Adams et al., 2004; Konstantinou et al., 2020).

Adherence Rates to Chronic Disease Regimens

There is wide variability in adherence rates depending on the patient sample and disease, what regimen component is being assessed (e.g., medications, diet, or exercise), how adherence is assessed, and the criteria sometime used to classify patients as adherent or nonadherent. Global estimates are that adherence averages between 50 and 75% for youth with chronic disease regimens (Burkhart & Sabate, 2003; Rapoff & Barnard, 1991). However, there is considerable variability in adherence rates for chronic disease regimens depending on the disease, regimen requirements, measure of adherence, and the criteria for classifying patients along adherence dimensions (see Table 1.1).

Table 1.1 summarizes adherence rates and methods of adherence measurement for the most common pediatric chronic diseases (see Supplemental Reference List for additional articles that contributed only to Table 1.1). Across studies, prescribed medical regimens varied from medication only to combined medication and healthy lifestyle (i.e., diet, exercise) to diet only (e.g., celiac disease). Methods of adherence measurement varied widely across studies, as well as the operational definition of adherence for each study (e.g., <90% versus <60% of medication use equaled nonadherence; subtherapeutic versus nondetectable assay level equaled nonadherence). The most common method of adherence measurement was parent and/or child report. However, many studies used objective measures of adherence such as electronic monitoring, pill count, pharmacy refill records, and direct observation. For some chronic diseases (e.g., asthma, cancer, GI disorders, rheumatic conditions), blood and urine assays were used to measure medication or diet adherence. Many studies used a combination of methods to assess adherence, which is recommended because there is no single gold standard for measuring adherence (Quittner et al., 2008).

Several conclusions can be drawn in reviewing the studies that contribute to Table 1.1. Adherence rates are highly variable among and between different measures of adherence, with biological measurements not always correlating with objective measurements (e.g., Cain et al., 2020; Creary et al., 2020). Adherence rates tend to be higher by parental or youth reports versus more objective measures of adherence such as assays or electronic monitoring. Also, adherence to regimens tends to decrease over time for youth with asthma (e.g., Arcoleo et al., 2019; Jónasson et al., 2000), cancer (e.g., McGrady & Pai, 2019; Tebbi et al., 1986), celiac disease (e.g., Pedoto et al., 2020; Sbravati et al., 2020), cystic fibrosis (e.g., Hommel et al., 2019; Rouzé et al., 2019), diabetes (e.g., King et al., 2014; Kovacs et al., 1992; Leggett et al., 2019; Niechciał et al., 2020), epilepsy (e.g., Lee et al., 2016; Smith et al., 2018), and even solid organ transplantation (Dew et al., 2009). Adherence also tends to be higher to medication regimens versus other nonmedication regimens, such as diet, exercise, and other self-care regimens (e.g., Narayanan et al., 2017; Psihogios et al., 2020; Yawn et al., 2016). Of all the disease categories, adherence is relatively higher for medication regimens for HIV/AIDS, which makes sense in that this is a more imminent life-threatening disease. Although

Table 1.1 Adherence rates by diseases, type of regimens, and adherence measure

	Medical regimens	Adherence rates			Types of Measurement		
Chronic disease		Report measures	Objective measurement	Biochemical measurement[a]	Report measures	Objective Measurement	Biochemical Measurement
Asthma	Inhaled steroids Inhaled beta-agonist Metaproterenol Theophylline Other asthma control strategies (e.g., buying a mattress cover, following action plan)	3–66%	17–87%	10–66%	Parent report Daily diary	Electronic monitor Canister weighing Counting remaining doses in inhaler Medication possession ratio Pharmacy claims	Serum assay Urine assay
Cancer	Prednisone Penicillin/antibiotics Trimethoprim/ sulfamethoxazole 6-Mercaptopurine	32–90%	40–95%	33–98%	Parent report Child report Provider report	Electronic monitor Medication possession ratio	Serum assay Urine assay
Cystic fibrosis	Medications Antibiotics Nebulized medications Inhalation therapy Chest physiotherapy Vitamins/enzymes Diet	22–100%	42–86%		Parent report Child report Daily diary Dietary recall Provider report in chart	Device utilization data Electronic monitor Medication possession ratio Pharmacy refill	

(continued)

Table 1.1 (continued)

	Medical regimens	Adherence rates			Types of Measurement		
Chronic disease		Report measures	Objective measurement	Biochemical measurement[a]	Report measures	Objective Measurement	Biochemical Measurement
Diabetes (type 1)	Blood glucose monitor Insulin Diet Exercise Other diabetes self-care tasks	6–95%	10–99%	34–69%	Parent report Child report Provider report Structured interview	Electronic monitor Pill count Blood glucose meters Observation Medical chart review	HbA1c monitor
Epilepsy	Benzodiazepines Anticonvulsant and antiepileptic medications Ketogenic diet	28–98%	22–87%	22–86%	Parent report Structured interview	Electronic monitor Medication possession ratio Pharmacy refill Medical chart review	Serum assay Saliva assay
GI disorders (celiac, IBD, Crohn's)	Aminosalicylates Thiopurines TNF inhibitors Recombinant human erythropoietin injections Gluten-free diet Enteral nutrition Vitamin & mineral supplements	30–97%	34–97%	19–96%	Parent report Child report Food diary Provider report Structured interview	Electronic monitoring Pharmacy refill Pill count Stopped treatment	Biopsy Serum assay Breath test

HIV/AIDS	Antiretroviral medications	44–95%	41–96%	44–94%	Parent report Child report Recall interview Semi-structured interview	Electronic monitor Medical chart review Pharmacy refill Pill count Clinic visit	Viral load serum assay Plasma drug concentration
Rheumatic diseases (JIA, lupus)	Penicillamine Hydroxychloroquine Immunosuppressive drugs TNF inhibitor Corticosteroids Nonsteroidal anti-inflammatory drugs Salicylates or naproxen Exercises Splints/wraps	53–95%	26–97%	64%	Parent report Child report Provider report	Electronic monitor Pharmacy refill Pill count Medical chart review	Serum assay
Sickle cell disease	Hydroxyurea Antibiotics Medications Immunizations Transcranial Doppler Other self-care requirements	13–100%	12–98%	33–96%	Parent report Child report Daily diary Nurse report Provider report Medical chart review	Electronic monitor Medical record review Medication possession ratios Pharmacy refill Pill count Video observation	Serum assay Urine assay

(continued)

Table 1.1 (continued)

	Medical regimens	Adherence rates			Types of Measurement		
Chronic disease		Report measures	Objective measurement	Biochemical measurement[a]	Report measures	Objective Measurement	Biochemical Measurement
Spina bifida	Bowel medications Catheterization Diet Exercise Skin checks	53–98%			Parent report Child report		
Transplantations	Immunosuppressive drugs Medications Diet	49–98%	57–98%	50–84%	Parent report Child report Daily diary Provider report Nurse report	Electronic monitor Pill count	Serum assay Plasma assay Medication level variability index Coefficient of variation

Note: [a]Subtherapeutic or negative biochemical values

it is difficult to aggregate adherence rates across or within disease categories, low adherence to medical regimens remains a significant problem which can threaten the health and well-being of young people with chronic diseases.

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Chapter 2
Consequences of Nonadherence and Correlates of Adherence

Consequences of Nonadherence

Nonadherence to medical regimens can adversely affect the health and well-being of patients, the cost-effectiveness of medical care, clinical decisions, and the results of clinical trials.

Health and Medical Outcomes

Lower medication adherence is associated with poorer medical outcomes across pediatric chronic illnesses. The most concerning of these poor medical outcomes is mortality related to rejected organ transplant and severe asthma attacks. While over 80% of pediatric patients who receive a solid organ transplant survive into adolescence and young adulthood (LaRosa et al., 2011), potentially serious health consequences can result from adherence failures. Incomplete adherence to immunosuppressive drugs is linked to heart, kidney, and liver transplant failures. In a large cohort (N = 400) of pediatric and adolescent patients who received a liver transplant, increased nonadherence was associated with increased rates of liver rejection over the first 2 years after liver transplant. Specifically, patients who were adherent in both year 1 and year 2 had a rejection rate of 4.4%, compared with a rejection rate of 22.9% for patients who were nonadherent during 1 of the years, and a rejection rate of 34.9% of patient who were nonadherent in both years (Shemesh et al., 2018). In a large study of 2070 pediatric heart transplant patients, the risks of mortality associated with immunosuppression medication nonadherence were 26% at 1 year and 33% at 2 years following transplant (Oliva et al., 2013). Similarly, in pediatric kidney transplant recipients, approximately 50% of experienced graft losses are secondary to noncompliance to immunosuppressant medication treatment after transplant (Almardini et al., 2017). Other studies have also documented high

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rates of nonadherence to immunosuppressant medications following solid organ transplant and associated high rates of graft dysfunction and graft rejection (e.g., Ettenger et al., 1991; Jarzembowski et al., 2004; Magee et al., 2004).

Nonadherence has also been implicated in mortality in the most common chronic childhood illness of asthma. In 2013, the International Study of Asthma and Allergies in Childhood (ISAAC) reported on a survey of almost 1,200,000 children in 233 centers in 98 countries, finding a high variability in mortality rates between countries, ranging from less than 0.1 per 100,000 inhabitants in countries such as Greece, Sweden, and Finland to more than 1.5 per 100,000 inhabitants in countries like South Africa, Turkmenistan, and Kazakhstan (Mallol et al., 2013). Pediatric patients who experience fatal asthma attacks tend to have a history of suboptimal adherence with preventative treatment regimens and fewer routine clinic visits (Fitzgerald & Gillis, 2015). Around the world, the majority of deaths from asthma occur in children from socioeconomically disadvantaged backgrounds (Asher & Pearce, 2014; Herrera & Fitzgerald, 2018). Children with poor adherence to asthma medications are also at increased risk for multiple asthma-related morbidities, including compromised lung functional status, increased acute clinic visits, higher emergency department and hospitalization rates, and increased school absences (Arcoleo et al., 2019; Bauman et al., 2002; Chan et al., 2016; Goldring et al., 1993; Taylor & Newacheck, 1992).

Other examples of poor medical outcomes related to lower medication adherence include increased number and severity of active (inflamed) joints for children with juvenile idiopathic arthritis (Feldman et al., 2007), higher viral loads in children with HIV/AIDS (Martin et al., 2007; Reddington et al., 2000), and poor metabolic control in type 1 diabetes (Alassaf et al., 2019). Nonadherence to antibiotic regimens has also been linked to treatment failure, relapse, development of amplification or drug resistance, and continued transmission of infection diseases such as tuberculosis (Alipanah et al., 2018; Bloom & Murray, 1992; Gibbons, 1992; Marais et al., 2011). Infection disease resistance is thought to be caused, in part, by incomplete adherence to medications which exposes offending microbes to less than optimal levels of antimicrobial action, thus making the organism stronger or more resistant to medications. In effect, incomplete adherence can "inoculate" microbial organisms against the effects of medications. The potential for drug-resistant microbes could be especially threatening to children with compromised immunity, such as those with cancer, cystic fibrosis, and HIV, who are prone to opportunistic infections (Cecinati et al., 2014; Pai et al., 2018; Palser et al., 2019; Vijayasekaran, 2011).

Quality of Life

Adherence failures can also affect the quality of life for patients and their families. For example, children who are nonadherent to their asthma medications can experience more wheezing and variability in their pulmonary function which can limit

their daily activities and negatively impact children's and parents' sleep and overall stress levels (Bauman et al., 2002; Bellin et al., 2015; Hossny et al., 2017). Nonadherence has been related to lower quality of life and poorer family functioning for youth who received a solid organ transplant (Fredericks et al., 2008; Kraenbring et al., 2019). Lower medication adherence to hydroxyurea in adolescents and young adults with sickle cell disease is associated with increased pain, fatigue, and symptoms of depression (Badawy et al., 2017). Across pediatric chronic diseases, patients who are less adherent to treatment regimens may be hospitalized more often, miss more days of school, participate less in sports, participate less with peers, and have high higher rates of family stress due to patent missed worked and burden on parents. These concerns aggregate in significantly reduced quality of life for many youth with poorly controlled disease due to medication nonadherence.

Cost-Effectiveness of Medical Care

The cost-effectiveness of medical care is substantially reduced by medication and clinical nonadherence. Between $100 and $300 billion of avoidable healthcare costs have been attributed to nonadherence in the United States of America (USA) annually, representing 3%–10% of total US healthcare costs (IMS Institute for Healthcare Informatics, 2013). Primary indicators of nonadherence costs include pharmacy costs of unused medicines, inpatient hospitalization costs, addition clinic outpatient costs, emergency department visit costs, and other additional medical costs (Cutler et al., 2018; Lloyd et al., 2019). In a 2018 systematic review, the annual adjusted disease-specific economic cost of nonadherence per person ranged from $949 to $44,190 (in 2015 US$; Cutler et al., 2018). In addition to chronic disease-related healthcare costs, the costs associated with drug-resistant infectious disease have rapidly increased in the past 20 years, with estimates exceeding $2 billion a year in the USA alone (Thorpe et al., 2018).

There is evidence that improving adherence may lower the costs of healthcare and improve medical outcomes. Estimates are that improved adherence to diabetes medication could avert 699,000 emergency department visits and 341,000 hospitalizations annually, and lead to a total savings of around $8.3 billion (Jha et al., 2012). In a cost-effectiveness simulation study, a Markov decision analytic model was used to simulate the potential cost-effectiveness of published adherence-promotion interventions for children with B-ALL compared with treatment as usual (McGrady et al., 2018). Researchers simulated superior health outcomes (increased quality-adjusted life years) and cost savings of $43,540.73–$46,675.71 compared to treatment as usual. Thus, medication and medical nonadherence cost hundreds of billions of dollars each year in the USA, as well as considerable patient and medical personnel time and resources.

Clinical Decisions

Variations in adherence can also negatively impact medical decisions. If physicians are unaware of adherence problems, they may incorrectly attribute poor outcomes to inadequacies in the treatment regimen and then change the treatment plan or prescribe more potent medicines with more serious side effects. Physicians may also order more invasive and risky procedures to determine the lack of treatment success.

The opposite pattern can also occur. Physicians may over attribute treatment failures to adherence problems, particularly when they use treatment outcome or medication serum blood assays as an indicant for adherence. Physicians may then fail to make appropriate and necessary changes in regimens in a timely manner. For example, given that family report of medication adherence does not always match serum medication levels (e.g., Eaton et al., 2018), graft rejection after solid organ transplant may initially be attributed to medication nonadherence when other underlying medical concerns are to blame. Without accurate patient-provider communication regarding medication adherence, poor treatment outcomes may be misattributed to patient nonadherence and result in suboptimal medical management.

Clinical Trials

Nonadherence can bias clinical trials of promising therapies. Consider an example of a randomized clinical trial comparing a promising new drug (Group A) with a placebo (Group B). Patients are matched on relevant characteristics (age, duration of disease, gender, etc.) and randomly assigned to Group A or Group B. If patients in Group A have less than optimal adherence, then the therapeutic benefits and side effects of the new drug would be underestimated (Urquhart, 1989). Also, several studies have shown that patients who adhere to active or placebo medications have better health outcomes compared to poorly adherent patients (Czajkowski et al., 2009; Horwitz & Horwitz, 1993). This has been called the "adherence main effect" (Epstein, 1984). Returning to our example, if a comparable number of patients in the placebo group are as adherent as those in the active drug group, there is less likely to be a significant difference in treatment outcomes. Thus, incomplete adherence among patients in the active drug group or adherence main effects would increase sample size requirements for demonstrating a significant difference between the two groups.

Nonadherence can also lead to overestimates of the effectiveness of a newly tested drug. In some trials, investigators discard treatment outcome results for patients who are nonadherent with the test drug, or they analyze nonadherent patients' outcome results with the placebo or comparison group (the rationale being they did not really "receive" the new drug). Although this may be justified when testing a drug under "ideal" circumstances ("efficacy" trials), it is not acceptable for

"effectiveness" trials or the testing of a drug under ordinary circumstances (Fletcher et al., 1988; Gartlehner et al., 2006). Nonadherence can also have a negative impact on pharmacokinetic studies that aim to determine the kinetics of absorption, distribution, and elimination of a drug in the body after administration (Hughes, 2008; Shiovitz et al., 2016; Vrijens & Goetghebeur, 1999).

Correlates of Adherence to Medical Regimens

By understanding why patients do or do not adhere to medical regimens, effective interventions may be designed to improve adherence. In contrast to the adult literature, there are few extant theoretical models which have been proposed and tested in pediatric chronic diseases. The most used model of adherence in children and adolescents is the health belief model. Briefly, the health belief model is a theory used to predict health behavior(s) (Janz & Becker, 1984; Rosenstock et al., 1988). Studies that have examined correlates from a specific theoretical position (such as the health belief model) will be reviewed in the next chapter.

In contrast to examining a priori predictors using a specified theory or model, most studies in pediatric chronic disease have utilized cross-sectional approaches or data from clinical trials to examine demographic, socioeconomic, patient/family, disease, and treatment regimen factors as predictors of nonadherence. There are some good reasons for examining correlates of adherence (Rapoff & Christophersen, 1982). *Firstly*, negative correlates of adherence that have been identified consistently can be used to develop "risk profiles" that clinicians can use (with appropriate cautions) to identify patients likely to be nonadherent. *Secondly*, some adherence correlates that have been consistently related to adherence are modifiable (e.g., complexity of regimens) and therefore can suggest potential remedies (e.g., reducing the complexity of regimens). *Thirdly*, correlates of adherence can be used as matching or control variables in clinical studies. For example, to improve the internal validity of studies, patients can be matched on relevant dimensions (e.g., age, gender, and socioeconomic status) and then randomly assigned to an adherence intervention or control group. *Finally*, correlates of adherence can be used to support or refute existing theories or help generate new theories.

Patient/Family Correlates

Demographics

Several patient and family-related demographic variables have been associated with adherence. *Adolescents* are more likely to be nonadherent than younger children to regimens across pediatric chronic diseases, including asthma, cancer, celiac disease, cystic fibrosis, diabetes, epilepsy, juvenile idiopathic arthritis, and

posttransplantation immunosuppressive medications (e.g., Arias Llorente et al., 2008; Anderson et al., 1990, 1997; Beck et al., 1980; Bond et al., 1992; Brownbridge & Fielding, 1994; Feldman et al., 2007; Feinstein et al., 2005; Gudas et al., 1991; Hullmann et al., 2015; Holmes et al., 2006; Jónasson et al., 2000; Kovacs et al., 1992; La Greca et al., 1990; McGrady & Pai, 2019; McQuaid et al., 2003; Myléus et al., 2020; Oliva et al., 2013; Serrano-Ikkos et al., 1998; Shetty et al., 2015; Stewart et al., 2003; Tebbi et al., 1986; Walders et al., 2005). While some individual studies do not observe a difference in adherence rates for younger children compared to adolescents (e.g., Katz et al., 2016; Litt & Cuskey, 1981), the overall pattern of adolescents being less adherent than younger children is consistent. This is due to several factors such as decreased parental oversight, forgetting/scheduling conflicts, privacy concerns in public and with peers, and lack of perceived consequences from nonadherence (Arias Llorente et al., 2008; Gabr & Shams, 2015; McGrady & Pai, 2019).

Studies have also examined patient *gender* as a correlate of adherence in children and adolescents, with mixed results. Some studies have found males to be less adherent than females to treatment regimens for asthma, cystic fibrosis, diabetes, and kidney transplant (Boucquemont et al., 2019; Chan et al., 2016; Lorenz et al., 1985; Patterson, 1985; Naar-King et al., 2006). In contrast, several studies found that females are less adherent than males to treatment regimens for diabetes, specifically (Adeyemi et al., 2012; Eaton et al., 2019; Johnson et al., 1990; Patino et al., 2005; Stewart et al., 2003). However, the majority of studies find no differences in medication or treatment adherence between males and females for cancer, celiac disease, diabetes, epilepsy, HIV/AIDS, juvenile idiopathic arthritis, sickle cell disease, and solid organ transplant (e.g., Bitarães et al., 2008; Katz et al., 2016; Kleinke & Classen, 2018; Leggett et al., 2019; Oliva et al., 2013; Pelajo et al., 2012; Sbravati et al., 2020; Sherr et al., 2009; Shetty et al., 2015).

Socioeconomic status (SES) and *family composition* variables have also been studied. Lower SES, in general, and lower parental education levels, specifically, have been associated with nonadherence to regimens for asthma, autoimmune disorders (Crohn's disease, juvenile arthritis) cancer, cystic fibrosis, epilepsy, diabetes, HIV/AIDS, juvenile idiopathic arthritis, and solid organ transplant (Alassaf et al., 2019; Brownbridge & Fielding, 1994; Denson-Lino et al., 1993; Gendelman et al., 2018; Gonzalez et al., 2016; Fortin et al., 2016; Killian, 2017; Killian et al., 2018; Mancini et al., 2012; Patterson, 1985; Rapoff et al., 2005; Vreeman et al., 2008; Yang et al., 2018). Having a single-parent household and parental separation/divorce are associated with lower adherence to medication regimens for asthma, epilepsy, and HIV/AIDS, as well as lower immunosuppressive medication adherence after liver, heart, or lung transplantation (Brownbridge & Fielding, 1994; Killian, 2017; Radius et al., 1978; Serrano-Ikkos et al., 1998; Shemesh et al., 2004; Shemesh et al., 2018; Vreeman et al., 2008; Yang et al., 2018). Higher family conflict and poorer family communication are further associated with lower treatment adherence across pediatric chronic health conditions (Loiselle et al., 2015; Killian et al., 2018; Psihogios et al., 2019; Smith et al., 2018). In addition, patients in larger families or where mothers work outside the home are less likely to be adherent to regimens for

cancer, cystic fibrosis, and epilepsy (Patterson, 1985; Tebbi et al., 1986; Yang et al., 2018). However, similar to other areas of study, this literature does demonstrate mixed results with some studies finding no impact of family structure on medication adherence (e.g., Lansky et al., 1983; Gayer & Ganong, 2006).

Ethnicity and race have also been examined as factors in predicting adherence. Members of minority groups (particularly African American and Hispanic) tend to have lower adherence to regimens for asthma, cancer, diabetes, epilepsy, and solid organ transplant (Adeyemi et al., 2012; Bhatia, 2004; Fortin et al., 2016; Gray et al., 2018; McQuaid et al., 2003; Oliva et al., 2013). However, ethnicity and race are compounded by socioeconomic status, access to medical care, nutrition, and other social determinants of health. The majority of studies in pediatric chronic disease examine ethnicity/race and other social determinants of adherence as single constructs when these constructs, in fact, overlap to influence families' daily behaviors and ultimately medical adherence. Tucker and her colleagues have argued for using a "culturally sensitive model," where researchers examine factors that relate to adherence within different racial groups rather than between them as being more informative (Tucker et al., 2001; Tucker et al., 2002). For example, difficulty swallowing pills, bad tasting medications, and complex regimens are associated with lower medication adherence for both African American and White children following renal transplant (Tucker et al., 2002), whereas knowledge and trust of their medication regimen versus forgetting are associated with nonadherence in African American versus White children following renal transplant, respectively (Tucker et al., 2001). Existing theories used to generate predictive models may also need to be modified when applied to minority samples. For example, Patino et al. (2005) found no support for health belief model factors (perceived severity and cues to action) predicting adherence among a sample of primarily African American children with diabetes. However, even when attempting to adjust for the influence of socioeconomic status on ethnicity/race, studies continue to demonstrate worse treatment adherence for patients of minority racial status (e.g., Bhatia, 2004; Cronin et al., 2018; Wadhwani et al., 2020). The complexity of this literature highlights the need for further and innovative research in this area.

Knowledge

Patients and parents who are less knowledgeable about their or their child's disease and treatment tend to be less adherent to regimens for asthma, cancer, cystic fibrosis, diabetes, epilepsy, HIV/AIDS, and solid organ transplant (Conn et al., 2005; Goodfellow et al., 2015; Gonzalez et al., 2016; Gudas et al., 1991; Holmes et al., 2006; La Greca et al., 1990; Lee et al., 2017; Loiselle et al., 2015; Martin et al., 2007; McGrady & Pai, 2019; Tebbi et al., 1986). Yet medical knowledge tends to account for a limited portion of medical adherence behaviors in both patients and parents (e.g., Beck et al., 1980; Elliott et al., 2001). Studies demonstrate that patient medical knowledge can be high but not lead to high adherence. For instance, in one study, older patients had more knowledge about asthma and more responsibility for

managing their asthma, but still had lower adherence (McQuaid et al., 2003). Parental medical knowledge may also be influenced by logistical or patient barriers to medication adherence, causing lower adherence for some families (Elliott et al., 2001; Jensen et al., 2005; La Greca et al., 1990).

Patient Adjustment and Coping

Patient adjustment and coping variables have consistently been linked with adherence. On the positive side of the adjustment and coping ledger, higher self-esteem, higher disease-related self-efficacy, and more positive outcome expectancies have been associated with better adherence to regimens for asthma, diabetes, chronic kidney disease, epilepsy, juvenile idiopathic arthritis, and other pediatric chronic diseases (Eaton et al., 2019; Friedman et al., 1986; Holmes et al., 2006; Jacobson et al., 1987; Jamieson et al., 2016; LeBlanc et al., 2003; Litt et al., 1982). Greater perceived age-appropriate autonomy and personal independence have been related to higher adherence to regimens for diabetes, epilepsy, and juvenile arthritis (Chew et al., 2019; Friedman et al., 1986; Goethals et al., 2020; Litt et al., 1982). However, too much autonomy, without appropriate levels of parental support and oversight, is frequently associated with poorer medication adherence during adolescence (e.g., Fiese & Everhart, 2006; Klostermann et al., 2021; Wysocki et al., 1996). A sense of optimism has been associated with better adherence to regimens for cystic fibrosis (Gudas et al., 1991), and higher hope has been associated with better adherence to regimens for asthma, diabetes, and solid organ transplant (Berg et al., 2011; Calkins-Smith et al., 2018; Maikranz et al., 2007). Furthermore, greater problem-solving skill is associated with higher adherence to diabetes and irritable bowel syndrome medical regimens (Greenley et al., 2015; Hill-Briggs & Gemmell, 2007; McCaul et al., 1987).

On the negative side of the adjustment and coping ledger, patients with behavioral problems (e.g., aggression, defiance) or emotional problems (e.g., depression, anxiety, pessimism) are less likely to adhere to regimens for cancer, cystic fibrosis, diabetes, epilepsy, HIV/AIDS, irritable bowel syndrome, systemic lupus erythematosus, and renal disease (Benton et al., 2019; Berg et al., 2011; Brownbridge & Fielding, 1994; Chang et al., 2021; Cohen et al., 2004; Gray et al., 2012; Gudas et al., 1991; Henning et al., 2019; Kennard et al., 2004; Kongkaew et al., 2014; Kovacs et al., 1992; Miller & Drotar, 2003; Naar-King et al., 2006; Penkower et al., 2003; Shubber et al., 2016). A history of substance abuse and repeating a grade or dropping out of school has been associated with lower adherence to regimens for HIV and inflammatory bowel syndrome and for those receiving liver transplants (Plevinsky et al., 2019; Shemesh et al., 2004; Shubber et al., 2016; Williams et al., 2006). Stressful life events have been associated with lower adherence to regimens for HIV (Williams et al., 2006). The use of avoidant coping strategies, such as denial, has been related to poorer adherence to asthma, cancer, and diabetes medical regimens in youth (Barton et al., 2003; Iturralde et al., 2017; Tamaroff et al., 1992).

Family Adjustment and Coping

Turning to the family unit, studies have examined both positive and negative aspects of family and parental adjustment and coping as correlates of adherence. On the positive side, greater family support, expressiveness, harmony, integration, cohesion, and organization have been associated with higher adherence to regimens across childhood chronic disease, including asthma, cystic fibrosis, diabetes, cancer, diabetes, HIV/AIDS, sickle cell disease, renal disease, and seizure disorders (Friedman et al., 1986; Hauser et al., 1990; Kurtin et al., 1994; La Greca et al., 1995; Leeman et al., 2016; Nabunya et al., 2020; McCaul et al., 1987; Patterson, 1985). Also, better communication and problem solving have been associated with higher adherence to regimens for asthma, diabetes, and HIV/AIDS (Chisholm et al., 2011; McQuaid et al., 2005; Nabunya et al., 2020). Greater father involvement (in terms of amount and helpfulness) has been related to better adherence for adolescents with asthma, cystic fibrosis, inflammatory bowel disease, phenylketonuria, and spina bifida (Wysocki & Gavin, 2006). Surprisingly, some positive aspects of family functioning have been associated with *lower* adherence to medical regimens. Increased family social and recreational activities outside the home have been associated with poorer adherence to regimens for cystic fibrosis, HIV/AIDS, and inflammatory bowel syndrome (Buchanan et al., 2012; Geiss et al., 1992; Hommel & Baldassano, 2010; Patterson, 1985; Spekhorst et al., 2016). Families frequently cite the child being away from home as a barrier to medical adherence.

On the negative side of family adjustment and coping, increased parental stress and poor parental coping have been associated with lower adherence to regimens for juvenile idiopathic arthritis, sickle cell disease, and renal disease (Brownbridge & Fielding, 1994; Gerson et al., 2004; Treadwell et al., 2005; Wynn & Eckel, 1986). Poor communication and negative parent-child interactions have been associated with lower adherence to regimens for diabetes and renal disease (Gerson et al., 2004; Lewandowski & Drotar, 2007; Miller & Drotar, 2007; Starkman et al., 2019). Increased parental depression has been related to increased barriers and poor adherence for asthma, cystic fibrosis, and renal disease (Barker & Quittner, 2016; Bartlett et al., 2004; Brownbridge & Fielding, 1994; Pak & Allen, 2012), and greater parental anxiety has been associated with lower adherence to asthma and seizure medications (Hazzard et al., 1990; Sancakli & Aslan, 2021). Also, parents who are more likely to place behavioral restrictions on their children tended to have children who were less adherent to their diabetes and seizure medications (Hazzard et al., 1990; Starkman et al., 2019).

Parental Involvement/Monitoring

The lack of parental monitoring of treatment-related activities has been found to contribute to nonadherence. Family situations where there is ambiguity about who assumes primary responsibility for regimen tasks or where parental monitoring is low are consistently associated with lower adherence to regimens across pediatric

chronic disease populations (Anderson et al., 1990, 1997; Bassi et al., 2020; Beck et al., 1980; Burgess et al., 2008; Feinstein et al., 2005; Holmes et al., 2006; Ingersoll et al., 1986; Tebbi et al., 1988; Wiebe et al., 2005). Parental monitoring typically decreased and shifts from the parent to the child around 12 years of age (e.g., Shemesh et al., 2004) and in one study, parental supervision virtually ceased by the time children with diabetes were 15 years of age (Ingersoll et al., 1986). Increased parental monitoring and parents continuing to take responsibility for children's medical regimens are associated with higher adherence (e.g., Bassi et al., 2020; Ellis et al., 2007; Robinson et al., 2016).

Reported Barriers

Patients and their parents are often interviewed or asked to complete questionnaires that assess barriers to treatment adherence. Simply forgetting to take medications is one of the most common barriers reported by patients and parents across pediatric chronic disease populations (Celano et al., 1998; Favier et al., 2018; Modi & Quittner, 2006; Ramsey et al., 2018; Shemesh et al., 2004; Shubber et al., 2016; Tucker et al., 2001; Venditti et al., 2018). The child being away from home and changes in the daily routine are also commonly reported as barriers to medical adherence across chronic disease populations.

Disease-Related Correlates

Duration

Diseases of longer duration tend to be associated with lower adherence. Longer disease duration has been associated with poorer adherence over time across childhood chronic disease populations, including asthma (e.g., Arcoleo et al., 2019; Jónasson et al., 2000), cancer (e.g., McGrady & Pai, 2019; Tebbi et al., 1986), celiac disease (e.g., Pedoto et al., 2020; Sbravati et al., 2020), cystic fibrosis (e.g., Hommel et al., 2019; Rouzé et al., 2019), diabetes (e.g., King et al., 2014; Kovacs et al., 1992; Leggett et al., 2019; Niechciał et al., 2020), epilepsy (e.g., Lee et al., 2016; Smith et al., 2018), juvenile arthritis (e.g., Litt & Cuskey, 1981), renal disease (e.g., Brownbridge & Fielding, 1994), and even solid organ transplantation (Dew et al., 2009). While nonadherence can occur early in the course of a medical regimen, adherence deteriorates significantly over time across childhood chronic diseases, with poor adherence being evident in the second year of treatment for many families.

Course

With chronic diseases, symptoms wax and wane over time, and adherence may be particularly difficult to sustain during periods when patients are relatively asymptomatic (Rapoff, 1989). Alternatively, some patients may be nonadherent early in treatment due to denial of their illness but have improved adherence later in treatment (Farinha et al., 2017).

Symptoms/Disease Severity

Increased disease severity, worse medical outcomes, and increased hospitalizations are associated with lower adherence to regimens for asthma (Engelkes et al., 2015), cancer (Gupta & Bhatia, 2017), diabetes (Borus & Laffel, 2010), epilepsy (Al-Aqeel et al., 2020), GI disorders (Myléus et al., 2020), juvenile arthritis (Feldman et al., 2007), HIV (Kahana et al., 2013), renal disease (Brownbridge & Fielding, 1994), and solid organ transplant (Berquist et al., 2008). While increased disease severity is associated with medical nonadherence in cross-sectional studies, greater disease severity at the time of diagnosis does not necessarily predict medical adherence across time (Mitchell et al., 2000; Yang et al., 2018).

Perceived Severity

Here we are speaking of patient or parental perceptions of severity, which appear to be more useful predictors of adherence than those of providers (Rapoff & Barnard, 1991). There is some evidence that parent and patient perceptions are differentially related to adherence. Adolescents with celiac disease who perceived the absence of symptoms after consuming a small amount of gluten reported lower overall adherence to a gluten-free diet (Czaja-Bulsa & Bulsa, 2018). Similarly, adolescents with cystic fibrosis were less adherent during periods of decreased symptoms (Dziuban et al., 2010). Maternal perceptions of higher disease severity have been associated with better adherence to medications for asthma in some studies (Radius et al., 1978), but severity perception was not associated with adherence in other studies (Montella et al., 2016). In contrast, patient perceptions of higher severity have been related to poorer adherence to chest physiotherapy in the treatment of cystic fibrosis (Gudas et al., 1991), medication and exercise adherence in juvenile arthritis (Feldman et al., 2007), and hospital readmission for children with chronic diseases (Amin et al., 2016).

Regimen-Related Correlates

Type and Complexity

Adherence tends to be lower with more complex regimens, such as chest physiotherapy for cystic fibrosis, dietary regimens for diabetes, medications for HIV/AIDS and kidney transplant, and exercise regimens for juvenile idiopathic arthritis (April et al., 2008; Feldman et al., 2007; Glasgow et al., 1986; Hayford & Ross, 1988; Jamieson et al., 2016; Ma et al., 2020; Martin et al., 2007; Rapoff et al., 1985). Lower adherence has been associated with pill versus liquid medications and for three times daily versus two times daily medication regimens for HIV (Haberer & Mellins, 2009; Van Dyke et al., 2002). Adolescents with chronic diseases express irritation at having to monitor their illness and take medications with them outside the home (Hafetz & Miller, 2010; Slack & Brooks, 1995).

Costs

Treatment costs can be prohibitive for some families. At a population level, children and adolescents in the highest poverty quintile are significantly less likely to fill prescriptions than their more affluent counterparts (Hensley et al., 2018). Economically disadvantaged youth with asthma demonstrate high rates of chronic nonadherence (Rohan et al., 2010). Treatment costs are also cited as primary considerations for taking medications in families of children with asthma (Davis et al., 2019) and epilepsy (Hrincu et al., 2021). One study found that lower medication costs were related to higher adherence among children with asthma (Bender et al., 2006). Studies are needed to specifically relate the effect of out-of-pocket expenses on adherence.

Side Effects

Regimens which produce more negative side effects are typically associated with lower adherence. Medication formulation (liquid versus pill), bad taste of medication, and size of medication (i.e., difficulty swallowing a pill) have all been related to lower medication adherence across multiple pediatric chronic diseases, such as asthma, epilepsy, and HIV (Celano et al., 1998; El-Rachidi et al., 2017; Laville et al., 2018; Ramsey et al., 2018; Reddington et al., 2000; Tran et al., 2017; Van Es et al., 1998). Adverse side effects, either experienced or anticipated, have been associated with lower adherence to regimens for asthma (Buston & Wood, 2000; Slack & Brooks, 1995), HIV/AIDS (Kacanek et al., 2019), juvenile idiopathic arthritis (Favier et al., 2018), kidney transplant (Jamieson et al., 2016), and sickle cell disease (Walsh et al., 2014).

Efficacy

Patient and parent perceptions (rather than providers') regarding the efficacy of medical treatments are most relevant to adherence. Higher levels of perceived benefits as rated by patients and parents have been associated with better adherence to regimens for asthma (Davis et al., 2019; Mammen et al., 2021), diabetes (Bond et al., 1992), and juvenile arthritis (Kelly et al., 2018). Conversely, patients report not taking medications for asthma because they believe they are ineffective (Buston & Wood, 2000; van Es et al., 1998). A related issue is the immediacy of benefits, which are often delayed for treatments of chronic diseases and may impact adherence. Minimal research to date has investigated immediacy of treatment benefits regarding long-term treatment adherence.

Clinical Implications Related to Adherence Correlates

While lower socioeconomic status, older patient age, and greater time since diagnosis are not modifiable demographic predictors of medical nonadherence, understanding these risk factors can guide clinical conceptualization and intervention to increase adherence. A clear overarching implication of the literature regarding predictors of nonadherence in childhood chronic disease is that parental involvement and family functioning are critically important. This implies the importance of family-based theories and interventions to improve adherence in childhood chronic disease, which will be further reviewed in Chaps. 7 and 8. Using information gained from review of predictors of nonadherence, we learn that interventions that target lower resourced families, adolescents, and patients who are more than 1 year from the time of diagnosis may be particularly important to increase overall adherence rates in childhood chronic disease populations. Clinicians and researchers may further target key variables within these demographic contexts that strongly impact adherence (e.g., level of parental monitoring of regimen tasks during adolescence). Clinicians should additionally focus efforts on obtaining psychological and behavioral interventions for the subset of patients who have significant emotional and behavioral problems, either comorbid with the child's disease or as a consequence of having to cope with the demands of a chronic disease, as emotional and behavioral problems independently predict worse adherence.

Implications related to medical regimen factors are very straightforward. Providers must be careful not to overburden families by prescribing unnecessarily complex and costly regimens. Families with ill children have a finite amount of time, energy, and resources to devote to medical regimens, and the family goal is always to maintain some semblance of a "normal" family life. Providers can help the problem of balancing the demands of a medical regimen with other family activities by prescribing the fewest number of medications necessary, prescribing generic medications that are less costly, and openly discussing medication schedules and barriers with families.

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Chapter 3
Adherence Theories: Review, Critique, and Clinical Implications

Importance of Theories in Clinical and Research Activities

Clinicians might be tempted to skip over this chapter, in part, because discussions of theories often seem pedantic, argumentative, and devoid of practical applications. So, why should clinicians be concerned about theories which speculate about why children and adolescents do or do not adhere to medical regimens? There are two major reasons why clinicians might consider theories.

First, theorizing is ubiquitous and must serve some useful purpose. As soon as humans become language-able, they begin to ask "why" questions. In a very real way, we are driven to make sense of our world, ourselves, and others around us. All clinicians have at least implicit theories about why people think, feel, and behave as they do. By explicating and critically analyzing their theories, clinicians can clarify how they conceptualize and approach adherence issues. The second reason why clinicians should consider theories is to get them out of their "conceptual ruts" (Wicker, 1985). Examining adherence issues from different perspectives will help clinicians find new ways to assess, analyze, and solve adherence problems.

It is easier to justify why researchers should critically examine theories. Like all scientific theories, those which seek to explain why patients adhere or fail to adhere to medical regimens can impact researchers in at least two ways (Johnston & Pennypacker, 1993; O'Donohue & Krasner, 1995). First, theories influence decisions made in planning and conducting studies including the experimental questions, measures, designs, and data analytic procedures. During a lecture to a group of physics students in Vienna, the philosopher Karl Popper gave them the following instructions: "Take pencil and paper; carefully observe and write down what you have observed." Naturally the students asked what he wanted them to observe, thus making his point that theories precede observations (Popper, 1963, p. 46). Second, theories affect the way investigators react to their data in terms of interpreting and relating their results to other studies, including the body of literature they chose to

M. A. Rapoff et al., *Adherence to Pediatric Medical Regimens*, Issues in Clinical Child Psychology, https://doi.org/10.1007/978-3-031-27484-8_3

relate their findings. Finally, in a practical vein, funding agencies require that investigators present an explicit theoretical framework for their research proposals.

Although not technically a theory, Modi and colleagues have proposed an ecologically based self-management framework for research, practice, and policy (Avani et al., 2012). They make the distinction between self-management ("the interaction of health behaviors and related processes that patients and families engage in to care for a chronic condition") and adherence ("the extent to which a person's behavior coincides with medical or health advice"). They identify nonmodifiable (e.g., age) and modifiable (e.g., coping style) influences that operate in the individual, family, community, and healthcare system domains. These influences or factors are empirically derived from correlational and intervention studies on adherence and self-management. This is a useful framework for clinicians, researchers, and policy makers and can serve as a theoretical framework for grant applications for randomized clinical trials of adherence interventions.

The Health Belief Model

Description

The health belief model (HBM) has been one of the most widely used theories in health behavior research over the past five decades (Clark & Houle, 2009; Strecher & Rosenstock, 1997). Originally developed in the early 1950s to understand why people failed to take advantage of preventive health services (such as hypertension screening), the HBM was later extended to adherence to prescribed medical regimens (Janz & Becker, 1984; Rosenstock, 1974).

The HBM posits five major sets of variables that predict or explain adherence:

1. *Perceived susceptibility* (including the person's perceived risk of contracting or recontracting a condition or acceptance of an existing condition)
2. *Perceived severity* (the person's evaluation of the medical and social consequences of contracting an illness or not receiving treatment)
3. *Perceived benefits* (the person's judgment of the perceived benefits of taking a particular health action)
4. *Perceived barriers* (the person's perception of impediments to adhere to recommended treatments, including a cost-benefit analysis where the person weighs the pros and cons of taking action)
5. *Cues to action* (internal cues, such as disease symptoms, or external cues, such as prompting by others, which trigger action)

In addition, more recent formulations of the HBM have included Bandura's concept of self-efficacy (Clark & Houle, 2009; Strecher & Rosenstock, 1997).

The HBM has been adapted for use with pediatric populations. The Children's health belief model (CHBM) is schematically represented in Fig. 3.1 (Bush &

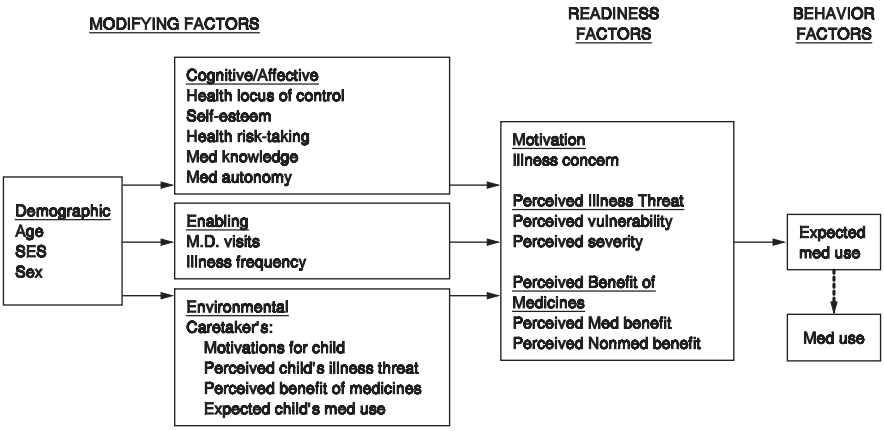

Fig. 3.1 The children's health belief model. (Adapted with permission from Bush and Iannotti (1990)

Iannotti, 1990). As can be seen, the CHBM includes similar dimensions as the classic HBM (e.g., perceived severity) but also emphasizes the role of caretaker influences on children's health beliefs and actions (e.g., caretaker's perceived benefit of the child taking medicines).

Critical Appraisal

Two comprehensive reviews found "substantial empirical support" for the HBM and concluded that perceived barriers were the most "powerful" predictor of a wide range of health practices (Becker, 1974; Janz & Becker, 1984). There is also correlational support for components of the HBM in the pediatric medical adherence literature. Higher susceptibility/vulnerability and severity, as rated by mothers, has been associated with better adherence to medications for asthma (Radius et al., 1978) and, as rated by patients, to better adherence to medications for cancer (Tamaroff et al., 1992). In contrast, higher perceived threat, or severity, as rated by adolescents, has been associated with lower adherence to regimens for diabetes and cystic fibrosis (Bond et al., 1992; Gudas et al., 1991).

Higher levels of perceived benefits, as assessed by mothers, have been associated with better adherence to asthma medications (Radius et al., 1978) and, as assessed by patients, with diabetes regimens (Bobrow et al., 1985; Bond et al., 1992; McCaul et al., 1987). Consistent with general reviews of the HBM, higher perceived barriers as rated by parents, children, and/or adolescents have been uniformly related to poorer adherence to regimens for asthma, HIV, cystic fibrosis, diabetes, and solid organ transplantations (Bender, 2002; Buchanan et al., 2012; Cushman et al., 2020; Glasgow et al., 1986; Marhefka et al., 2004; McCaul et al., 1987; Modi & Quittner, 2006; Radius et al., 1978; Zelikovsky et al., 2008). The presence of relevant cues to

action, as assessed by adolescents, has also been associated with better adherence to diabetes regimens (Bond et al., 1992).

Only one analog study has been conducted with the CHBM (Bush & Iannotti, 1990). This study found that 63% of the variance in children's expected medication use was predicted by the CHBM, with two readiness factors (perceived severity and benefit) accounting for most of the variance. However, this study is limited by its analog nature and failure to measure actual medication use. One study involving primarily African American youth with diabetes failed to find support for HBM factors in predicting adherence, suggesting that the HBM may not be as relevant for minority populations (Patino et al., 2005).

Despite its track record in the literature, primarily with adults, the HBM can be criticized on the following conceptual and methodological grounds:

1. There are variations in the way HBM constructs have been conceptualized and measured. This has resulted in lack of standardization of measures and variable performance of these constructs as predictors of adherence (Janz & Becker, 1984; Strecher & Rosenstock, 1997) despite efforts in the early 1980s to standardize and develop measures of HBM constructs (Champion, 1984). One measure (*The Diabetes Health Beliefs Questionnaire*) was adapted from the HBM to measure HBM constructs with adolescents who have diabetes and internal reliabilities were sufficient except for the cues to action subscale (Brownlee-Duffeck et al., 1987). Another measure (*The Health Belief Model Scale-Revised*) was modified to measure HBM constructs with children and adolescents with cystic fibrosis, and this measure supported the relationship between HBM constructs and adherence, particularly the constructs of barriers and cues to action (Dempster et al., 2018).
2. Perceptions of health risks (such as perceived vulnerability and severity in the HBM) are subject to an "optimistic bias," or the well-known tendency for people to underestimate their own health risks compared to others (Stroebe & Stroebe, 1995). This may be particularly true of adolescents who tend to view themselves as relatively invulnerable to health risks and behave accordingly by driving too fast, not wearing seat belts, having unprotected sex, and smoking (Coleman & Hendry, 1990; Millstein et al., 1993).
3. The HBM is limited to accounting for variance in adherence-related behaviors that can be predicted by attitudes and beliefs. Social psychologists have oft cited the tenuous relationship between attitudes and behavior (Stroebe & Stroebe, 1995). Supporters of the HBM acknowledge that changes in health-related behaviors are rarely achieved by direct attempts to change health-related attitudes (Strecher & Rosenstock, 1997). Other influences on adherence need to be considered such as social contingencies, physiologic factors, and perceptions of self-efficacy (Guerin, 1994; Janz & Becker, 1984).
4. The HBM fails to suggest specific strategies for altering relevant health beliefs. Therefore, there is a dearth of studies designed to experimentally manipulate HBM-related factors to improve adherence (Janz & Becker, 1984). Supporters of the HBM have called for such studies rather than replications of previously con-

firmed correlational findings (Strecher & Rosenstock, 1997). One promising area in pediatrics is to identify barriers to adherence, which could then presumable be used to tailor interventions to specific barriers for different regimen tasks. Such measures of barriers have been developed for youth with asthma, cystic fibrosis, diabetes, and sickle cell disease and for transplant recipients (Bursch et al., 1999; Glasgow et al., 1986; Logan et al., 2003; Modi & Quittner, 2006; Simons & Blount, 2007).

Clinical Implications of the HBM

Consider the example of an 8-year-old boy who has moderately persistent asthma that requires daily inhaled anti-inflammatory medication and an inhaled bronchodilator medication as needed. The boy has also been asked to monitor his peak flow levels once per day and after he takes his bronchodilator medication. His parents have been asked not to smoke in the house and to take steps to minimize his exposure to other allergens in the home, such as dust and pet dander. Applying the HBM to this clinical example would suggest the following strategies for assessing and modifying factors related to adherence:

- *Perceived Susceptibility and Severity*: The clinician could assess whether the patient and his parents have accepted his condition and have a realistic view of the severity of his asthma. If they have an unrealistic view of severity, the clinician could review peak flow records and encourage the patient and parents to monitor his symptoms more closely to gain a more realistic perspective about severity. Information about severity should be balanced with positive information and encouragement that conveys a sense of optimism about the patient's and parents' ability to control his disease with increased monitoring and better adherence to prescribed regimens.
- *Perceived Benefits*: The clinician could assess how confident the patient and parents are that the prescribed regimen is beneficial, especially in terms of quality-of-life benefits. If confidence is low, the clinician could review potential benefits of the prescribed regimen, such as increased participation in social and recreational activities. Clinicians should be alert to the possibility that prescribed treatments may not be beneficial for particular patients, in spite of optimal adherence. In these instances, the patient and parents should be encouraged to communicate this information to the physician and ask for modifications/additions to increase regimen efficacy.
- *Perceived Barriers*: The clinician could interview the patient and parents to identify logistic barriers that prevent them from fully adhering to the regimen. For example, taking inhaled bronchodilator medications "as needed" requires the patient or parents to make judgments about "need." They may need assistance in how to monitor symptoms and decide when bronchodilator medications are required. They may need to be instructed to monitor peak flow rates following

vigorous exercise and to administer bronchodilator medications if peak flows drop significantly below the patient's baseline levels (National Asthma Education and Prevention Program, 1997 for such guidelines). The parents may also perceive multiple barriers to reducing their son's exposure to indoor allergens, such as finding the time to remove dust and pet dander on a regular basis and going outside to smoke during the winter. A good general question to ask of patients and parents would be: "What gets in the way or prevents you from doing…?" The answer to this question should lead to practical recommendations from clinicians (e.g., smoke in the garage during the winter). The clinician can also use validated and reliable measures of barriers to adherence in asthma treatments to target specific barriers identified by patients and parents; the Illness Management Survey (Logan et al., 2003; Rhee et al., 2009), an adolescent self-report questionnaire, and the Barriers to Adherence Interview-Asthma (Modi & Quittner, 2006), which may be conducted with patients or their parents.

- *Cues to Action*: The clinician could assess for the presence of reliable internal and external cues to prompt adherence. If the patient is relatively asymptomatic, there may not be consistent internal cues (such as dyspnea) to prompt adherence behaviors. Therefore, external prompts may be required, such as having the patient set his watch alarm for times when medications are to be taken or encouraging the parents to monitor and prompt adherence behaviors.

Social Cognitive Theory (Self-Efficacy)

Description

Social cognitive theory (SCT) is a comprehensive theory of human behavior originally proposed and promoted by Albert Bandura (Bandura, 1986, 1997). SCT proposes a *triadic reciprocal causation* model that focuses on the interdependence and reciprocal interactions among three major determinants of human agency: behavior, internal personal factors (cognitive, affective, and biological events), and the external environment. The central mechanism of human agency (and the one most relevant to medical adherence) is beliefs of personal efficacy or *perceived self-efficacy*.

Perceived self-efficacy refers to "*...beliefs in one's capabilities to organize and execute the courses of action required to produce given attainments*" (Bandura, 1997, p. 3). Competent functioning (such as adhering to complex medical regimens) requires both skills and self-beliefs of efficacy to use skills effectively. Children and adolescents who have the necessary skills to perform adherence tasks and have a strong belief in their capabilities to perform are more likely to:

1. Approach difficult regimen tasks as "challenges" to be mastered rather than "threats."

2. Set challenging health-enhancing goals for themselves and remain strongly committed to these goals.
3. Increase and sustain efforts to achieve their goals even when they are faced with failure.
4. Quickly recover from failures or setbacks to achieve their goals, in part, by attributing these setbacks to knowledge or skill deficiencies which are remediable.
5. Realize personal accomplishments, reduce stress, and lower their vulnerability to negative affective states, such as depression (Bandura, 1996).

Two major pathways for self-efficacy influences on health have been proposed (O'Leary, 1992). One pathway involves its direct effect on adoption of health practices and adherence to medical regimens. Those high in self-efficacy are more likely to adhere to medical regimens and thereby improve or maintain their health. The other pathway concerns its effect on physiological stress responses. Those high in self-efficacy may experience less stress and negative emotional states which can exacerbate chronic diseases, such as asthma, arthritis, and diabetes in children and adolescents.

Self-efficacy is thought to be influenced by five major sources (DeVellis & DeVellis, 2001): (1) enactive mastery or learning through experience; (2) vicarious experience or observing competent models; (3) verbal persuasion; (4) physiological states (e.g., viewing physiological arousal as positive energy); and (5) affective states (e.g., positive mood states contribute to a heightened sense of self-efficacy).

SCT also emphasizes the role of *outcome expectancies* or judgments of the likely consequences of one's actions (Bandura, 1997). Self-efficacy judgments (whether one can produce certain actions) are distinguished from outcome expectations (the anticipated consequences of producing actions), but perceived self-efficacy is the more powerful determinant of behavior (Bandura, 1986). Figure 3.2 is a schematic representation of self-efficacy theory.

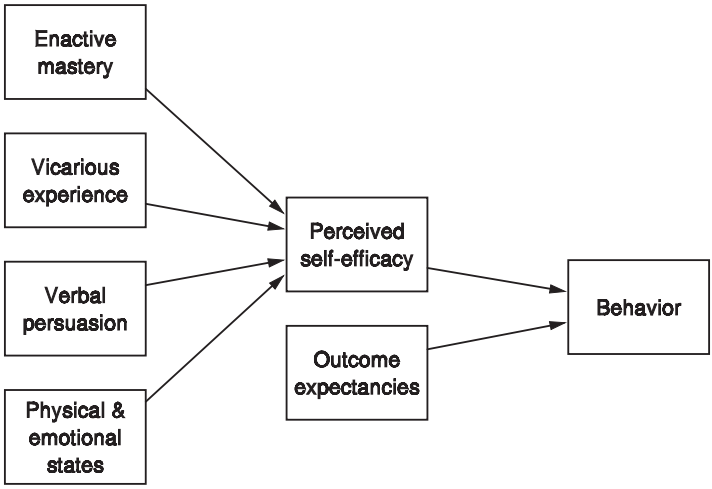

Fig. 3.2 Self-efficacy theory

Critical Appraisal

SCT and its central construct of self-efficacy have been a robust predictor of human functioning in such diverse areas as cognitive, affective, social, and organizational domains (Bandura, 1997). Self-efficacy has also been an important predictor of a variety of health-related behaviors in adults, including breast cancer screening, smoking, physical exercise, weight control, pain management, and risky sexual behaviors (Bandura, 1997; O'Leary, 1985, 1992; Schwarzer & Fuchs, 1995; Strecher et al., 1986). Also, the success of self-efficacy as a predictor of health-related behaviors is evident from its more recent inclusion in well-established theories such as the HBM. Although much of this work has been done with adults, there have been some attempts to develop and validate illness-specific self-efficacy scales for children and adolescents with asthma (Schlösser & Havermans, 1992) and diabetes (Grossman et al., 1987). Also, one study found that higher outcome expectancies and self-efficacy among children with asthma predicted greater adherence to inhaled steroid medications (Branstetter-Rost et al., 2010). Another study found that higher self-efficacy as rated by adolescents with asthma predicted lower barrier perceptions, higher outcome expectations, better asthma control, and higher medication adherence (Rhee et al., 2018).

Even the most vocal critics of self-efficacy theory acknowledge that it is an influential and useful theory in psychology (Catania, 1995; Hawkins, 1995). However, self-efficacy theory can be criticized on the following conceptual and methodological grounds:

1. Self-efficacy is not a cause but a reflection of behavior change. It represents an index of the positive and negative outcomes of past performances, a sort of "running average" (Hawkins, 1992). Bandura (1995) counters by citing numerous studies that show self-efficacy retains its predictive power even after controlling for past performance.
2. Self-efficacy theory is also said to minimize environmental influences, including response contingencies and verbally controlled (rule-governed) behavior (Catania, 1995; Hawkins, 1992; Hayes & Wilson, 1995). Bandura has noted that "incentive inducements" or reinforcement contingencies are not sufficient causal agents, particularly as humans gain facility with language and self-referent thought assumes a more critical mediational role in person-environment interactions (Bandura, 1996, 1997).
3. A related criticism is that there is no evidence that self-efficacy (or any other) beliefs have been directly changed. The so-called evidence rests on the direct manipulation of some environmental event; no one "randomly assigns" research participants to different levels of self-efficacy (Hayes & Wilson, 1995).
4. Conceptual confusion has led to variability in how self-efficacy has been operationalized and measured (Corcoran, 1995). Bandura (1996, 1997) acknowledges this criticism and notes that the predictive utility of self-efficacy is attenuated by excessively long intervals between self-efficacy and performance assessments (as self-efficacy may have changed in the interim); the limited scope of

self-efficacy assessments (e.g., measuring efficacy beliefs related to dieting but not exercising when predicting weight loss); global versus domain-specific assessments of efficacy; and errors in measuring criterion performance variables.

Clinical Implications of SCT (Self-Efficacy)

Consider the example of a 7-year-old female with cystic fibrosis (CF). Her complex and time-consuming medical regimen included the following components: oral pancreatic enzyme replacement to be taken with each meal and snack; increased caloric intake (especially high-protein and high-calorie foods); an inhaled bronchodilator and antibiotic to be taken three times per day; chest physiotherapy three times per day; and DNase (to break up mucus in the lungs) delivered via a nebulizer once a day. This girl also had to take inhaled or oral corticosteroids and intravenous antibiotics, with exacerbations in her disease. She lives in a two-parent family with both parents working outside the home. The patient also has a 6-month-old sister (who does not have CF).

Applying SCT to this clinical example would suggest the following assessment and intervention strategies:

- Although SCT primarily focuses on self-efficacy, it also emphasizes the importance of prerequisite skills for carrying out tasks. The clinician could directly observe how well the patient and parents execute regimen tasks (such as proper technique for using a metered-dose inhaler to deliver bronchodilator and antibiotic medications) and give corrective feedback, training, and practice as needed. This will ensure that the patient and parents know how to carry out regimen components.
- Self-efficacy is the most important and relevant component of SCT. Therefore, the clinician would want to assess self-efficacy perceptions of the patient and the parents. For example, the clinician could ask the parents: "How confident are you in being able to be help your daughter be consistent in taking medications, doing chest physiotherapy, and following dietary recommendations related to CF treatment?" Parents could respond using a five-point scale, ranging from "not at all sure" to "very sure" (Parcel et al., 1994). If parents (or the patient) are not very confident about managing regimen tasks, efforts can be made to enhance self-efficacy through three major processes: enactive mastery, vicarious experiences, and verbal persuasion (Bandura, 1997).
- Enactive mastery is the most powerful source of self-efficacy and refers to taking steps to ensure that the patient and parents are successful in managing the CF regimen and that they attribute their successes to their efforts. The clinician could provide parents and the patient with social reinforcement for managing regimen tasks and emphasize the importance of their efforts in achieving hard-won successes. Because of the inherent aversiveness of some regimen tasks (such as chest physiotherapy), the patient may need more tangible positive consequences for adherence, such as tokens which can be exchanged for special privileges.

- Vicarious experiences can be promoted by having the patient and parents observe or visualize competent models. For example, the patient and parents could be paired up with other patients and their parents who have encountered and mastered similar problems with regimen tasks.
- Verbal persuasion is the route that most clinicians take to enhance self-efficacy and is most effective if the persuader is viewed as trustworthy and competent. This essentially involves "pep talks" or trying to persuade the patient and parents that they can do what they need to do. However, clinicians should be careful to avoid overemphasizing this approach and to help the patient and parents experience successes in managing the regimen. Otherwise, parents and patients may discount any attempts to boost self-efficacy just by verbal persuasion.
- Clinicians would also need to assess outcome expectancies, particularly patient and parental perceptions of the likelihood that their efforts to manage CF would reap positive benefits. If expectations of beneficial outcomes are low, the clinician may need to emphasize the purpose and potential benefits of prescribed regimens. Also, physicians and nurses can provide disease outcome data (such as pulmonary function test results) or have the patient and parents monitor disease symptoms to demonstrate the benefits of prescribed regimens. In some cases, low outcome expectancies are accurate (patients are not benefiting from treatment), and clinicians can refer patients and parents to their medical providers for reassessment of their condition and changes in their regimen.

The Theory of Reasoned Action/Planned Behavior

Description

The theory of reasoned action/planned behavior (TRA/PB) is an extension of the theory of reasoned action (TRA) and incorporates predictors from the TRA (Montaño et al., 1997). The TRA was originally introduced in 1967 to help understand why attitudinal measures often were poor predictors of behavior and to improve the predictive utility of attitudinal measures (Ajzen & Fishbein, 1977; Fishbein, 1967). The TRA proposed that attitudinal measures were more likely to predict behavioral outcomes when measures of both contain four elements: (1) the *action* or behavior to be performed; (2) the *target* at which the action is directed; (3) the *context* or situation; and (4) the *time* frame. Thus, attitude-behavior consistency is more likely if measures of attitudes and behaviors "match" in terms of the level of specificity across these four elements. The TRA also proposed that the most proximal determinant of behavior is "intention," or the perceived likelihood of the person performing the behavior. Behavioral intentions are, in turn, influenced by several factors (see Fig. 3.3).

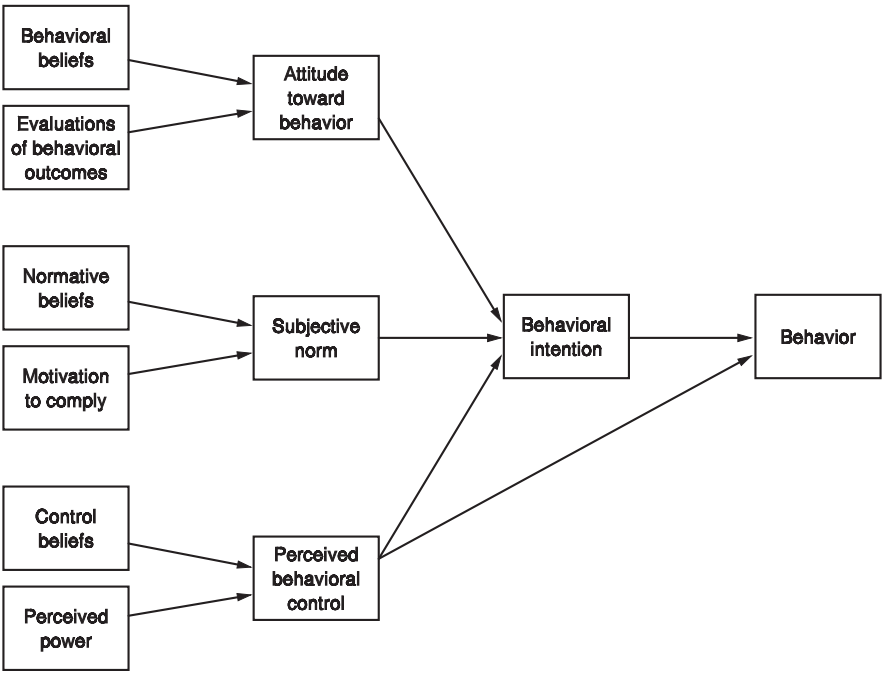

Fig. 3.3 The theory of reasoned action/planned behavior

Intentions are determined by three major factors:

1. *Attitude toward the behavior* (incorporating specific opinions about the behavior and the potential consequences of performing that behavior).
2. *Subjective norms* (whether important people in the person's life approve or disapprove of the action and whether the person is motivated to meet their expectations).
3. *Perceived behavioral control* (whether the person believes they can perform the behavior and the expected outcome of performing). The construct of perceived behavioral control was the major variable added to the TRA to form the TRA/PB (Ajzen, 1991). Perceived behavioral control can influence behavior directly or indirectly through its effect on intentions (see Fig. 3.3).

Critical Appraisal

The TRA/PB has been applied to the prediction of a variety of behaviors, from academic performance to shoplifting (Clark & Houle, 2009; Stroebe & Stroebe, 1995). These studies tend to provide correlational support for the major components of the theory (Ajzen, 1991). The relatively few studies that have used the TRA/PB to predict health-related behaviors have focused on adults and specific areas such as exercise and mammography screening (Montaño et al., 1997). One study with secondary

education students in Holland found that attitudes toward condom use, perceived norms, and perceived control were predictive of intentions to use condoms, while AIDS-related knowledge was not predictive (cited in Stroebe & Stroebe, 1995).

Despite its promise, the TRA/PB can be criticized on several points:

1. Although verbal "intentions" may be useful (particularly when it is hard to measure behavior directly), they are not foolproof (Guerin, 1994). After all, the "road to perdition" is paved by well-meaning intentions. This criticism is particularly relevant when more direct measures of behavior are available and measures of intention are used in place of these direct measures (e.g., asking adolescents with IDDM about their intentions to test blood glucose levels rather than relying on glucometers that record and store blood glucose testing results).
2. The degree of specificity of attitudinal and behavioral measures need to match or be contextually relevant. Mismatches have resulted in low correspondence between attitudinal and behavioral measures.
3. The construct "perceived behavioral control" appears to be conceptually like Bandura's construct of self-efficacy (Montaño et al., 1997). This apparent redundancy needs to be evaluated, both conceptually and empirically.
4. Like all "attitudinal" theories, the burden is on proponents of the TRA/PB to show that experimental manipulations designed to change attitudinal variables result in behavior change.

However, a meta-analysis of 47 experimental studies of intention-behavior relations (most of which targeted a change in a health-related behavior, such as using sunscreen) did find that a medium-to-large change in intention ($d = 0.66$) led to a small-to-medium change in behavior ($d = 0.36$). The authors concluded that intentions do have a significant impact on behavior but less so than what correlational studies have suggested (Webb & Sheeran, 2006).

Clinical Implications of the TRA/PB

Consider the example of a 15-year-old female with systemic lupus erythematosus (SLE), which is a rheumatic disease that effects multiple organ systems, most notably the musculoskeletal system. The patient's oral medication regimen includes a once-daily antimalarial drug (plaquenil) and a corticosteroid (prednisone) every other day. She also must avoid exposure to sunlight. The patient lives with her mother and stepfather. The patient and her mother have frequent conflicts which often results in the patient staying over at her friends' house, sometimes during the week and almost exclusively on the weekends.

Applying the TRA/PB to this clinical example might suggest the following strategies:

- Given the centrality of intentions as the most immediate determinant of behavior, the clinician could assess the patient's intentions relevant to her medication regimens.

For example, the patient could be asked: "How likely are you to consistently take your medications?" and provided with a three-point response format ("very likely, somewhat likely or not likely"). The clinician could further ask about intentions to adhere to medications at home or when she stays at her friend's home.

- The clinician could also ask about the patient's attitude toward taking the prescribed medications, how significant others (such as friends and parents) react to her regimen (whether they approve or disapprove), whether she believes she can carry out the regimen, and what she expects to gain by adhering to the regimen.
- If the clinician determines that the patient has weak intentions to adhere to the regimen because significant others provide little support and the patient is doubtful about her ability to be consistent and/or effectively control her disease, then several remedial steps can be taken. Perhaps the mother and stepfather could provide increased monitoring and support for the patient. In this example, family therapy would be needed to address ongoing conflicts so that the mother and stepfather could function as agents of support, and the patient could be more motivated to meet their expectations.
- In addition (or as an alternative), the patient's friend and her parents could be enlisted as sources of support, since the patient spends many hours at her friend's house.
- To address the issue of low perceived behavioral control, the clinician could ask the patient's physician to provide further information about the purpose and benefits of therapy and disease outcome data that supports the efficacy of the prescribed regimen for this patient. The patient can also monitor disease symptoms and demonstrate to herself that better disease control occurs when she is more consistent in following her regimen.

Transtheoretical Model

Description

The transtheoretical model of change (TTM) was originally applied to systems of psychotherapy (Prochaska, 1979) and then extended to smoking and other additive behaviors (DiClemente & Prochaska, 1982; Prochaska & DiClemente, 1983; Prochaska et al., 1992, 2009). The TTM has also been recently applied to other health-related behaviors such as exercise, dieting, mammography screening, and diabetes care behaviors (Ruggiero, 2000). The TTM focuses on intentional change and has two major dimensions. The first dimension, *stages of change*, specifies "when" shifts occur in attitudinal and behavioral change. In the process of changing a particular health-related behavior (such as quitting smoking), people are said to progress through a series of five stages (Prochaska et al., 1997, 2009):

1. *Precontemplation* (the person has no intention to change in the foreseeable future, usually within the next 6 months)
2. *Contemplation* (the person intends to change within the next 6 months);
3. *Preparation* (the person intends to change in the immediate future, usually within the next month)
4. *Action* (the person has been making overt changes in their lifestyle in the past 6 months)
5. *Maintenance* (the person is working to sustain changes and avoid relapse) Progression through these stages may not be linear. People may relapse and recycle through previous stages, particularly with addictive behaviors.

The second major dimension of the TTM is *processes of change* which is concerned with "how" people change. They include overt and covert activities people employ to progress through stages of change (Prochaska et al., 1997). These are empirically supported processes derived from various theoretical perspectives in psychotherapy (thus the term "transtheoretical"). People are said to use different processes at different stages of change. Therefore, interventions designed to help people change should "match" particularly processes to particularly stages of change (see Table 3.1).

Two additional constructs have been added to the TTM (Prochaska et al., 1997). Like the HBM and TRA/PB, one construct is *decisional balance*, which refers to a person's relative weighing of the pros and cons of changing. The other construct is *self-efficacy*, adapted from Bandura's self-efficacy theory, but reflecting two components: (1) the degree of confidence people have to cope with high-risk situations without relapsing to unhealthy habits and (2) temptation or the intensity of the person's urges to engage in an unhealthy habit (e.g., the degree of self-efficacy a teenager has to avoid smoking during a social event with friends who smoke).

Critical Appraisal

The TTM has been applied to a wide range of health-related behaviors with adults, including smoking, weight control, condom use, exercising, and mammography screening (Prochaska et al., 1994, 2009). In general, there has been good empirical support for the major constructs of the TTM (Prochaska et al., 1997). Processes of change seem to be employed at different stages of change (e.g., more action-oriented strategies such as reinforcement management employed during action and maintenance stages), consistent with the depiction in Table 3.1. Also, people in the action versus the contemplation stage tend to discount the costs or cons of changing (Prochaska et al., 1994). The construct of self-efficacy is a recent and untested addition to the TTM. Given its similarity to Bandura's conceptualization of self-efficacy, it should be a similarly robust predictor of health-related behaviors.

Table 3.1 Transtheoretical model

Stages of change in which particular processes of change are emphasized				
Precontemplation	Contemplation	Preparation	Action	Maintenance
Consciousness raising (increasing information about self & problem)				
Dramatic relief (experiencing & expressing feelings about one's problems & solutions)				
Environmental reevaluation (assessing how one's problem effects physical environment)				
	Self-reevaluation (assessing how one feels & thinks about oneself with respect to a problem)			
		Self-liberation (choice & commitment to act or belief in ability to change)		
			Reinforcement management (rewarding oneself or being rewarded by others for making changes)	
			Helping relationships (being open & trusting about problems with someone who cares)	
			Counterconditioning (substituting alternatives for problem behaviors)	
			Stimulus control (avoiding or countering stimuli that elicit problem behaviors)	

Note. From "In search of how people change: Applications to addictive behaviors", by Prochaska et al. (1992, pp. 1108–1109). Copyright 1992 by the American Psychological Association. Adapted with permission

Despite being one of the most popular theories in health psychology, the following conceptual and methodological criticisms can be raised about the TTM (Bandura, 1997):

1. The "stage" aspect of the TTM has been questioned on grounds that human functioning is too complex to be categorized into specific stages. Also, the TTM stages of change violates the three defining properties of a stage theory: qualitative changes across stages (such as Piaget's theory, where preoperational thinking changes qualitatively to operational thinking); an invariant sequence of change (one does not skip stages); and nonreversibility (one does not recycle through stages; e.g., an operational thinker does not recycle back to preoperational thinking, unless a catastrophic event occurs, such as brain damage).
2. It is not clear that change processes are sequenced in the same way across stages for all health-related behaviors. With smoking, people may use cognitive strategies before deciding to quit and behavioral strategies during abstinence. However, for exercise and dietary changes, cognitive and behavioral strategies may increase in tandem across stages (Rosen, 2000).
3. The TTM stages of change are circular in that the stages are defined in terms of the very behavior to be explained. In studies using the TTM, people are categorized into stages based on their self-reports of health-related behaviors, such as smoking and exercising. For example, people might be asked to report how many days per week, how many minutes per session, and how intensely they engage in exercises and whether they intend to increase their exercise activity within the next month (Myers & Roth, 1997). They are then categorized into stages (e.g., in the "precontemplation" stage if they do not exercise and do not plan to in the next month) based on their self-reports of whether they exercise or intend to exercise. This is circular and the correlations between stages and behavior patterns would be spurious.
4. The specific temporal dimension of stages in the TTM appears to be arbitrary and contrived. In studies on addictive behaviors, people have been classified as being in various stages depending on their reported behavior patterns over a 6-month interval or with exercising, over a 1-month interval (Myers & Roth, 1997). The point here is that one could segment the "stream of behavior" anywhere in time. Also, 6-month or 1-month time frames seem ill-conceived when applied to chronic disease regimens. It is difficult to imagine a child recently diagnosed with type 1 diabetes and her parents "precontemplating" for 6 months about whether insulin should be given to treat hyperglycemia.
5. It remains to be seen whether the TTM is applicable to people with chronic health problems, particularly pediatric populations. TTM developers admit that empirical support for the model comes from studies with convenience or volunteer samples and focus on single, rather than multiple, health-related behaviors (Ruggiero & Prochaska, 1993). Also, the stages and processes which apply to decreasing or eliminating damaging health-related behaviors (such as smoking) are likely to be quite different than those relevant to increasing healthy behaviors (such as exercising).
6. Although a potential strength of the TTM is the matching of specific behavior change strategies to specific stages of change, there is limited support for the superiority of matched versus standard or "mismatched" interventions. Also,

there is the potential for contradictory recommendations derived from a "transtheoretical" approach that draws from behavioral, psychodynamic, and existential perspectives (Bandura, 1997).

Clinical Implications of the TTM

Consider the example of a 16-year-old male with type 1 diabetes. His daily regimen is typical of patients with this disease and consists of insulin injections three times per day, blood glucose testing four times per day, following a meal plan which avoids concentrated sweets, and exercising (while balancing diet and insulin requirements). The patient is active in sports and other extracurricular activities at school and has an active social life. The patient has been diagnosed with diabetes since he was 8 years of age and until recently his disease has been under good control. In the past year, however, control of his disease has been in the "fair to poor" range.

Applying the TTM to this example might suggest the following clinical strategies (Ruggiero & Prochaska, 1993):

- To "stage" this patient, the clinician could ask the following questions: "Do you always time your insulin injections, check your blood glucose, follow your special diet, or balance exercising with diet and insulin requirements as you were instructed to do?" The patient would then be classified in one of the TTM stages depending on his choice of one of the following response options for each regimen task: "No, and I don't intend to in the next 6 months" (precontemplation); "No, but I plan to in the next 6 months" (contemplation); "No, but I plan to in the next month" (preparation); "Yes, but for less than 6 months" (action); or "Yes, for more than the past 6 months" (maintenance). Once the patient has been "staged," behavior change strategies suited to his current stage could then be implemented.
- If the patient is in the precontemplation or contemplation stage, the clinician might provide more personalized education, opportunities for emotional expression, and supportive networks. This would allow him to increase his awareness and acceptance of diabetes and increase confidence in his ability to carry out the regimen.
- If the patient is in the preparation stage, the clinician might assist him in setting specific and achievable goals (e.g., testing his blood glucose at least before each meal) and reinforcing any progress (however small) toward meeting these goals. This is a shaping process, and the clinician may have to settle for less-than-optimal performance as long as the patient progresses toward achieving his goals.
- If the patient is in the action stage, the clinician might provide behavioral skills training and self-management strategies, such as self-monitoring and self-reinforcement. Because the patient is trying to establish a new behavioral pattern, he would also require frequent positive reinforcement and social support.

- If the patient is in the maintenance stage, the clinician might help him anticipate and strategize about how to manage obstacles to maintaining adherence. For example, if he goes out to eat with friends, how can he handle social pressures to eat forbidden foods that his friends are eating? Also, the clinician can help the patient cope with lapses in management by putting these into perspective (e.g., "just because I ate the wrong foods today, doesn't mean I have to in the future") and problem-solving about ways to cope with future temptations (e.g., "what can I do if I am out with my friends, and they are eating what I am not supposed to eat?").

Applied Behavior Analytic Theory

Description

Applied behavior analytic (ABA) theory has its historical roots in the foundational work on operant conditioning by B.F. Skinner and has been explicitly related to understanding and modifying adherence to medical regimens (Rapoff, 1996; Zifferblatt, 1975). The ABA model emphasizes two general processes whereby human behavior is shaped: *contingency-shaped* and *rule-governed* behavior (Hayes, 1989; Skinner, 1974).

Contingency-shaped behavior refers to behavior directly shaped by environmental contingencies, and its basic form is schematically represented by the *three-term contingency*:

$$S^D \rightarrow R \rightarrow S$$

For example, a discriminative stimulus (pain) sets the occasion for or prompts a response (taking pain medications) and the probability of that response is altered by a consequent stimulus (pain relief).

Four basic operant processes can be distinguished based on whether a consequence is added or subtracted contingent on a behavior and the resulting effect on behavior in terms of increasing or decreasing the probability of that behavior in the future (see Fig. 3.4). *Positive reinforcement* occurs when a response-contingent consequence increases a behavior (e.g., symptom relief increases the probability the person will take prescribed medications). In contrast, *positive punishment* occurs when a response-contingent consequence decreases a behavior (e.g., taking prescribed medications results in negative side effects, thereby "punishing" medication taking). *Negative reinforcement* occurs when response-contingent removal of a consequence increases a behavior (e.g., taking antacids terminates or allows one to avoid gastrointestinal irritation caused by some medications). *Negative punishment* (or extinction) occurs when response-contingent removal of a consequence decreases a behavior (e.g., a child does not comply with a parental request to take medications and loses privileges).

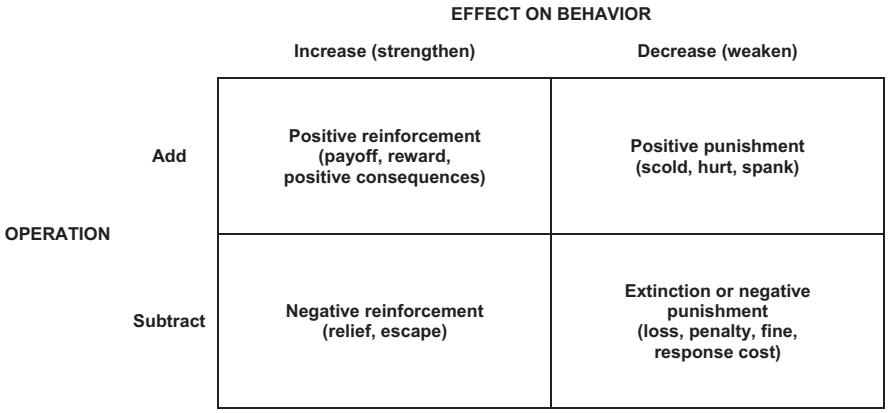

Fig. 3.4 Operant theory

Behavior analysts are also giving increased attention to the unique role of verbal antecedents in the control of human behavior, so-called rule-governed behavior (Hayes, 1989). Rules are ubiquitous and can take many forms, such as instructions, laws, maxims, proverbs, advice, grammar, and scientific propositions (Riegler & Baer, 1989). They are valuable because people can learn them more quickly without having directly experienced (or without ever experiencing) the consequences implied or specified by the rule (Skinner, 1974; Riegler & Baer, 1989). Parents count on rules, such as "look both ways before crossing the street," to keep their children out of harms' way.

Whether rules are followed or not depends on the following factors (Hayes, 1989; Riegler & Baer, 1989): (1) a generalized history of reinforcement for following rules (or punishment for failing to follow rules); (2) immediate local consequences for following rules (often in the form of social approval or disapproval); (3) contact with the contingencies described in a rule (e.g., taking medications and experiencing symptom relief); and (4) automatic or self-given consequences (e.g., positive or negative feelings and thoughts).

There are, however, problems and limitations of rule-governed behavior. Children may not be able to follow rules because they lack the prerequisite skills (Poppen, 1989). Also, following rules may result in negative consequences, such as taking medications and experiencing aversive side effects. Children may also fail to generate rules when it is advantageous to do so or they may form inaccurate or unrealistic rules (Hayes et al., 1989). For example, a teenager with lupus in one of our studies said she took steroid medication more often or less often than prescribed, depending on how she felt (Pieper et al., 1989). This rule was unhelpful because by following this rule she did adequately control the symptoms of her disease.

A critical dimension of the ABA approach is doing a functional analysis, which involves identifying "... important, controllable, causal functional relationships applicable to a specified set of target behaviors for an individual client" (Haynes & O'Brien, 1990, p. 654). Relating this approach to medical adherence would involve

the following steps: (1) operationally defining adherence behaviors; (2) identifying antecedent events that set the occasion for or predict adherence behaviors; (3) generating hypotheses about consequences that maintain adherence behaviors; and (4) collecting observational data (when feasible) to provide at least correlational confirmation of the hypothesized associations of antecedent and consequent events with adherence behaviors (Horner, 1994; Yoman, 2008). Once the functional analysis is completed, a treatment plan can be formulated, implemented, and tested.

Critical Appraisal

There is strong empirical support for behavioral interventions that are solely or partially based on the ABA model in improving adherence to pediatric medical regimens for chronic diseases and health outcomes (Graves et al., 2010; Kahana et al., 2008; McGrady et al., 2015; Meichenbaum & Turk, 1987; Pai & McGrady, 2014; Rapoff & Barnard, 1991; Rapoff, 2000; Varni & Wallander, 1984). Interventions generated from an ABA perspective have primarily involved contingency management procedures, such as token systems. There does not appear to be any studies which have explicitly examined medical adherence from a rule-governed behavioral perspective, though this would seem feasible. For example, older children and adolescents with chronic diseases could be taught to identify unrealistic or unhelpful "rules" about medications (e.g., "medications can be taken depending on how one feels") and challenge these rules by verbal and experiential means (as with traditional cognitive therapy methods). There is also a growing literature on "third wave" cognitive-behavioral approaches to improving adherence, such as acceptance and commitment therapy (see Chap. 7).

Despite strong empirical support, ABA approaches have been criticized on the following grounds:

1. The ABA model is too simplistic to account for the richness and complexity of human behavior. It is based on studies which modify the "...rate of trivial responses emitted by animals in barren controlled settings" (Bandura, 1995, p. 185) or what has been referred to as the "behavior of small animals in boxes" (Todd & Morris, 1992, p. 1441). This criticism underlies many which follow here and partly reflects the foundational work on operant conditioning with simpler organisms in highly controlled experimental settings. Not surprisingly, behaviorists have countered that research with simpler organisms can reveal basic processes (as in medical research) but acknowledge that elaborations and extensions are needed when moving to the study of more complex organisms (Skinner, 1974; Todd & Morris, 1992). They would also point to an extensive and diverse body of applied literature that speaks to the utility of ABA approaches in addressing socially significant problems in medicine, education, business, family life, and community settings (see Kazdin, 2000 and representative issues of the *Journal of Applied Behavior Analysis*).

2. Concerns have also been raised that "external" or "extrinsic" rewards may undermine "intrinsic" motivation (Deci & Ryan, 1985). For example, highly adherent patients may become nonadherent when offered external rewards for adhering to medical treatments. A variant of this criticism is voiced by parents who sometimes object to providing external rewards for something their child "should do" without being explicitly rewarded. Behavior analysts have addressed this issue and concluded that detrimental effects of rewards are rare, and easily avoided, and they agree that more "natural" reinforcers are preferable (Eisenberger & Cameron, 1996).
3. The "cognitivist challenge" to the ABA model contends that human beings respond to "cognitive representations" of the environment and not the environments per se (Mahoney, 1974). ABA theory is criticized for minimizing or rejecting the causal role of cognitions and other "private events" (such as feelings and sensations) in human functioning (Bandura, 1996). ABA adherents counter with an oft quoted remark by Skinner (1974): "What is inside the skin, and how do we know about it? The answer is, I believe, the heart of radical behaviorism" (pp. 211–212). Though they recognize that behavior analysts have traditionally ignored the study of private events, they also cite recent theoretical and empirical developments that seek to rectify this situation, such as relational frame theory and acceptance and commitment therapy (Anderson et al., 1997; Hayes et al., 1999; Wilson et al., 1997).
4. ABA approaches have been characterized as manipulative, totalitarian, and punitive (Todd & Morris, 1992). Some have even argued that it denigrates freedom and undermines personal agency (Bandura, 1997). The counter to this criticism is that controlling influences are omnipresent and need to be delineated so people can understand and counter these influences (Skinner, 1974). Also, behavior analysts have argued for greater use of positive reinforcement-based procedures and have actively worked to reduce aversive control and to safeguard the rights of vulnerable groups, such as children and individuals with disabilities (Kazdin, 2000; Todd & Morris, 1992).

Clinical Implications of ABA Theory

Consider the example of a 14-year-old male who was diagnosed with polyarticular JRA 2 years ago. His disease has been under poor control as evidenced by multiple active joints, extended joint stiffness in the morning, severe limitations in daily activities, and moderate to severe joint pain reported by the patient. His regimen consists of an oral anti-inflammatory medication (naproxen) two times a day, range of motion exercises once per day, and wearing joint splints on his wrists at night. The referring rheumatologist suspected that nonadherence to this regimen contributed significantly to the patient's poor disease control. The patient lived with both parents, who worked outside the home, and an older sister.

Applying an ABA perspective to this case might suggest the following strategies:

- Focusing on the complexity of the regimen (response costs), the clinician might discuss with the patient's physician and occupational therapist ways to simplify the regimen. For example, the patient may be able to switch to another anti-inflammatory medication (Feldene) that is taken once per day rather than twice and reduce the number of range-of-motion exercises.
- The clinician's assessment might reveal that the patient tends to be more adherent to his regimen on days when he has increased joint pain and stiffness. On these days, his symptoms "remind him" to take his medications, do his exercises, and wear his splints. The clinician might need to help the patient and parents find specific and reliable cues or prompts for adherence on days when his disease symptoms are not as severe. For example, the patient may be asked to monitor and record adherence tasks as he completes them using a calendar chart posted in a prominent place or use a daily pill box.
- Considering potential negative regimen effects, the clinician may need to provide advice about how to reduce aversive consequences of adhering to the regimen. For example, anti-inflammatory drugs often cause gastric irritation and pain. The patient could be reminded to take medications with foods and along with his parents, to consult with his physician about the use of antacid medications to reduce gastric irritation and pain.
- Attending to potential positive consequences for adherence, sometimes these occur for this patient when he is symptomatic and adherence results in relief of disease symptoms, such as pain. During relatively asymptomatic periods, positive consequences may need to be specifically programmed to reinforce adherence behaviors. For example, the patient could be exposed to a token system program, whereby he earns points for adhering to regimen tasks and exchanges points for routine and special activities. The token system might also need to include point fines for nonadherence.
- Taking a rule-governed perspective, the patient may operate on unrealistic or unhelpful rules about his disease and regimen. For example, he may think he needs to be vigilant about following his regimen only when he is symptomatic. The clinician would need to help him challenge the utility of this rule and to formulate more helpful rules to advance his health status (e.g., "I need to take my medications, do my exercises, and wear my splints at night, even when I feel ok, in order to control my arthritis and to prevent flare-ups").

Summary and Implications of Adherence Theories

At the theoretical and philosophical level, there may be little hope (or need) for agreement between proponents of different theories about why people do or do not follow prescribed medical regimens. Proponents of competing theories "...practice their trades in different worlds," and communication across the theoretical divide is "inevitably partial" (Kuhn, 1970, pp. 149–150).

Agreement can be reached about the content and behavior change processes addressed by various theories. The content refers to the focus on adherence behaviors or what people do in relation to a prescribed regimen (even within the TRA/BP, the intermediary step of "intentions" leads to adherence-related behavioral requirements). Behavior change processes can be summarized as two basic types: (1) cognitive or self-mediated thought processes (e.g., self-efficacy in Bandura's theory and rule-governed behavior in ABA) and (2) environmental contingencies (e.g., cues to action in the HBM and consequences in ABA). What clinicians do to activate these processes is similar despite differing theoretical frameworks and constructs. That is, clinicians can promote adherence to medical regimens by:

- Verbally persuading patients and their families of the value of prescribed regimens
- Providing competent role models who demonstrate how to successfully manage regimens
- Helping patients and families set specific goals and monitor progress to these goals
- Teaching patients and families the necessary skills for carrying out regimen tasks
- Helping patients and their families arrange more reinforcing consequences for adherence, be they direct, vicarious, or self-generated

Those of different theoretical persuasions may have more in common than they thought. Clinicians and researchers should direct their energies and talents to applying generic principles and strategies while retaining their unique perspectives and cherished theoretical constructs. Patients and their families would be better served by taking this integrative approach.

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Chapter 4
Developmental Considerations in Assessing and Improving Adherence

Though there is an extensive body of evidence assessing and addressing adherence across ages of pediatric patients, much of it does not take a developmental perspective (Michaud et al., 2007). Yet, the nature and clinical impact of adherence barriers can vary by developmental period (Gutierrez-Colina et al., 2018). To adequately promote pediatric adherence, it is important to understand developmental changes in youth and family roles across the developmental span (Markowitz et al., 2015). In contrast to adults, supporting self-management and adherence in pediatric patients is different (Lozano & Houtrow, 2018). First, unlike largely autonomous adults, children rely on parents and other caregivers for assistance with disease care (Lozano & Houtrow, 2018). In fact, it has been argued that for youth, the term "shared management" is more appropriate than "self-management" (Kieckhefer et al., 2009). Second, across the pediatric age range, a wide variety of cognitive, language, emotional, and social capacities align with developmental stages (Lozano & Houtrow, 2018) and are relevant to adherence. Knowledge, skills, beliefs, and attitudes around illness and self-management change tremendously over time in youth, which presents a significant challenge to clinical practice supporting adherence.

Developmental Stages

There can be reciprocal effects between a chronic health condition and development (Michaud et al., 2007). Some health conditions (e.g., cystic fibrosis, diabetes, end-stage kidney disease) and treatments (e.g., steroids) can delay or impact growth, puberty, and general maturation. Chronic disease and treatment also can impact other developmental factors such as self-image, psychosocial changes, education/academic functioning, peer relations, family relationships, etc. In turn, a child's developmental level affects their conceptualization of illness, need for treatment,

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and consequences of non-adherence. Moreover, developmental levels can impact children's understanding of medical information and thus their ability to make medical decisions and self-manage their health condition.

In *early childhood* (ages 0–5), development is rapidly growing with respect to brain structures, language, motor skills, and social skills (Markowitz et al., 2015). This period is when children become more mobile, challenge their parents during mealtimes with picky eating, and start to develop friendships (Markowitz et al., 2015). Young children are not cognitively capable and, depending on the treatment component, may not be physically capable of completing care tasks (e.g., self-administering an insulin injection). Hence, parents are typically fully charged with organizing and implementing care routines for these young children. Thus, concerns regarding adherence focus on ensuring that parents have adequate disease and care knowledge, sufficient behavior management skills (e.g., to address child resistance), and adequate supports (e.g., financial, logistical) to adhere to the child's regimen (Landier, 2011). One key challenge is for parents to learn to recognize symptoms (e.g., asthma exacerbation, infection, hypoglycemia) in children who may be too young to verbalize them.

For *middle childhood* or school-aged children (ages 6–12), the pace of development begins to slow down (relative to early childhood) but continues to evolve (Markowitz et al., 2015). Motor and language skills (including reading) become more refined. Though cognitively still characterized by concrete thinking, children in this developmental period shift dramatically in their understanding of physiological concepts around the structure and function of the human body (Eiser, 1989). Peer relationships become more important during this time too. Parents may still have primary responsibility for care strategies, but youth begin to learn more about self-management and take on some autonomy for aspects of daily living, including some of their treatment regimen (Markowitz et al., 2015).

Adolescence (ages 13–18) is the transitional period in shifting from being a child to becoming an emerging adult. Note that adolescence also has been defined more broadly as spanning ages 10–19 years (WHO, 1999). This developmental period is characterized by significant neurodevelopmental changes that impact the biological, psychological, and social functioning of youth. The limbic system – which is pertinent to emotional functioning, impulsivity, and motivation – develops in full early in adolescence, whereas the prefrontal cortex, which is critical to executive functions (i.e., judgment, impulse control, planning, problem-solving, decision-making), does not fully mature until mid-20s (Vandermorris et al., 2020). Adolescents can understand information provided to them yet struggle with integrating that information into their decision-making. Further, they tend to focus on short-term consequences when making decisions about treatment (Landier, 2011; Stein et al., 2019). Along these lines, deficits in executive function skills have been related to lower levels of autonomy in youth (ages 8–15) with spina bifida, even after controlling for age, IQ, and degree of disability (O'Hara & Holmbeck, 2013).

Adolescents have greater capacity for abstract and complex reasoning (Stein et al., 2019), recognize differences from parents, and are even more sensitive to issues around social dilemmas and peer relationships than younger children (Christie

& Viner, 2005; Markowitz et al., 2015; Michaud et al., 2007). This developmental period also can involve significant risk taking that impacts health (Michaud et al., 2007). Not surprisingly, adolescence comes with shifting roles, which can lead to family stress and conflict. Identity formation is central to adolescence (Markowitz et al., 2015), and chronic health conditions can be a key part of personal identity. It is developmentally appropriate for adolescents to test boundaries and reject parental values in search of their own identities. Adolescents may have difficulty tolerating parental authority in their illness management and get frustrated with illness-related constraints in their daily lives (Landier, 2011). These feelings can lead to active and passive behaviors contributing to non-adherence and health risk (Landier, 2011). Family, community, and school support can serve as protective factors against many health risk behaviors in adolescents.

Emerging adults (late teens–20s) develop more complex abstract thinking, improved impulse control, better planning skills, greater social autonomy, and further completion of personal identity (Michaud et al., 2007). Though they should have the cognitive abilities and skills to adhere to medical regimens, this period also is characterized by shifting and competing demands with education, occupation, and social pursuits. These new roles and their demands also can hinder good self-management and adherence in young adults. Like adolescents, these emerging adults may still see themselves as "bulletproof" and reject medical professionals and explore risk-taking behaviors as part of their individuation process from parents (Michaud et al., 2007).

Youth Cognitive Factors Related to Adherence

The cognitive abilities of the child or adolescent play a strong role in various issues pertaining to adherence and self-management in chronic health conditions. Self-management for chronic health conditions involves the individual's and the family's capacity to navigate barriers and challenges and solve problems around self-care, including adherence (Lozano & Houtrow, 2018). Cognitive factors involved in self-management and adherence include how the patient perceives their health condition, their ability to comprehend medical information, their understanding of potential consequences associated with care, how well they can recognize and report symptoms, their ability to report on their adherence, and their self-regulation and medical decision-making skills.

Perception of Their Health Condition

There is a large body of research reporting on the role that beliefs and attitudes play in predicting adherence to treatment regimens. These beliefs include perceptions on the seriousness of the child's health condition, the severity of consequences that

may follow non-adherence, and possible negative consequences for adherence (e.g., hypoglycemia if taking insulin) (DiMatteo, 2004). Some treatments can be lengthy, even lifelong, and with adverse side effects; thus, open and honest communication between children, parents, and healthcare professionals can help to establish trust and improve adherence through the child's greater understanding of the importance of treatment (Stein et al., 2019). For example, several studies have shown that children and adolescents who are aware of their HIV status have better adherence to antiretroviral therapy (e.g., Cluver et al., 2015). In a study evaluating the utility of a new self-report questionnaire (Illness Identity Questionnaire, IIQ) with a sample of adolescents and young adults (ages 14–25) with type 1 diabetes, self-reported adherence was lower, and HbA1c values were higher with illness rejection (e.g., "I'd rather not think of my diabetes"), whereas adherence was higher with illness acceptance (e.g., "I am able to place my diabetes in my life") (Oris et al., 2016).

Parental health beliefs are particularly important to consider with younger children, when parents are largely responsible for medication adherence. Parental anxiety regarding the child's health in pediatric epilepsy is positively associated with medication-giving behavior (Hazzard et al., 1990). Cultural and religious beliefs can impact caregiver attitudes around adherence as well. Negative religious coping (e.g., feeling punished by God) in parents of children (ages 13 and younger) with cystic fibrosis was associated with poorer adherence measured by the daily phone diary technique (Grossoehme et al., 2015). In the context of clinical encounters, it is not common for providers to query about health beliefs, including religious and cultural practices. As a result, this important factor can often be missed. Also, we have more to learn, however, in studying children's health beliefs and how they relate to their parents' beliefs or how they change over time and influence adherence (DiMatteo, 2004).

Understanding Medical Information

Most research around understanding of medical information has pertained to adult populations or parents of children, usually in relation to health literacy. Very little research has been devoted to child or adolescent understanding of medical information. A qualitative study of children (ages 7–16 years) with epilepsy revealed that parents are the "key information gatekeepers," further suggesting that education needs to be more engaging than a pamphlet to engage children in understanding their health condition and its treatment (Harden et al., 2021). In another study, observations showed that children can lack the requisite skills to properly complete regimen tasks, such as correct use of inhalers for asthma (e.g., Capanoglu et al., 2015). Adolescents (aged 12–17) also had suboptimal disease knowledge about their cystic fibrosis and its care, as measured prior to transition to adult care (Faint et al., 2017). Yet, disease knowledge was significantly associated with adherence to inhaled hypertonic saline, a mucolytic medication, as measured by pharmacy refill

records (Faint et al., 2017). Given the relative paucity of research on children's understanding of medical information, particularly treatment instructions, this area is poised for future directions in research.

Appreciating Consequences Associated with Care

Health beliefs also include perceptions on the severity of consequences that may follow non-adherence as well as possible negative consequences for adherence (e.g., medication side effects; hypoglycemia if taking too much insulin) (DiMatteo, 2004). School-aged children and early adolescents are most interested in current or short-term aspects of their health condition and its care; they are less able to imagine long-term or alternative futures (Michaud et al., 2007). With their concrete thinking, school-aged children also struggle with their interpretation of adherence dilemma situations, as compared to adolescents who have more abstract interpretations. The example below illustrates those differences:

- *Concrete interpretation* – "You said I wouldn't know the right insulin dose if I didn't measure my glucose before taking my insulin with lunch, but I was fine today at school. So, I don't need to check my blood glucose before every meal."
- *Abstract interpretation* – "I missed measuring my glucose before lunch today and took my insulin anyway. I was fine, but it might have been my P.E. class in the morning that helped, or maybe I just got lucky that my glucose was normal before lunch even though I didn't check. To be safe, I shouldn't take these kinds of chances."

In qualitative interviews, a relative lack of perceived consequences for non-adherence was reported by adolescents and young adults with cystic fibrosis (ages 16–21) and their parent as a barrier to adherence, whereas recognizing the significance of therapies was a facilitator of regimen adherence (Sawicki et al., 2015). More specifically, *lack of perceived consequences* consisted of not seriously placing value in treatments, thinking there was no need to do treatments if feeling well, thinking that therapies do not have a significant impact on how one feels, and not seeing a more immediate negative impact from skipping treatments or medications (Sawicki et al., 2015). In contrast, it was noted that learning more about medications/treatments and their purpose and accepting responsibility for cystic fibrosis care and one's health were facilitators in *recognizing the significance or importance of treatment* (Sawicki et al., 2015). In sum, children and younger adolescents have difficulty appreciating consequences, particularly long-term, of adherence and non-adherence. Healthcare providers likely will be more effective in promoting adherence in these youth if they focus more on present or short-term consequences (e.g., improved sports performance in a young teen with asthma) rather than long-term consequences (e.g., visual deficits stemming from poorly managed diabetes).

Recognizing and Reporting Symptoms

Multiple factors may play a role in children's ability to complete patient-reported outcome measures, including symptom reports; these can include developmental level, literacy, vocabulary, concentration, and previous health experiences (Withycombe et al., 2019). Children with lower or emerging reading skills may still understand measures, when provided with reading assistance or audio versions, especially if they have good vocabulary comprehension skills and/or prior health experiences (Withycombe et al., 2019). In pediatric asthma, symptom reporting can take different forms, including numerical guess of current peak flow values, categorical description (e.g., "good" vs. "not good"), or rating on a visual analog scale (Fritz et al., 1996). Some approaches (e.g., numerical prediction), however, may be more challenging than others (e.g., categorical description) for young children, due to their cognitive abilities (Fritz et al., 1996). To simplify children reporting asthma symptom perception, the Brown Asthma Visual Analog Scale was developed, using verbal and cartoon pictures as anchors (Fritz et al., 1994).

Symptom perception accuracy is measured as the relationship between objective or physiological indices and subjective reports (Rietveld & Prins, 1998). Some studies have found no significant age effects (ages 7–15) in symptom perception accuracy (Fritz et al., 1990), whereas others have shown that adolescents are more accurate than school-aged children (Yoos & McMullen, 1999). Relatedly, school-aged children (ages 6–11) with type 1 diabetes demonstrate poor abilities to detect low blood glucose levels, which places them at risk for hypoglycemia (Gonder-Frederick et al., 2008). Higher accuracy also has been associated with better morbidity outcomes (e.g., degree to which asthma interferes with the child's daily functioning) (McQuaid et al., 2007; Yoos & McMullen, 1999). It has been argued that for children with asthma who are younger than age 11, reports from parents and children together provide "complementary" input; however, for adolescents (ages 11+), parents provide little unique information beyond that of the adolescent (Logan, 1997). For more information regarding children's ability to report on factors related to adherence, such as pain and health-related quality of life, consult Chap. 6 in this text.

Reporting Accurately on Adherence Behaviors

Due to their cognitive limitations, children under the age of 6 years are not good at self-reporting adherence behaviors given their difficulties in distinguishing past, present, and future (Arbuckle & Abetz-Webb, 2013). For example, a 5-year-old child likely would struggle reporting their adherence behavior over the past week, though they may be capable of reporting on their current or present behavior. By middle childhood, youth have the capacity to recall specific concrete events (e.g., the last time they missed using their inhaler) but less reliable in reporting "average"

behavior over a vague timeframe (e.g., average number of days missing their medication over the past 2 weeks). In general, we currently do not know what time interval is best for obtaining accurate patient (or parent) recall of adherence behaviors. It is likely that it may differ depending not only on the age of the child but also on the frequency of dosing and type of treatment component. Future research will need to explore this important question (Rand & Wise, 1994), given the widespread use of self-report data.

Adolescents often view themselves as being more independent and competent in their treatment regimens than their parents do, with these discrepancies rising during mid-adolescence and then declining in later adolescence (Butner et al., 2009). Using a developmental and transactional perspective of the parent-child relationship, Butner et al. (2009) examined parent-adolescent discrepancies in perception of the adolescent's competence in diabetes management (e.g., adherence, independence in completing tasks) in a large sample of youth with type 1 diabetes, aged 10–14 years. Adolescents perceived themselves to be more competent and independent than did their parents, and these discrepancies were related to adolescents having greater autonomy and their parents encouraging that autonomy. Nevertheless, greater mother-adolescent discrepancies aligned with poorer diabetes outcomes (i.e., higher HbA1c values). The authors posit that these findings are consistent with normative developmental processes, with discrepancies reflecting adolescent autonomy seeking, which likely is "adaptive in the long run but may entail short-term costs" with respect to adolescents' diabetes self-management (Butner et al., 2009, p. 845). Relatedly, when reporting over more proximal periods (e.g., the past 7 days), adolescent and parent report seem to be similar; however, when asked to report estimates of general adherence over longer periods of time (e.g., past 6 months), combined youth and caregiver reports appear to be better measures (Usitalo et al., 2014).

A variety of approaches can be taken when querying youth about their adherence. For example, when integrated into routine care, a provider might ask the pediatric patient, "How many doses did you miss in the last week (or month)?" or "When did you last miss a dose of your medication?" Some argue, however, that this approach results in socially desirable responding. Like all research comparing subjective report of adherence to electronic monitoring data, studies have found that children overestimate their adherence by self-report (e.g., Burkhart et al., 2001; for peak flow monitoring in children aged 7–11 with asthma). The use of less face-valid measures, like the 24-hour recall interview, may help reduce social desirability in youth responding with respect to adherence (Farley et al., 2008; Marhefka et al., 2006). Nevertheless, when a child or adolescent candidly reports that they are not adhering to their regimen (or aspects of it), the provider can feel confident that such self-report is valid given that most self-report overestimates adherence.

When choosing child-report measures for adherence, it is important to consider the psychometric qualities of an instrument. By example, although the Medication Adherence Report Scale (MARS-5; Thompson et al., 2000) has been useful in clinical practice and research, it was found to be inaccurate when using with children with asthma (Garcia-Marcos et al., 2016). For instance, the Diabetes Management

Questionnaire (Mehta et al., 2015) has solid psychometric properties for child – report, though a bit stronger for children aged >13 years. Nevertheless, researchers and clinicians should remain aware that self-report measures may correlate significantly with more objective measures (e.g., HbA1c levels), yet these correlations still can be relatively small in magnitude (e.g., Schilling et al., 2009). Given the ease of using self- or parent-report measures in clinical settings, but concerns with accuracy, some researchers have suggested devising correction factors to address the overestimation effect (e.g., Wu et al., 2013, for inflammatory bowel disease; Modi et al., 2011, for epilepsy).

Measuring self-reported outcomes in young children (e.g., ages 5–8) can be challenging. When behaviors are observable, parent report is more reliable than child report for this young age group (Arbuckle & Abetz-Webb, 2013). Nonetheless, it is important to recognize that parent reports of their child's adherence are typically overestimates – something common across health conditions. Parent report of adherence can be a useful proxy with older children too. Yet, in certain circumstances (e.g., less reliable in adolescents with type 1 diabetes who also report depressive symptoms), caution in relying on parent report is warranted (Guilfoyle et al., 2011). In fact, child adherence may best be assessed through both parent- and child-report measures, given that agreement between those reports often is low (e.g., Klitzman et al., 2018).

There are numerous, validated scales available, some generic and some disease-specific (e.g., Hilker et al., 2006, screening tool for adherence in pediatric sickle cell disease; Holmbeck et al., 1998, for multidimensional, multitasks questionnaire for parents of youth with spina bifida; Lewin et al., 2009, for the Self-Care Inventory for type 1 diabetes adherence behaviors). Consult Chap. 5 in this text, as well as a recent systematic review patient- and proxy-report measures of pediatric adherence and self-management (Plevinsky et al., 2020), for more guidance. Arbuckle and Abetz-Webb (2013) also provide a guide (see Table 1, page 148) by age, describing children's developmental milestones, approach to choosing informant(s) in qualitative assessments, and suggestions regarding who is the best reporter on outcome measures.

Making Medical Decisions and Ability to Self-Regulate

Though published some time ago, Weithorn and Campbell (1982) conducted an interesting study where they assessed developmental differences (at age 9, 14, 18, and 21 years) in an individual's capability to make informed treatment decisions according to legal standards. Participants were presented with "dilemma vignettes" describing treatment alternatives for medical and psychological concerns. Although 9-year-olds expressed reasonable preferences regarding healthcare decision-making, they were less competent in understanding and reasoning of treatment information (Weithorn & Campbell, 1982). Adolescents, on the other hand, appeared as competent as adults (Weithorn & Campbell, 1982).

Relatedly, regimen adherence requires a complex self-regulation process, in addition to the capacity to use sound judgment in making decisions around medical care. Self-regulation encompasses a person's ability to control their behavior, emotions, and cognitions to attain important goals, like effective disease management (Berg et al., 2014). Executive functioning skills (i.e., planning, organizing, inhibiting, etc., in the face of competing emotions and cognitions) are at the core of self-regulation (Berg et al., 2014). Deficits in self-regulation have been significantly associated with non-adherence. For example, with a sample of high school seniors with type 1 diabetes, Berg et al. (2014) found that adherence was significantly related to various types of self-regulation skills, as measured by parent and youth report. Moreover, adolescents with adequate self-regulation skills could potentially struggle with daily adherence (e.g., sustaining good blood glucose levels) due to fluctuations in their self-regulation across time (Berg et al., 2014).

It has been argued that self-regulation skills not only impact the adolescent at an individual level but also play a role in the youth's interpersonal functioning, which in turn can impact chronic illness self-management in its social contexts (e.g., parental supervision, peer support; Lansing & Berg, 2014). Youth with type 1 diabetes are at risk for cognitive deficits (Ohmann et al., 2010; Suchy et al., 2016) that may impact adherence and glycemic control. Similarly, young people (ages 6–18 years) with high cholesterol who had better problem-solving skills (e.g., able to generate alternative ways to cope with situations) exhibited better dietary adherence than those with poorer problem-solving abilities (Hanna et al., 1990). In contrast, Eaton et al. (2020) did not find a significant relation between parent and self-report of adolescent executive functioning skills and electronically measured adherence to daily antihypertensive medication in a sample of adolescents (ages 11–20) with chronic kidney disease (CKD). The researchers suggested that this lack of significant association may result from the fact that a daily oral medication routine is simpler than more complex regimens, like that for diabetes (Eaton et al., 2020).

In a review article (Bauer et al., 2020), it has been purported that future research should not only focus on youth self-regulation but also consider parental self-regulation skills and how those interact with youth self-regulation to impact illness management and treatment regimen adherence. These authors further suggest and review a range of evidence-based strategies (e.g., simplifying treatment regimen, using behavior checklists for regimen tasks, setting phone alarms/reminders) that might be useful not only in addressing self-regulation deficits in adolescents but also with their parents who have similar concerns (Bauer et al., 2020).

Implications for Assessment of Adherence and Related Factors

Developmental Trends for Adherence Rates

Across the literature, many studies have reported lower levels of adherence in adolescents with chronic health conditions than their younger peers (e.g., Thomas et al., 1997 for type 1 diabetes; Adeyemi et al., 2012 for type 2 diabetes; Wang et al., 2022

for childhood nephrotic syndrome), as well as decreasing trends in adherence across time as youth age into adolescence (e.g., Silva & Miller, 2019 and King et al., 2014 for type 1 diabetes). Aside from the cognitive issues discussed above, several other factors related to the adolescent and their environment are relevant to adherence. These can include emotional/psychological factors (e.g., depression, body image), peer influence, and family functioning.

Emotional and Psychological Factors

Depression is a known risk factor for non-adherence to medications and treatment components (e.g., Benton et al., 2019; Wagner et al., 2009). Though findings can be mixed with respect to the relation of emotional functioning to adherence, internalizing symptoms (i.e., depression, anxiety, and post-traumatic stress) were significantly and inversely related to medication adherence in adolescents who had received solid organ transplants (McCormick King et al., 2014). In addition, adolescents with chronic illness report higher body dissatisfaction than their healthy peers (e.g., Neumark-Sztainer et al., 1995; Pinquart, 2013). Body image issues can center on weight, particularly in nutrition-related illnesses such as diabetes and cystic fibrosis (e.g., Simon et al., 2020), which can lead to non-adherence as a risky weight-loss practice (e.g., not taking sufficient insulin in diabetes; not consuming adequate calories in cystic fibrosis).

Peer Influence Factors

Issues around developing and maintaining peer relationships may conflict with self-management behaviors for a chronic illness (Michaud et al., 2007). Balancing time demands between typical child and adolescent activities (e.g., social events, sports team) with that for disease care can be challenging. Treatments can place restrictions on activities and interfere with the academic and social lives of youth. Moreover, decisions to carry or wear treatment or monitoring equipment (e.g., inhalers, pressure garments, glucometers, EpiPens, insulin pumps) may be impacted by how young people balance or negotiate their priorities (e.g., O'Callaghan & Barry, 2000). Adolescents with type 1 diabetes (ages 11–17) demonstrate better problem-solving abilities (e.g., identifying multiple alternatives) when reacting to social pressure situations than do children (ages 8–10) with T1D (Thomas et al., 1997). However, when presented with situations where regimen adherence conflicts with social pressure, adolescents were more likely to choose actions that fit with peer acceptability, suggesting heightened psychosocial vulnerability (Thomas et al., 1997).

Youth with chronic illness desire a sense of normalcy (Vandermorris et al., 2020) and want to "fit in" with their peers (i.e., peer acceptance) and thus may be reluctant

to be transparent about some of their disease care. For example, an adolescent with celiac disease might struggle in adhering to a gluten-free diet in certain social situations and at school (White et al., 2016). Likewise, a high school football player may be reluctant to use his albuterol inhaler prior to the game for fear that he may appear "weak" or different than his fellow players. Indeed, during adolescence, the salience and influence of peers increases substantially (Stein et al., 2019). Consequently, healthcare providers may consider helping their pediatric patients identify a good friend who cares about the patient and their health and then determine ways that this friend can provide strategic support (e.g., provide reminders, social buffering).

Family Functioning Factors

With all children, the family is a key foundation to health maintenance and treatment in pediatric chronic illness. Managing a pediatric chronic health condition can place a great deal of stress on the family unit. A well-adjusted family can provide support and guidance to help a child adhere to their medical regimen. On the contrary, families with overall poor functioning are more likely to miss medication doses or treatments for epilepsy (Bakula et al., 2022), pediatric renal transplant (Kraenbring et al., 2019), and inflammatory bowel disease (Mackner & Crandall, 2005), for instance. Family difficulties can limit the necessary emotional support that youth receive, increase role strain, and impede the practical aspects of behaviorally and logistically managing treatments.

Some family factors are not necessarily modifiable, but nevertheless represent situations where potential risk might be identified, and relevant resources could be provided. For example, it is well known that single-parent families are at risk for higher rates of child non-adherence (e.g., Drotar & Bonner, 2009; Frey et al., 2007; Zhang et al., 2016). Single parents often have fewer resources, less time, and greater barriers (e.g., access to care) that likely impact disease management. A more novel recent finding has been that children with older caregivers have lower adherence levels (e.g., Zhang et al., 2016). This finding could have been confounded by the age of the child (i.e., older caregivers typically have older children); however, it would be interesting for future research to investigate this more comprehensively and consider whether grandparents serving as primary caregivers increase risk for non-adherence. In Zimbabwe, grandparent guardians of HIV-infected children described many challenges (e.g., memory deficits) they face in helping their grandchildren sustain adherence to antiretroviral therapy (Skovdal et al., 2011). More research is needed to understand the role and difficulties that grandparent guardians experience with other chronic health conditions.

Other potential family influences on pediatric medical adherence are modifiable. These can include family interactions, parental involvement, family stress, family conflict, caregiver psychosocial difficulties, and perceived social support (Modi et al., 2012). In a longitudinal study with a sample of youth (ages 8–15 years at time

1) with spina bifida, family stress was identified as a barrier to self-reported adherence (Psihogios et al., 2017). Parents who endorsed high levels of family stress were also more likely to report their non-adherence with their child's bowel regimen program (Psihogios et al., 2017). The researchers posit that parents are challenged in finding a balance among supporting their child's developing autonomy, establishing age-appropriate limits, and managing their own stress experiences (Psihogios et al., 2017). Additionally, adolescents experiencing difficulties in self-regulation (e.g., impulse control) have been associated with greater family conflict pertaining to diabetes management (Vaid et al., 2018), as well as poorer blood glucose control and adherence (Silva & Miller, 2019; Vaid et al., 2018). Thus, interventions targeting family conflict, in addition to youth responsibility, family communication, and self-regulation (e.g., Anderson et al., 1999; Wysocki et al., 2008), can be critical to optimizing adherence (Vaid et al., 2018).

Positive family characteristics, like consistent use of routines, also have been linked to better treatment adherence (Drotar & Bonner, 2009). For instance, in families of children with sickle cell disease (ages 8–18), open family communication was related to greater parent-reported adherence levels, while greater use of child routines was significantly linked to greater child-reported adherence (Klitzman et al., 2018). Successful family problem-solving also is important to adherence. In youth (ages 8–16) with type 1 diabetes or cystic fibrosis, parent-child dyads described a recent discussion of a problem related to illness management. Not resolving the problem during the discussion was significantly associated with lower adherence (Friedrich et al., 2016).

Family support mediated the relation between adolescent responsibility and adherence in Hispanic youth with type 1 diabetes (Hsin et al., 2010). When youth (ages 10–17) were more independent in their diabetes care tasks, adherence was lower when family support was perceived to be lower (Hsin et al., 2010). Because the study was cross-sectional in nature, it was not possible to determine whether family support impacted adherence or whether families found it easier to be supportive when the adolescent was more adherent (Hsin et al., 2010).

Implications for Designing Adherence-Promotion Interventions

Vandermorris et al. (2020) devised a developmentally informed model of influential factors on adherence in adolescents and young adults with cancer. In this framework, they identified four dimensions relevant to adherence behavior: treatment context and engagement; patient emotional and cognitive functioning; knowledge, beliefs, and attitudes; and social dynamics. Along these four dimensions, they also elucidated common challenges (e.g., concern for social acceptance) and provided specific adherence-enhancing strategies (e.g., promote opportunities for peer engagement) identified in the intervention literature with adolescents and young

adults with cancer and other chronic illnesses (see Table 4 in Vandermorris et al., 2020). Interventions with developmental considerations include optimizing provider communication (e.g., communicating directly with the child; engaging youth in shared decision-making), encouraging parent involvement and supervision, addressing the transfer of responsibility from parents to youth, promoting transition readiness, and engaging youth as key stakeholders in intervention development. These topics are briefly addressed in the remainder of this chapter.

Optimizing Provider Communication

Along with factors related to the pediatric patient and the family, factors concerning the provider and their communication during clinical encounters can impact regimen adherence. Providers play a key role in sharing information about health conditions and their treatment. Healthcare providers not only give information about the content of a treatment plan or regimen but also can encourage strategies to successfully integrate treatment components into a patient's daily life (e.g., incorporate tasks within routines) (Drotar, 2009). Communication directed at children during clinical visits is infrequent (Dowell et al., 2020), yet taking a parent- rather than patient-centered approach can be "disempowering" (Lin et al., 2020).

Discrepancies exist in what providers convey regarding treatments, including medication information, and what patients and families recall (e.g., Riekert et al., 2003). As a result, adherence cannot be optimized if a patient or family does not understand how to implement their treatment. Deficits in parent and child knowledge of the child's treatment regimen have been linked to non-adherence (Szabo et al., 2016). Good communication behaviors include checking for understanding, providing opportunities for parents and children to ask questions, provide visual and verbal information, give information to take away, use simplicity as much as possible, be honest, avoid jargon, explain technical information, and pause when delivering a lot of information (Stein et al., 2019). Language should be adapted to the developmental and/or cognitive level of the child (Michaud et al., 2007), using accessible but not patronizing language (Stein et al., 2019). This approach can help deter misunderstandings for the child and their family.

Healthcare providers should strive to establish a safe, trusting, and empathic relationship with their pediatric patients. In this context, privacy and confidentiality are important aspects of care, particularly with adolescents. Depending on the age of the patient and relevant legislation, it is best to clarify the provider's policy regarding confidentiality up front (Michaud et al., 2007). In particular, the healthcare providers should not share information with parents without the consent of the patient, unless the young person discloses the possibility of harm.

Clinicians can use open questions and reflective listening strategies to elicit the child's perceptions and feelings around their health condition, its treatment, and its prognosis (Michaud et al., 2007). Open questions elicit greater expression of thoughts and feelings. Children report that they will readily share information with

providers if they are included in discussions during clinic encounters (Dowell et al., 2020). When referring to "perceived support," adolescents with a chronic health condition (e.g., epilepsy, juvenile rheumatoid arthritis) noted that they prefer when their provider shows interest in them as a person (rather than focus solely on their disease), attends to their life situation, asks about problems they may have in implementing their treatment, encourages self-care, and avoids simply "ordering" them what to do (Kyngas & Rissanen, 2001).

Providers also should assess for patient-specific barriers to adherence. After all, research has demonstrated little agreement among clinicians, caregivers, and children regarding barriers to daily medications (Arnold et al., 2018). Open, straightforward, and trusting communication can help the clinician elicit patient and family perspectives on adherence and possible solutions to adherence struggles (Michaud et al., 2007). Surveys (e.g., Illness Management Survey; Logan et al., 2003) also exist to explore factors such as social desirability, perceived problems in taking medication, and risk behaviors that may pose as barriers to adherence in youth.

To ensure patient understanding, clinicians can use the "teach-back" method, asking patients (or parents) to use their own words to share back what was taught (Badaczewski et al., 2017). An adapted procedure is the "show-me" method, where a clinician asks the child (or parent) to demonstrate their skills in a regimen task (e.g., skills in using an inhaler, blood glucose meeting, airway clearance device). The AHRQ provides an excellent document to guide the use of these strategies (https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/quality-patient-safety/quality-resources/tools/literacy-toolkit/healthlittoolkit2_tool5.pdf), like suggesting that providers pause and assess throughout a clinical encounter, rather than wait until the end of the appointment. Although these strategies have been shown effective in use with adult patients, more research is needed to understand their utility and application in pediatrics.

Monitoring and providing feedback on adherence, via electronic devices or prescription refill data, also has been effective in improving adherence (Burgess et al., 2010), technique (Spaulding et al., 2012), and clinical outcomes (Burgess et al., 2010). Most research, however, has only tested the utility of feedback over relatively brief intervention periods (e.g., Driscoll et al., 2017); thus, it is not clear if feedback would maintain its saliency and utility over longer periods of time. At the very least, this approach can help identify patients who have suboptimal adherence, which in turn can prompt providers to investigate and problem solve around possible barriers to adherence.

Despite these various suggestions, little attention in the empirical literature has been devoted to examining the impact of provider-patient (child or adolescent) communication on adherence (DiMatteo, 2004). More research is needed to better understand how specific provider communication behaviors, and interventions targeting those behaviors, can improve adherence in youth with chronic health concerns.

Obtaining Partnership with Youth for Shared Decision-Making

Shared decision-making in pediatric care is different than in adult healthcare. Children's decision-making involvement around illness management is important to consider, particularly when recognizing the complex regimen tasks required each day. As children age and mature, they seek more autonomy in decision-making regarding their treatments.

Decision-making involvement (DMI) is a "multidimensional construct that includes both active participation by the child (e.g., asking parent for advice, expressing an opinion, giving information) and adult attempts to facilitate the child's involvement (e.g., asking for the child's opinion, soliciting questions, sharing information with the child)" (Miller & Jawad, 2019, p. 62). These behaviors are measured in the parent- and child-report *Decision Making Involvement Scale* (DMIS; Miller & Harris, 2012), with items pertaining to a jointly identified recent discussion about an illness management problem. The DMIS yields scores for five subscales: Parent Express (shares information or opinion with child), Parent Seek (asks for information or opinion from child), Child Express (shares opinion or information with parent), Child Seek (askes for advice or information from parent), and Joint (negotiation or problem-solving between parent and child) (Miller & Harris, 2012). Youth with type 1 diabetes who were more engaged and active in illness management discussions (i.e., higher Child Seek, Child Express, and/or Joint scores) had better adherence (Miller & Jawad, 2014, 2019).

Shared decision-making between providers and patients is related to better adherence, outcomes, and satisfaction with care (Blaiss et al., 2019). So, healthcare professionals should evaluate and consider the individual and joint involvement of youth and their caregivers in illness management decision-making (Turner et al., 2020). Indeed, oftentimes, a treatment regimen can be tailored to the adolescent's preferences, needs, and lifestyle, when feasible (Michaud et al., 2007). For example, an adolescent with asthma, who sings in a choir, may be more adherent in using a metered-dose inhaler than a dry powder diskus inhaler for their daily controller medication because it is less irritating to their throat. Whenever possible, youth should have freedom to help make choices around treatment. Sometimes, shared decision-making may mean choosing a less efficacious treatment (e.g., replace vest oscillation treatment with exercise of airway clearance in cystic fibrosis); however, adherence likely will be higher and thus better than no adherence to a non-preferred treatment option. Overall, adolescents typically prefer to be involved in treatment decision-making, even though they may recognize the benefits of trusted others' insight and advice (e.g., Weaver et al., 2015).

Encouraging Parental Supervision and Involvement

Parental monitoring includes consistent interaction with youth during their daily activities as well as knowledge about and supervision of those activities (Young et al., 2014). It has been argued that parental involvement is multidimensional, incorporating separate but related factors: relationship quality (i.e., acceptance, independence encouragement, communication), behavioral involvement (i.e., intrusive support, frequency of help), and monitoring (i.e., general, disease-specific) (Palmer et al., 2011). The amount of parental involvement is not the only key factor to consider, but also the types of monitoring (e.g., problem-solving) and the quality (e.g., parental warmth) of involvement (Young et al., 2014). When entered together in separate "parent" models, relationship quality and monitoring predicted better self-reported adherence each for mothers and fathers in a sample of youth (ages 10–14) with type 1 diabetes (Palmer et al., 2011). Conversely, fathers' behavioral involvement was related to poorer adherence (Palmer et al., 2011). These findings support the notion of parental involvement as a multidimensional construct, which should be considered when devising interventions to promote parental involvement. In other words, interventions should target not only frequency and type of involvement but also parent-youth relationship quality.

Along these lines, parent involvement in promoting child adherence to treatment regimens can take many forms. It can involve direct observation and/or assistance, youth disclosure (i.e., telling the parent that they completed a regimen task), and parent solicitation (i.e., parent asking their child if they completed a task) (Lansing et al., 2017). Williams et al. (2007) created a Fig. 4.1 (see below) depicting the mutual and changing roles that parents and children play in initiating and

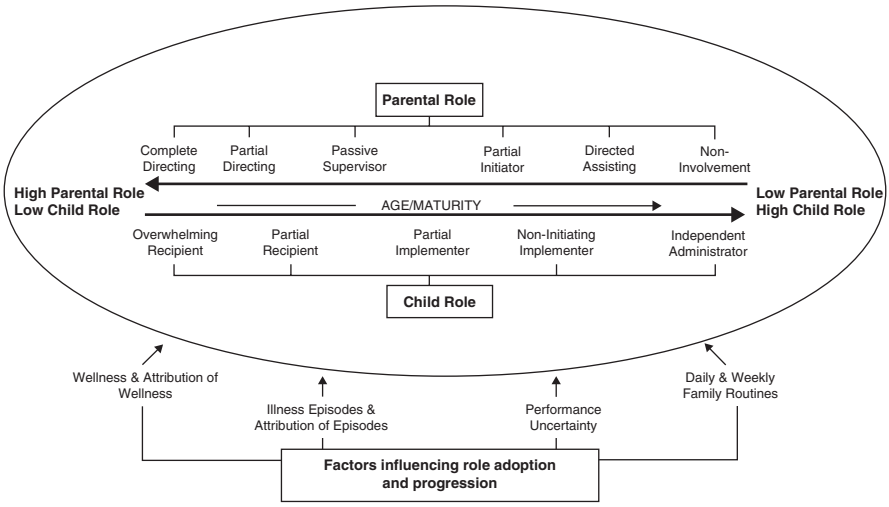

Fig. 4.1 Parental and child roles in management of chronic health condition. (Reprinted with copyright permission from: Williams et al. (2007). Copyright Elsevier)

maintaining physiotherapy (airway clearance) treatment for cystic fibrosis. Parental involvement spans the continuum from "complete directing" to "partial directing" (e.g., coaching), to "passive supervisor," to "partial/passive initiator" (prompt but not supervise), to "directed assisting" (only becoming involved when requested by the child) to "noninvolvement" (Williams et al., 2007, p. 2139).

Parent involvement in treatment regimens has been identified as a facilitator for adherence. For instance, Butcher and Nasr (2015) used several 24-hour recall interviews and home visit observations to assess parent supervision of respiratory treatments in school-aged children (ages 6–12) with cystic fibrosis, which was then compared to electronic monitoring data for airway clearance time. They found that parental presence and positive attention (e.g., praise, reflective statements) were significantly associated with higher respiratory adherence rates (Butcher & Nasr, 2015). Though the sample was small, study results support the importance of obtaining naturalistic data to better inform interventions, such as parent training, to improve young children's adherence to treatments. In another study, Lansing et al. (2017) innovatively identified a child behavioral characteristic – delayed discounting – as potentially being key to understanding their ability to self-manage treatment regimens. Delayed discounting refers to the extent to which a child prefers immediate rewards over delayed or long-term rewards. For example, a child with type 2 diabetes may choose to eat a calorie-dense food for the short-term reward of enjoying it, rather than avoid eating it with the long-term reward of potential weight loss. In adolescents with poorly controlled type 1 diabetes, it was found that direct parental observation of diabetes care, not indirect parental monitoring (e.g., asking child), moderated the relation between greater delayed discounting (i.e., preferring short-term rewards) and higher HbA1c levels (Lansing et al., 2017). These findings suggest the need for tailoring parental involvement to the child's ability to choose long-term rewards over short-term ones, and perhaps to target delayed discounting in adherence-promotion interventions with adolescents.

Maintaining some degree of parental involvement in disease management across adolescence has been suggested as highly beneficial not only for promoting adherence (e.g., Ellis et al., 2007; Modi et al., 2008; Psihogios & Holmbeck, 2013) but also relevant factors (e.g., self-efficacy) (King et al., 2014; Marhefka et al., 2008). Indeed, it has been argued that the transfer of responsibility for diabetes management be "titrated" to the adolescent's sense of self-efficacy (Wiebe et al., 2014). When adolescents (ages 14–18) and their caregivers were interviewed post-kidney transplant regarding strategies used to ensure adherence to immunosuppressant medication, only caregiver reminders to take medication and caregiver verification that medication was taken were significantly related to higher adherence rates via electronic monitoring data (Ingerski et al., 2011). Although youth (ages 8–15) gained more responsibility and independence skills in self-managing spina bifida across a 2-year period (measured at two time points), this shift was associated with poorer adherence to self-care (Psihogios et al., 2015). Results such as these underscore the importance of continued caregiver involvement, even with adolescents, to support adherence to treatment regimens.

Lagged multilevel modeling analysis revealed that declines in parental monitoring predicted subsequent decreases in adolescent adherence in type 1 diabetes (King et al., 2014), signifying that some degree of parental involvement is beneficial. Similarly, in a path analysis with 99 youth (ages 12–18) with type 1 diabetes, diabetes-specific parental monitoring was significantly related to parent and youth report of adherence; this monitoring also had an indirect effect on HbA1c levels (metabolic control) through adherence (Ellis et al., 2007). Finally, Zhang et al. (2016) found that parent and adolescent (ages 12–18) report of total parental monitoring (particularly observing or being present during different diabetes tasks, like blood glucose monitoring and insulin administration) was significantly associated with higher youth frequency of daily blood glucose testing.

Parental involvement or supervision is significantly related to child age, such that it is less when children are older (e.g., Landers et al., 2016; Modi et al., 2008). Indeed, in a sample of young children (ages 6–9) with asthma, child and parent ratings of the child's responsibility increased with age; however, ratings of parental responsibility remained rather constant across the child age range (Wade et al., 1999). This stability in parent responsibility may stem from the rather young and narrow age range of this sample. In contrast, with wider age ranges (e.g., 8–18 years), parental involvement has shown to decrease with the child's increasing age (e.g., Lancaster et al., 2015). Nevertheless, it has been argued that a "family teamwork approach," especially during school-aged and early adolescent years, is optimal for establishing good self-management habits and adherence (Anderson et al., 1999; Markowitz et al., 2015). Moreover, using age solely as a means for transferring responsibility can be problematic if the child's skills or maturity are not sufficient to be independent (Wysocki et al., 1996).

In a 3-year longitudinal study involving early adolescents with type 1 diabetes (Wu et al., 2014), autonomy support and frequency of blood glucose monitoring decreased over time, whereas responsibility for diabetes care transferred from the caregiver toward the youth across time. Greater levels of parental or caregiver autonomy support were related to better diabetes care – i.e., blood glucose monitoring checks recorded on their meter – during this important developmental period (Wu et al., 2014). Similarly, in a sample of children (ages 8–16) with cystic fibrosis, parents rated by children as having greater autonomy support was significantly associated with self-reported adherence at baseline but was not predictive of adherence at a 2-year follow-up (Murphy & Miller, 2020). Only parental warmth (e.g., affection, acceptance) at baseline was predictive of parent-reported adherence at follow-up (Murphy & Miller, 2020). These represent just some of the mixed findings in the literature with respect to parenting style and adherence. It will be important for future research to use longitudinal models and objective measures of adherence to truly understand the relation of parenting approach to adherence in pediatric chronic health conditions.

Still, what makes for a parent who is autonomy supportive? It has been suggested that key parental characteristics are taking their child's perspective, providing choice whenever feasible, encouraging problem-solving, fostering exploration in decision-making, and providing a good rationale when the child's choice is limited

or controlled (Caruso et al., 2021; Perlberg et al., 2021), all of which is consistent with self-determination theory (Deci & Ryan, 2002). Better parental autonomy support is related to higher levels of adolescent-reported competence in diabetes care (Perlberg et al., 2021) and regimen adherence in youth with chronic headache (Caruso et al., 2021), type 1 diabetes (Perlberg et al., 2021), and asthma (Blaakman et al., 2022), for example. Nevertheless, many parents need guidance in how to provide this support yet maintain boundaries and provide appropriate supervision. Otherwise, their support can be perceived by their child as being intrusive, critical, and controlling (Young et al., 2014).

Paternal Involvement

Although samples of convenience often result in measures of parental involvement largely describing that of mothers, some researchers have examined the specific association of paternal involvement in adherence and other outcomes. Specifically, Wysocki and Gavin (2006) conducted a cross-sectional study of paternal involvement in the care of youth (ages 2–18) with one of the six different health conditions: persistent asthma, cystic fibrosis, type 1 diabetes, phenylketonuria (PKU), inflammatory bowel disease, and spina bifida. Paternal involvement was measured by the *Dads' Active Disease Support* (DADS) scale (Wysocki & Gavin, 2004), which measures the frequency with which the father completes care tasks ("amount" score) and the perceived helpfulness of this involvement ("helpfulness" score). To be consistent across health conditions, adherence was measured via a disease-specific structured interview. Children were separated into four different age groups: 5 and younger, 6–11, 12–14, and 15–18. Paternal involvement was significantly related to maintenance of treatment adherence, such that fathers with higher amounts of involvement with older adolescents (ages 15–18) were associated with higher adherence scores (Wysocki & Gavin, 2006). In contrast, paternal involvement was not significantly related to adherence in the three younger groups (Wysocki & Gavin, 2006). Because mothers often are the ones who bring their children to their healthcare appointments, fathers may be lacking targeted instruction and thus not feel informed in their role of parenting a child with chronic illness needs (Swallow et al., 2012). Thus, providers need to ask key questions around paternal involvement to better understand how to guide fathers in supporting adherence in their children.

Parent-Child Agreement Regarding Responsibility

It is not surprising that like agreement in parent and child report of adherence, agreement between parents and children with respect to responsibility for regimen management can be low. Oftentimes, caregivers report having more responsibility than the youth report their caregivers having (e.g., Naar-King et al., 2009; Wade et al., 1999), or youth overestimating their responsibility relative to what the

caregiver reports (e.g., Psihogios & Holmbeck, 2013; Wade et al., 1999). These discrepancies seem to be more common among older children, perhaps because division or allocation of responsibility within families becomes less clear as children age into adolescence (Naar-King et al., 2009).

Addressing the Transfer of Responsibility from Parents to Youth

Pediatric adherence takes place within the family context. Parents, grandparents, and other family members often share responsibility with children and adolescents for administering the child's medications. As noted by the discussion above, during adolescence, roles regarding responsibility for illness management get reorganized and often can be ambiguous (Landier, 2011). In other words, families may not adequately define who is "in charge" of various aspects of the treatment regimen. Middle adolescence is a period when young people seek individuation and often want to establish more autonomy from their parents and control over their health condition (Michaud et al., 2007). It is during this developmental period when youth may resist to accepting their health condition (e.g., Carmody et al., 2022). Some parents can struggle with wanting to control their child's disease and its care, even to the point of being overly protective. Other parents may feel frustrated and perhaps disengage from their child's disease management due to other factors like their own emotional reaction, arguments that arise from their involvement, etc. (Michaud et al., 2007). Some parents also may overestimate their adolescent's ability to self-manage their treatment regimen.

Across time, responsibility for disease management generally shifts from a parent focus with younger children to a patient focus in young adults (see Graphical Abstract in Markowitz et al., 2015). The transfer of responsibility ideally should be gradual, with adolescents progressively taking on more independence while parents little by little distance themselves (Bell et al., 2011; Michaud et al., 2007), yet remain adaptive and flexible, as needed. This might mean accepting suboptimal adherence, though recognizing that tighter parental control likely will be less productive over the long term (Michaud et al., 2007). While some parents view the transfer of responsibility as a positive and important process, others report significant distress, sense of losing control, and anxiety about consequences when shifting health management to their adolescent or young adult (Hanna & Guthrie, 2000; Heath et al., 2017). In fact, the transfer of responsibility is rarely a linear process. Rather, as learned during in-depth interviews with children (ages 7–17) with cystic fibrosis and their parents, responsibility can revert from youth to caregivers during times of mistrust or illness exacerbation (Williams et al., 2007).

Although the focus of self-management naturally shifts from parents/caregivers for younger children to the patients when they are older, there is little empirical evidence to guide the transfer of responsibility or locus of control (Lozano & Houtrow, 2018; Williams et al., 2007). For example, there are no disease-specific guidelines for how families should divide diabetes management or what regimen

tasks are appropriate at different ages (Markowitz et al., 2015). This is true of all pediatric chronic health conditions. Moreover, the actual process of shifting responsibility is not well-defined for families. A parent-youth teamwork intervention for asthma was effective in increasing and maintaining controller medication adherence via a structured program to fade parental involvement and increase adolescent independence contingent on adherence levels (Duncan et al., 2013).

It is challenging, particularly because adolescents taking on more responsibility for treatment regimen care have often been associated with lower levels of adherence (e.g., Naar-King et al., 2009; Silva & Miller, 2019). Competency and mastery of key skills are central to this transition. In fact, King et al. (2014) found that longitudinal associations between parental involvement and adherence were mediated by self-efficacy in adolescents with T1D, such that parental involvement contributed to higher self-efficacy for diabetes management. It is noteworthy that developing youth will likely experience a different transition trajectory than those youth with developmental disabilities. Therefore, the transition process should be tailored to the idiographic needs of the child and family.

In applying self-determination theory (Deci & Ryan, 1985), Lee et al. (2020) speak to the importance of a "feedback loop" where adolescents and young adults establish competence, develop autonomy, and assume greater responsibility for successfully managing their chronic illness, and then parents develop more trust and become less fearful of their child's wrongdoing in disease management. Otherwise, when parents are worried about negative consequences resulting from their child's autonomy in completing complex self-management tasks, it hinders the transfer of responsibility (Lee et al., 2020). When children begin to spend more time taking their medications and performing their own treatment components, it is important to make sure that they have the requisite knowledge and skills to do so (Quittner et al., 2008). Some measures have been developed to assess skills and readiness for independent self-care, such as the *Readiness for Independent Self-Care Questionnaire*, with teen (RISQ-T) and parent (RISQ-P) report versions for type 1 diabetes self-care needs (Goethals et al., 2020).

In youth (ages 8–15 years) with spina bifida, impaired gross motor skills and low IQ were barriers to youth assuming medical responsibility, while executive dysfunction was a barrier to responsibility and self-reported adherence (Psihogios et al., 2017). These findings imply that individuals with more severe spina bifida and/or neurocognitive impairments may struggle to become more autonomous with their care and may need additional supports to gain independence skills (Psihogios et al., 2017). Similarly, deficits in impulse control skills were related to lower adherence and higher HbA1c levels in youth (ages 8–16 years) with type 1 diabetes (Silva & Miller, 2019). Consequently, it appears that targeting executive functioning skills should heighten the impact of interventions devised to promote youth responsibility for self-management.

To assist with understanding roles of responsibility and perhaps assess the impact of intervention research, various measures have been devised and validated to assess shared responsibility for disease management within families. Some are disease-specific, while others are generic. For example, the *Diabetes Family Responsibility*

Questionnaire (Anderson et al., 1990; Vesco et al., 2010) was developed to evaluate division of responsibility, the relation of responsibility to adherence, and factors associated with patterns of shared responsibility within families. Similarly, validated questionnaires are available to measure parent involvement in treatment regimens (e.g., *Collaborative Parent Involvement Scale*, also for type 1 diabetes management; Nansel et al., 2009). Other areas, like pediatric rehabilitation, however, are limited by an apparent lack of well-developed and validated measures of parent engagement or involvement in at-home therapies (D'Arrigo et al., 2018).

Promoting Transition Readiness

As healthcare improves for children and adolescents with potentially life-limiting conditions (e.g., cystic fibrosis, HIV infection, cancer), patients are surviving longer and entering adulthood. Thus, transition from pediatric healthcare settings to adult healthcare settings has become an important issue to consider, and adherence is a key component. It is not surprising that during this transition period, adherence can decline (Campagna et al., 2020). Patients may "fall through the cracks" in missing their routine clinic appointments with an adult care team and thus may not be monitored for adherence to their treatment regimen too. Structured transition programs can facilitate a successful shift for patients, though such formal programs are not always used by care teams (Heath et al., 2017). Transition programs address the educational, logistical (e.g., provide points of contact), and psychosocial needs of patients and families (Campagna et al., 2020). By example, transition programming was successful in promoting adherence posttransition with pediatric heart transplant recipients (Anton et al., 2019) and youth with inflammatory bowel disease (Erős et al., 2020). The current literature on the efficacy of transition programming is limited by several factors, such as small sample sizes, sampling bias, overreliance on self-report adherence measures, and focus on patient (rather than family) (Campagna et al., 2020). Future research not only needs to address these limitations but also should take additional steps to address mental healthcare needs during the process and to gain more insight into the transition experience of youth from diverse and underserved backgrounds (Campagna et al., 2020).

Healthcare transition is a process that is characterized by three intersecting phases: preparation, transfer, and integration (White et al., 2018). During the preparation phase, adolescents (ideally) learn requisite self-management skills and then transfer to adult care as they approach adulthood, and finally, the patient is fully integrated into adult healthcare (White et al., 2018). As noted earlier, gradual and progressive shifting of responsibility for completing medical regimen tasks from parents to youth is key to the preparation phase (Lee et al., 2020). Successful transfer of responsibility during adolescence also boosts the young adult's sense of personal control (Lee et al., 2020). Effective self-management skills and personal responsibility are required for the young adult to successfully engage in adult-based healthcare (Lee et al., 2020), which is qualitatively different than pediatric

healthcare (Heath et al., 2017). Heath et al. (2017) conducted a systematic review and thematic synthesis of parental experiences (across six countries) during healthcare transitions for their children and provide rich descriptions along with practice implications.

Facilitators and barriers for a successful healthcare transition have been identified. Planning and education are a critical part, and checklists of key tasks and milestones for the AYA to attain before transition can be incredibly helpful (Bell et al., 2011). A popular transition readiness checklist is the TRAQ (Wood et al., 2014). Another example with parent and teen report is the *Readiness for Transition Questionnaire* (RTQ), which measures overall perceived transition readiness, adolescent responsibility, and parental involvement in the teen's healthcare and treatment regimen (Gilleland et al., 2012). The STARx Questionnaire, in contrast, uses patient and provider input with respect to self-management and transition skills in adolescents and young adults across a variety of chronic health conditions (Cohen et al., 2015). STARx scores correlate significantly with self-reported adherence (Cohen et al., 2015). Although these tools assess "readiness" for transition, there also are measures of transition outcomes that might be useful to consider, particularly when evaluating the efficacy or effectiveness of transition programs. By example, the *Healthcare Transition Outcomes Inventory* (HCTOI) was rigorously developed for use with young adults with type 1 diabetes; it provides scores for five outcome domains (navigation, self-management, integration, ownership, and parental support) and includes several items on healthcare utilization (Pierce et al., 2017, 2019, 2020). Chiefly, many of these measures ask respondents to report on the adolescent's perceived ability, rather than the adolescent's demonstrated competence or skills. Even when skills are specifically queried, like with the TRAQ (Wood et al., 2014), results are based on parent and/or self-report, rather than behavioral observation.

Providers should consistently create time to meet with the adolescent alone during clinic visits and hospital encounters. They also may want to meet alone with the parent(s), as well as see the family together. It is important to recognize that some adolescents and young adults value having their parents involved in their clinical consultations (Stein et al., 2019). Clinicians also should consider the need to "reeducate" adolescents and young adults, particularly those who were diagnosed as young children (Zanni et al., 2014).

Engaging Youth as Key Stakeholders in Intervention Development

Stakeholder involvement is a critical aspect of implementation science given the importance of acceptability and uptake of interventions (Wiener et al., 2020). As interventions are devised, policies and care guidelines are created, and individual patient treatment plans are established, and key stakeholders are critical to include throughout all stages. To this end, community participatory research methods should

be the foundation of developing, implementing, and disseminating our adherence-promotion interventions, and researchers should attend closely to purposively sampling participants who represent important communities (e.g., underserved, diverse) (Wiener et al., 2020). Thus, children, adolescents, and young adults and their families, each with their lived experiences in managing a chronic health condition, provide valuable perspective and expertise not only in designing behavioral interventions for adherence but also in creating their own personal treatment plans in consultation with their medical providers.

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Chapter 5
Assessing Adherence and Methodological Considerations

Why Assess Adherence?

The aims or functions of adherence assessment are consistent with those applicable to assessing any behavioral phenomenon: (1) screening or diagnosis; (2) prediction; (3) selection of intervention strategies; and (4) evaluation of intervention process and progress (Johnston et al., 2019; Youngstrom & Prinstein, 2020).

Screening and Diagnosis

Although nonadherence is a common clinical concern, not all patients are candidates for adherence promotion interventions. Clinicians may do more harm than good if they intervene with those patients who are maintaining an acceptable level of adherence (Finney et al., 1993). Patients may require varying degrees or types of assistance to elevate their adherence levels. Screening is helpful in determining who would benefit from an adherence promotion intervention and to limit the time and expense of monitoring and intervening with patients who do not require assistance. This could be done by monitoring adherence in a group of patients, setting a minimum criterion for nonadherence (e.g., <80% of medications taken), and offering interventions to those classified as nonadherent.

The *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013) contains a supplementary (or "V") code labeled "Nonadherence to Medical Treatment" (V15.81) (American Psychiatric Association, 2013). V codes are not diagnoses, per se, but rather significant issues that directly require clinical attention and/or impact the patient's mental disorder (e.g., nonadherence to medication for depression may worsen the patient's prognosis). Alternatively, a clinician may choose the DSM-5 diagnosis of "Psychological Factors Affecting Other Medical Conditions" (316), where poor adherence to a

M. A. Rapoff et al., *Adherence to Pediatric Medical Regimens*, Issues in Clinical Child Psychology, https://doi.org/10.1007/978-3-031-27484-8_5

prescribed medical regimen is considered a maladaptive health behavior. When assigning V15.81 and 316 codes, the clinician must identify adherence problems that are severe enough to require independent clinical intervention. This, in turn, requires some measure of adherence and specific criteria to determine the severity of adherence problems (neither of which are specified in the code description). Although assessment and intervention services tied to the V15.81 are not likely reimbursed by third-party payers (like all V codes), 316 should be. Another possible avenue for pursuing reimbursement for adherence screening (and interventions) in youth is Health and Behavior Assessment Codes (https://www.apaservices.org/practice/medicare/medicare-payment/health-and-behavior-codes). Services tied to these billing codes require only a medical diagnosis (e.g., type 1 diabetes).

To be maximally effective, screening should become routine practice in clinical settings. Yet, there can be several barriers to implementation, such as clinics feeling pressured for time, patients and families feeling reluctant to share adherence concerns, healthcare providers lacking access to or confidence in the results of screening tools, and obstacles in obtaining behavioral health services when concerns are identified. Moreover, given the range of potential factors (e.g., depression, family conflict) impacting or underlying nonadherence, identifying patients at risk for problems in disease management requires more comprehensive routine screening (e.g., Schwartz et al., 2011) and intervention services.

Prediction

Isolating predictors of adherence requires an adequate measure of adherence. Also, the best predictor of future adherence to a specific regimen is current or past adherence to that same regimen (confirming the old maxim that the best predictor of future behavior is past behavior). Because nonadherence for some therapies may result in unique adverse consequences (e.g., drug resistance), it can be particularly important to predict those patients who are ready to initiate treatment. For example, Fernandez and colleagues (2011) devised and tested a range of psychometric properties for an audio computer-assisted self-interview to measure treatment readiness in adolescents and young adults with HIV during routine clinical care. Adherence has also served as a predictor of disease and health status outcomes. Kunkov and Crain (2010) conducted screening of "risk for nonadherence (RN)" (e.g., worry about side effects, feels medications are not useful, child refuses to take medication) and "admitted nonadherence (AN)" (e.g., did not fill prescription, gave less medicine that prescribed) via self-report and brief interview with families of children (ages 3–11 years) following emergency department care for an asthma exacerbation. Both RN and AN were associated with greater morbidity indices (e.g., symptomatic days, rescue inhaler use, nighttime awakening due to symptoms) over an 8-week follow-up period (Kunkov & Crain, 2010). Thus, adequate assessment of adherence contributes meaningfully to more accurate predictions about the outcomes of various medical treatments.

Intervention Selection

To effectively devise adherence interventions, clinicians need to know the extent and nature of adherence problems. Severity of adherence problems often translates into the degree of complexity in intervention approach. For example, patients who occasionally forget to take medications may be provided with simple strategies to prompt adherence (such as setting a phone alarm). In contrast, those patients who frequently miss doses and actively resist their parents' attempts to prompt adherence might need a more complex intervention (e.g., structured reward or response cost program; time-out). To adequately devise adherence promotion strategies, it is important also to distinguish intentional or volitional nonadherence (i.e., purposeful decisions to take no or less medication) from unintentional or non-volitional adherence (e.g., forgetting, misunderstanding) (Garfield et al., 2011).

The nature of adherence problems also informs the type of intervention needed. Patients who underdose (the most common medication adherence error) may require a different intervention (e.g., instructing them about the importance of maintaining a therapeutic drug level to optimize treatment benefits) than those who overdose (e.g., instructing them to avoid trying to make up missed doses by taking extra doses) or who misunderstand their treatment approach (e.g., providing enhanced education via role-play). Expanding assessments to include a functional assessment of variables that impact adherence (such as antecedent and consequent events) would greatly enhance the ability of clinicians to select individualized interventions that match the unique history and life circumstances of their patients. In this context, assessment of an individual's or family's barriers to adherence can be useful in choosing or devising an intervention (e.g., Gray et al., 2012; Varnell et al., 2017). Disease-specific questionnaires to measure such barriers exist (e.g., Cushman et al., 2020; Simon et al., 2012).

Evaluation of Intervention Efforts

Adequate assessments of adherence are necessary to evaluate and compare different approaches (e.g., educational vs. behavioral strategies) to improve adherence to medical treatments. In their meta-analysis, Graves et al. (2010) found that using behavioral and educational strategies together had a greater impact on health outcomes than employing either strategy alone. Clinicians can also determine whether adherence interventions can be successfully faded out or modified if they fail to address adherence problems. Moreover, adherence assessments are needed to evaluate the efficacy or effectiveness of medical treatments. If adequate adherence can be demonstrated, then the relative merits of various medical treatments can be more accurately determined in clinical and research contexts. Relatedly, Pai and Drotar (2010) proposed that researchers and clinicians consider taking a multifactorial measurement and analysis approach to examine "treatment adherence impact (TAI)"

or "the quantification of the effects of adherence behaviors on medical, psychological, or social outcomes" (page 384). It can be challenging, however, to determine TAI given the multifactorial nature of adherence behavior as well as the complexity, availability, and variability in measures (e.g., self-report, bioassay) and outcomes (e.g., healthcare utilization, family functioning) within and across illness populations (Pai & Drotar, 2010).

What to Assess?

Adherence is about behavior. Yet, which behaviors are selected for assessment depends on the type of illnesses and their associated treatments. Regimens for chronic health conditions require multifaceted classes of behaviors over an extended or indefinite period. Therefore, complex and long-term assessments of adherence may be necessary. Given these multicomponent regimens, which behaviors should be selected for assessment? Guidelines for target behavior selection from the general behavioral assessment literature offer some direction (Friman, 2009; Haynes et al., 2011; Kratochwill, 1985; Sharp et al., 2006; Sturmey, 1996; Youngstrom et al., 2020).

Guidelines for Selecting Target Regimen Behaviors

1. *Select them all (or at least baseline them all).* The rationale for selecting all relevant adherence behaviors for a particular treatment regimen is that there is currently no empirical basis for selecting one behavior over another in terms of its impact in achieving medical treatment goals. In theory, they are all considered equally important and need to be assessed.

   Although in theory all regimen behaviors should be given equal weight, this does not seem to be the case in clinical practice. Providers often emphasize certain regimen components over others (e.g., medications), possibly because they consider these components more critical to the health of their patients or because they have more expertise in and responsibility for certain components (e.g., medication management for physicians; nutritional intake for dietitians). Consequently, the choice of which regimen behaviors to select for measurement may ultimately depend on the provider's judgment.

   A variant of this approach would be to conduct baseline or screening assessments of all relevant regimen behaviors and then target for further assessment and intervention any low-rate behavior or one that fails to meet some minimum standard (e.g., <80% adherence). This approach would establish some empirical basis for selecting target behaviors; nevertheless, minimum standards of adherence (other than arbitrary ones) have not been determined for most pediatric medical regimens.

2. *Select behaviors that are identified as most problematic or disturbing to others.* With reference to medical adherence issues, these "others" typically are parents and providers. The patients themselves may not acknowledge problems with adherence. Interviewing parents or providers can reveal which behaviors need to be the focus of assessment (Sharp et al., 2006). Most likely, these will be behaviors perceived as critical to the patient's health and those that have been difficult to establish or maintain for a particular patient. This guideline would appear to be the most socially or ecologically valid, as it addresses the specific concerns of patients as well as relevant and important stakeholders in their lives.
3. *Select critical or "keystone" behaviors.* Originally, "keystone" behaviors were described as those behaviors that produce response generalization, i.e., altering the keystone behavior would produce desirable changes in other target behaviors (Sturmey, 1996). Some behaviors are chained together or may be part of the same functional class, such as insulin injections in relation to eating and exercise for youth with diabetes. Altering one behavioral requirement may produce changes in other related behaviors. However, adherence to different behavioral requirements (such as diet, exercise, and medication taking) within the same treatment regimen may not be highly correlated (e.g., Modi et al., 2006). Thus, altering one behavior may fail to produce changes in other adherence behaviors.

   The general concept of keystone or critical behaviors, however, might prove useful. Providers who treat patients with chronic diseases prescribe a myriad of treatment behaviors which to the best of their knowledge and experience are likely to improve the health and well-being of their patients. The key in selecting keystone behaviors is to identify which of these behaviors are critical to optimal medical treatment outcomes. These critical regimen behaviors can be gleaned from medical textbooks, surveys of relevant providers, and consensus treatment guidelines from governmental and medical associations that set empirically validated criteria for standard medical practice (Johnson, 1993). For example, consistency in taking inhaled corticosteroids in the treatment of moderate to severe asthma may be more critical for reducing morbidity and mortality for large numbers of patients than environmental control measures, such as minimizing indoor allergen exposure. Nonetheless, it is important to recognize that even if critical behaviors or treatment components can be identified for groups of patients with a particular disease, they may not be relevant to every patient.
4. *Select behaviors that are the easiest to change.* The rationale for this guideline is that behaviors that are more easily changed can create positive momentum to change other, more difficult behaviors. This approach maximizes the likelihood of patients experiencing initial success in managing their illness and should enhance their self-efficacy and confidence in addressing more challenging adherence concerns.

Who Should Be Assessed and Who Should Assess?

Adherence assessment in pediatrics is arguably more complex than in adult medicine, in that others (particularly parents) have varying degrees of responsibility in helping children carry out medical regimens (e.g., Netz et al., 2020). In fact, for younger children, parents are primarily or exclusively responsible for ensuring that treatments are consistently maintained. Therefore, the focus needs to be on assessing patient and parent regimen-related behaviors (Desai & Oppenheimer, 2011). For school-aged children, this might also involve assessing the behaviors of school nurses who supervise and/or sometimes administer treatments at school. As a result, like most clinical assessments, it may be necessary to employ a variety of informants or assessors to obtain a more complete picture of adherence concerns. Indeed, consistent with the Pediatric Self-management Model (Modi et al., 2011) and its different sources of influence on adherence, significant others can provide rich data on adherence because of their unique and regular contact with patients in their homes, schools, clinics, and the community.

In research contexts particularly, data obtained from participant observers or raters needs to meet rigorous criteria of validity, reliability, and accuracy (Johnston et al., 2019). This requires proper training and quality controls, regardless of whether the observer is a researcher or lay person. For example, in a series of clinical studies on improving regimen adherence in pediatric rheumatic diseases, parents were trained to conduct observations or pill counts and subsequently demonstrated acceptable levels of agreement with independent observers (Pieper et al., 1989; Rapoff et al., 1984, 1988a, b).

How to Assess Adherence?

A variety of strategies exist for assessing adherence, including biological assays, electronic monitors, pharmacy refill data, pill counts, observations, provider estimates, and patient/parental reports (e.g., Al-Hassany et al., 2019; Quittner et al., 2000). Adherence measures can be classified as subjective (e.g., self-report) vs. objective (e.g., pill count) or direct (e.g., metabolite concentration) vs. indirect (e.g., electronic monitoring) (Lam & Fresco, 2015). Each of these strategies has associated assumptions, assets, and liabilities, which are briefly summarized in Table 5.1. Some liabilities are common to all these measures and will be discussed later in this chapter. Also, some of these strategies are only applicable to certain types of regimens (e.g., some medications cannot be measured by assays; not all regimen components can be assessed via electronic monitoring). Several recent reviews provide detailed discussion of these methods as well as their relative strengths and weaknesses and provide recommendations for researchers and clinicians (e.g., Al-Hassany et al., 2019).

Table 5.1 Assumptions, advantages, and disadvantages of adherence measures

Measure	Assumptions	Advantages	Disadvantages
Biological assays	Assay is reliable and valid Recent patient adherence is reflective of long-term adherence	Objectively verifies drug ingestion Accurate and direct measure Can inform necessary adjustments to drug dosing Quantifiable	Results can vary as a function of pharmacokinetic factors (e.g., intra- and inter-patient metabolism) Available only for certain medications Provides data on short-term medication adherence and may be impacted by "white coat adherence" Static measure May be invasive Delay between testing and results Expensive
Electronic monitors	Each recorded dose represents medication consumed Device is activated only once per dose No device actuation means no medication consumptions Multiple actuations represent device error or improper use (e.g., "dumping") Novelty or stimulus control aspect of the device will wear off with time	Objective and highly accurate Provides precise and relevant data (e.g., dosing, dosing interval) Yields real-time continuous data, over long periods, which can provide insight into patterns of behavior Typically, non-invasive Helps identify drug reactions (e.g., dizziness with overdosing)	Usually does not measure consumption Can lead to reactivity Potential equipment problems can result in missing data May be challenging for complicated medication regimens May require patients to change typical routines (e.g., use pill bottle instead of pill organizer), which can change adherence behavior Often requires software, equipment maintenance, and technical expertise Costly
Pharmacy refill measures	Patient has not stockpiled medications or received samples Patient is not using other family members' medication Pharmacy provides accurate data Prescription changes have been noted in calculations	Easy to use Lower reactivity because patient is not aware of monitoring Particularly specific in identifying nonadherent patients Non-invasive Inexpensive	Overestimates adherence Does not measure consumption Calculations can become complex when considering changes in prescriptions, multiple pharmacies, and hospitalizations

(continued)

Table 5.1 (continued)

Measure	Assumptions	Advantages	Disadvantages
Pill counts	Results of pills prescribed minus pills returned equals the number of pills consumed No pills were missing for other reasons (e.g., discarded, lost) Pills returned were accurately counted Patient will provide pill container at time of study or clinic visit	Simple and feasible Widely accessible Non-invasive Inexpensive Can be used to validate provider or patient estimates of adherence	Relies on patients to return unused medications Overestimates adherence Does not measure consumption
Observation	Behavioral sample is representative of typical behavior Coding procedures and results are reliable and valid	Direct measure of non-medication regimens (e.g., insulin injection skills) Allows for repeated measurements Necessary for a functional assessment	Obtrusive and reactive Oftentimes clinically impractical Difficult to obtain representative samples of behavior
Provider estimate	Provider is unbiased Provider has adequate and accurate information on which to base an estimate	Feasible/easy to use More accurate than global patient reports More sensitive in identifying adherent patients Non-invasive Inexpensive	Overestimates adherence Generally inaccurate, regardless of provider training or experience Estimates are global or non-specific
Self-report (patient and caregiver)	Informant has necessary cognitive, reading, and memory skills Negative consequences for reporting nonadherence do not exist Questionnaire/scale score(s) are reliable and valid Scale is clear in content and has appropriate response options Scale is culturally sensitive Social desirability is minimized or assessed in the form of a validity scale	Easy to use and readily available Can be used for behaviors (e.g., dietary intake) not amenable to other assessment approaches Validation is possible More accurate if patient is asked in nonjudgmental fashion Patient has continuous access to own behavior Particularly sensitive for nonadherence Non-invasive Inexpensive	Overestimates adherence Patient is aware that adherence is being measured Subjective, with results potentially influenced by reporting bias (e.g., "faking good") and recall error Caregiver may not have adequate access to patient behavior (e.g., for adolescents) Not feasible for younger children to self-report

References: Anghel et al. (2019), Lehmann et al. (2014), Park et al. (2015) and Williams et al. (2013)

Therapeutic Drug Monitoring

Description

Biological assays can be used for therapeutic drug monitoring (Al-Hassany et al., 2019) by measuring drug levels, metabolic products of drugs, or markers (pharmacologically inert substances or low-dose medications) added to target drugs in bodily fluids, such as serum or plasma, urine, and saliva (Al-Hassany et al., 2019), and in hair (e.g., Olds et al., 2015). Interpreting assays requires some basic knowledge of clinical pharmacokinetics, which is concerned with the absorption, distribution, and elimination of drugs in the body (for general and relatively non-technical overviews, see Benet et al., 1990; Beringer, 2018; Johanson, 1992).

Absorption of drugs depends initially on the dose administered and route of administration. Drugs can be delivered orally, parenterally (intravenous, intramuscular, or subcutaneous), by inhalation into the lungs, transdermally (skin patches), and via mucosal routes (the nose, mouth, or rectum). Some routes (e.g., intravenous) result in more immediate onset of action than other routes (e.g., oral). There are important concepts to consider when interpreting assays. The *bioavailability* of a drug is that percentage or fraction of the administered dose which enters the patients' systemic circulation (Beringer, 2018). Several factors can affect bioavailability of a drug, including its intrinsic dissolution and absorption properties, how it is administered, its form (tablet or capsule), the stability of its active ingredient in the gastrointestinal tract, and the extent of drug metabolism before reaching the circulatory system. The rate of elimination is directly related to plasma drug concentrations or the *half-life* of a drug, which is the time required for the total amount of a drug in the body to decrease by one-half (Beringer, 2018). For most drugs in clinical situations, it can be assumed that the entire drug has been effectively eliminated after three to four half-lives (Beringer, 2018).

Advantages

Therapeutic drug monitoring confers several advantages. Assays yield quantifiable results; they are clinically useful for determining subtherapeutic, therapeutic, and toxic levels of drugs; and they provide information on dose-response relationships (Rand & Wise, 1994). By example, research on adherence and therapeutic management of HIV-infected children has incorporated drug assays (e.g., Van Rossum et al., 2002). Also, therapeutic drug monitoring is completely objective, void of potential bias. Most importantly, assays confirm that drugs have been ingested.

Disadvantages

Assays have some serious limitations. They measure adherence over relatively short time intervals and thus fail to provide information about consistency in medication adherence over extended periods of time. Most assays reflect medication ingestion that has occurred (at best) no further back than five half-lives (Rudd, 1993). Indeed, the pharmacokinetic properties of some medications can yield typical therapeutic levels of drug concentration (or active metabolite) in as few as one or two doses; thus, patients who take their medication a day or so before their clinical visit can create a false impression of good adherence. Adherence tends to be higher before and after clinical visits because these visits serve as a reminder or prompt, and then adherence declines in the interim. This pattern is known as "white coat adherence," a term coined by Feinstein (1990). Consequently, "spot checks" of drug levels may not accurately reflect long-term "steady-state" drug serum concentration.

Assays also can be expensive and invasive, which makes them less feasible for routine use in pediatric settings (Al-Hassany et al., 2019). Chronically ill children may not want another, and from their perspective, unnecessary painful procedure like having their blood drawn. Even collecting scalp hair samples to analyze medication levels proved challenging in a study on antiretroviral therapy adherence in youth from rural Uganda (Olds et al., 2015). When assays are obtained in relation to dosing is also a complicating factor. Samples for assays are usually drawn just before the next medication dose (at trough levels), requiring knowledge of when the last dose was taken, which in turn often depends on the accuracy of patient report (Backes & Schentag, 1991).

Finally, pharmacokinetic variations in the way drugs are absorbed, metabolized, and excreted can account for variability in drug levels unrelated to or in addition to adherence. Such examples of factors that can impact pharmacokinetics include the route of drug administration or type of preparation (e.g., enteric coated vs. uncoated), contents of the stomach, drug interactions, age, gender, puberty status, body fat/muscle mass, and disease states, particularly compromised liver or renal functioning (Backes & Schentag, 1991; Beringer, 2018; Johanson, 1992). This is further complicated by the relative paucity of data on the relation between pharmacokinetics and drug treatment effects in pediatrics, as compared to adult medicine (Batchelor & Marriott, 2015), although developmental pharmacology has been a recently growing field (Van den Anker et al., 2018).

Electronic Monitors

Description

Technological advances in microprocessors have led to the development of electronic adherence monitoring devices (EAMDs) (Al-Hassany et al., 2019; Riekert & Rand, 2002; Wu & Hommel, 2014; Wysocki, 2015), which often are referred to as

the "gold standard" for adherence measurement (e.g., Cramer, 1995). EAMDs are now available to record and store information on the date and time of many adherence and health behaviors, including (a) removing tablet or liquid medication from standard vials (e.g., Alili et al., 2016; Greenley et al., 2015); (b) removing pills from blister packages (e.g., De Bleser et al., 2010); (c) using topical medication (e.g., Tusa et al., 2006); (d) opening an electronic pillbox (e.g., Harry et al., 2020; Ingerski et al., 2011); (e) actuating a metered-dose inhaler (e.g., Lee et al., 2021); (f) utilizing a nebulizer (e.g., Chen et al., 2020); (g) using a high-frequency chest wall compression vest (for airway clearance therapy) (e.g., Benoit et al., 2020; Mikesell et al., 2017; Oates et al., 2015); (h) obtaining blood glucose test results (e.g., Marks & Wolfsdorf, 2020); (i) managing an insulin pump (e.g., Patton et al., 2017); (j) noting health behaviors or symptoms (e.g., pain) via electronic momentary assessment (EMA) (Van Diest et al., 2016); and (k) documenting physical activity and/or sleep via accelerometer (e.g., Meredith-Jones et al., 2019; Michaliszyn et al., 2018). Data storage and transmission capacity varies across monitors. For instance, real-time usage data can be stored on a device for up to several months and then later downloaded into data files for analysis, or real-time data can be transmitted remotely (i.e., via cellular connectivity or Bluetooth connection) to HIPAA-secure cloud-based storage (McGrady et al., 2018; McGrady & Ramsey, 2020).

This is an exciting area of adherence measurement that becomes broader and more sophisticated with time. A task force review of evidence-based assessments in pediatric psychology concluded that electronic monitors were "well-established" measures of adherence (Quittner et al., 2008). Recent reviews of various electronic monitoring devices for adherence assessment provide a wealth of detailed information and guidance in using these tools (see Chan et al., 2015; Ingerski et al., 2011; Park et al., 2015; Wu & Hommel, 2014).

One such device for measuring removal of pills is the commonly used Medication Event Monitoring System (MEMS®) Cap available from the AARDEX Group (https://www.aardexgroup.com). The hardware consists of a MEMS® Cap with self-enclosed electronic circuitry that fits on a standard pill vial. It stores up to 4000 dose events and can be used daily for up to 3 years without recharging or connecting to a communication network. It has several other key features, including optional LCD display and child resistance functionality. Data are transferred wirelessly; however, these data also are stored on the device safely for years after the device loses battery power. AARDEX also created technology to electronically monitor adherence to pills in a blister or carton packaging, cream medication, and injectable medications.

Figure 5.1 shows a typical printout from an earlier version of the MEMS® for a child with juvenile rheumatoid arthritis (JRA) who participated in one of our studies on improving adherence to nonsteroidal anti-inflammatory medications (NSAIDS). This patient was prescribed diclofenac (a NSAID) on a twice daily schedule, and the half-life of the drug was set at 14 h, in consultation with the treating rheumatologist. The top portion of Fig. 5.1 shows the month (mm), day (dd), year (yy), hour (hh), minutes (mm), and seconds (ss) the cap was removed and the days, hours, and minutes that elapsed between openings. The bottom portion shows the calendar plot or

Physician:	Lindsley		
Medication:	Voltaren		
Patient Name:	Blake		
Prescribed Regimen:	BID		
Medical Record Number:	004		
Drug Duration Action:	14 h		
Observation Period:	Start:	10/10/92	00:01:00
	Stop:	10/16/92	23:59:00
Total Recorded Events:	10		
Events Listed for Time Zone:	Central		

Dose Time (Cap Removed) mm/dd/yy	Dose Interval (Elapsed Time) hh:mm:ss	dd:hh:mm	Notes
10/10/92	07:22:40	0:13:58	
10/10/92	17:10:24	0:09:47	
10/11/92	20:50:40	1:03:40	E
10/12/92	05:34:56	0:08:44	
10/12/92	17:13:36	0:11:38	
10/13/92	05:57:20	0:12:43	
10/14/92	05:41:52	0:23:44	E
10/14/92	20:10:08	0:14:28	E
10/15/92	21:14:40	1:01:04	E
10/16/92	16:04:48	0:18:50	E

Notes Legend:
E - Dose Interval EXCEEDS Drug Duration of Action
F - Dose Time FILTERED due to less than 15 minutes separation from previous Dose Time
I - Dose Time INSERTED at end of Cap Open Length greater than 2 hours

Date	Mon	Tue	Wed	Thur	Fri	Sat	Sun
				–	–	–	–
Oct 5	–	–	–	–	–	2	1
Oct 12	2	1	2	1	1	–	–
Oct 19	–	–	–	–	–	–	–
Oct 26	–	–	–	–	–	–	–

Therapeutic Coverage = 76.3%

Fig. 5.1 Example of data from an electronic monitor (MEMS)

the number of times the cap was removed each day. Several parameters can be obtained from the MEMS® (using hypothetical data from Fig. 4.2): number and percent of doses removed (10 of 14; 71%); number and percent of optimal daily dosings (3 of 7 days where two doses were taken; 43%); an estimate of therapeutic coverage over the 7-day time course based on the half-life (76.3%); and the average and range of interdose intervals (based on 10 doses taken over 7 days, in this example, yields a mean interdose interval of 16.66 h and a range of 8.73–27.67 h, which can be compared to the ideal interval of 14 h). As can be seen, different results are obtained depending on the parameter used to reflect adherence. For example, using

"percent of doses removed" (which is analogous to pill counts) yields a 71% adherence rate, in contrast to using "percent of optimal daily dosings," which yields a much lower adherence rate of 43%. Although this figure provides an illustration of data obtained from EAMDs, it is important to note that contemporary EAMDs (including current version of MEMS® Cap) typically transmit their data electronically in the form of a database.

Advantages

EAMDs provide a continuous and long-term measure of medication adherence in real time, which is not available with any other measure. Monitors can reveal a spectrum of adherence problems, including (1) underdosing (the most common dosing error); (2) overdosing (which can contribute to toxic effects); (3) delayed dosing (exceeding recommended dosing intervals, which can reduce therapeutic coverage); (4) drug "holidays" (omitting doses for several days in succession without provider authorization); and (5) "white coat adherence" or giving the appearance of adequate adherence by dumping medications or taking medications consistently several days before clinic visits (Riekert & Rand, 2002; Urquhart, 1994). Moreover, patterns of adherence (e.g., sporadic, partial, and consistent) can be identified from electronic monitoring data (Lam & Fresco, 2015) regardless of who is responsible for administering the medication (Riekert & Rand, 2002). In one of our intervention studies for pediatric asthma (Duncan et al., 2013), electronic monitoring of inhaler use revealed that a young teen misunderstood the use of her spacer. She was prescribed two puffs per dose; however, electronic monitoring data revealed that she rapidly discharged two puffs into her spacer and then inhaled. As a result, she was not receiving a full dose even though she thought that she was being adherent. Given the detailed information yielded regarding patterns of adherence, these devices are quite useful and valid in measuring the effects of adherence-promotion interventions (Riekert & Rand, 2002; Wu & Hommel, 2014). Moreover, EAMD data can be a useful tool for clinicians to engage patients and families in discussions about their medication and disease beliefs, barriers, and adherence behaviors (Chan et al., 2015), especially when healthcare providers obtain informed consent and use an empathic approach to the discussion (Lehmann et al., 2014). Clinicians also can provide targeted feedback and counseling to patients and their families during brief clinic visits or by telephone (Cramer, 1995; Spaulding et al., 2012).

The close monitoring conferred by electronic devices can also help distinguish probable from improbable drug reactions or side effects (Rudd, 1993). For example, a drug reaction reported by a patient (such as dizziness) can be correlated in real time by an electronic monitor with inappropriate medication dosing, such as shortened intervals between doses or taking extra doses. Conversely, improbable drug reactions can be revealed if the patient reports a side effect when the monitor indicates low adherence (Rudd, 1993).

EAMDs can also help identify "actual" drug resistance (low efficacy despite high adherence to an adequate dosing regimen) versus "pseudo" resistance due to delayed or underdosing (Rudd, 1993). Similarly, EAMDs are useful in assessing

dose-response relationships (Riekert & Rand, 2002). Combined with plasma assays, monitors can also help identify within-patient variation in plasma concentrations, as they provide information about the timing of drug administration (Rohan et al., 2017).

Disadvantages

When referring to the capability of electronic monitors, it is more precise to say that they measure "presumptive" dosing. The presupposition here is that patients ingest what they dispense. Thus, the major drawback of most electronic monitors is that they generally do not confirm ingestion or proper inhalation of medications and may overestimate actual adherence. A few devices (e.g., insulin pump), however, do measure actual consumption or use (Wu & Hommel, 2014). Assays, when feasible, are needed to help confirm ingestion for those that do not (e.g., Cain et al., 2020). Although purposeful falsification of adherence is possible, most devices provide rather detailed time-specific information for each dose, and thus it is easy to detect purposeful "dumping" (i.e., patients rapidly and repeatedly discharging/activating the device prior to an appointment). Although the degree of effort needed to falsify adherence would seem substantial, it is possible that patients may do so (Lam & Fresco, 2015). Moreover, for pill monitors, patients may intend to ingest the medication after removing it, but perhaps forget, or decide to take it later but then forget (Cain et al., 2020). Similarly, monitors could also underestimate adherence if patients take out several doses at once to carry with them when they are away from home or to load pill reminder boxes. Finally, a device might be accidentally actuated, leading to overestimation of adherence (Lam & Fresco, 2015).

EAMDs are complex to use. McGrady and Ramsey (2020) provide a detailed step-by-step guide for researchers on the use of EAMDs, beginning with defining adherence and selecting an EAMD through conducting EAMD pre-testing and educating research staff, healthcare providers, and patients to transforming data and computing adherence. One critical step is for researchers and clinicians to choose an EAMD based on its features (which vary across devices) which will address the research questions as well as the clinical needs of the patient or participant (McGrady et al., 2018). Example features to consider may be whether the device comes with integrated reminders, whether patients can access their adherence data or not, and whether cellular connectivity is required (in case the participant/patient may not have it). Such technical complexity also may not be practical for routine use by care teams in clinical settings. Nevertheless, medical care teams have implemented routine download from some EAMDs, like blood glucose monitors and insulin pumps, during clinic encounters (Quittner et al., 2008). Although their practical guide for clinicians specifically targets the use of electronic monitoring to measure inhaler adherence, Chan et al. (2015) provide an excellent discussion of various issues in choosing, pre-testing, implementing, and interpreting data from EAMDs in the context of patient care.

The costs of EAMDs usually are quite expensive, but prices often are not publicly available and vary across devices (McGrady et al., 2018). Though it is

anticipated that insurers will eventually cover the costs of these devices with emerging evidence regarding their cost-effectiveness and increased demand for e-health solutions, EAMDs currently are not covered (Chan et al., 2015). Therefore, the clinical utility or feasibility of implementing EAMDs in routine practice is limited by the relatively high costs for the rental or purchasing of monitors, communicators, and proprietary software (Lam & Fresco, 2015; Lehmann et al., 2014). Indeed, a survey of pediatric diabetes healthcare professionals revealed that a lack of financial or insurance coverage for costly, yet effective technologies (i.e., continuous blood glucose monitors, insulin pump) had the greatest impact on limiting the likelihood that they would recommend them to certain patients (Dos Santos et al., 2021). High costs of EAMDs also limit their routine use in resource-limited settings (e.g., developing world), thereby suggesting the importance of finding less costly electronic alternatives (Müller et al., 2011).

Electronic monitors, like any mechanical device, also can malfunction (Ingerski et al., 2011; Riekert & Rand, 2002). They may record events that did not occur, fail to record events that did occur, simply stop working because batteries expired, or malfunction for other reasons, including patient intentional and unintentional behavior. For example, in one of our studies, a child's inhaler was accidentally crushed when the parent ran over it with their car, while another was broken when doing laundry in the family's washing machine. However, most of these mechanical failures can be avoided with quality control processes (e.g., extensive data-checking protocols) (e.g., Patel et al., 2013). Sometimes failures occur when devices are used in ways not designed by the manufacturers. For example, in a study monitoring prophylactic penicillin adherence among a sample of children with sickle cell disease, the investigators used liquid medications for some children, and it penetrated the device resulting in loss of data (Berkovitch et al., 1998).

There are also practical problems regarding the convenience and portability of the monitors. The monitors are somewhat oversized and heavier relative to standard vial caps, which may make them cumbersome to transport outside the home (Lam & Fresco, 2015). Also, to download data from some monitors, they may need to be retrieved from patients, and in some cases, the monitors can be lost. Ethical objections can also be made to using electronic monitoring (Campbell et al., 2016; Riekert & Rand, 2002), particularly if patients are not informed about the capabilities of monitoring devices; thus, it is important to consider ethical principles as well as state and federal guidelines for protecting children's privacy (Wu & Hommel, 2014). A major obstacle in the past has been that patients are not willing to use electronic monitors for pills because they use a pillbox to help them be organized and remind them to take medications (Shellmer & Zelikovsky, 2007). Currently, though, electronic pillboxes exist with multiple compartments like a pill box organizer (e.g., Med-eMonitor→ by InforMedix in Rockville, MD; MedSignals®, San Antonio, TX). These devices also can come with additional features, such as audible beeps or chimes to prompt taking medication, display screens, and text messages on the screen. Electronic pillbox devices will be very helpful for researchers studying diseases that require multiple daily medications.

Lastly, white coat adherence needs to be considered when obtaining and interpreting adherence data, including electronic monitoring (Driscoll et al., 2016; Modi et al., 2012). For example, care teams for youth with type 1 diabetes often download monitoring data (e.g., insulin pump) for the 1–2-week period prior to the clinic visit. With white coat adherence, by doing so, the patient's actual adherence likely is overestimated. Thus, it is important to capture a larger monitoring period to obtain truly representative data of the patient's adherence.

Pharmacy Refill Measures

Description

Pharmacy data regarding pick-up or refill rates for medication is an objective, but indirect measure of adherence. It is assumed that adherence can only happen if medication is available via refills; thus, pharmacy refill data serves as a proxy measure for potential adherence and can flag patients who may need a more in-depth assessment (Wu et al., 2018). These data also can be used as a collateral measure for commonly used self-report (Yildirim et al., 2019). Clinic staff (e.g., nurses, pharmacists) obtain these data from pharmacies directly or from pharmacy databases. When using such data, adherence can be measured as a *Medication Possession Ratio* (MPR) or as *Proportion of Days Covered* (PDC), for example. MPR is the percentage of day supply obtained (i.e., refill) over the period of the refill interval (Anghel et al., 2019). In contrast, PDC is "the number of days that a (particular) medicine has been dispensed to a patient in a defined period, divided by the total number of days in that time period" (Al-Hassany et al., 2019; p. 1185). See Lam and Fresco (2015) for a description of other refill adherence variables.

A systematic review of refill adherence measures in pediatric patients (Chua et al., 2020) found that most studies were conducted in high-income countries, with the most common condition being asthma. However, pharmacy refill data has been used successfully in research with other populations, including HIV (Yildirim et al., 2019) and leukemia (Wu et al., 2018), for example. Pharmacy refill adherence has been associated with improved economic (e.g., reduced healthcare utilization) and clinical outcomes (Chua et al., 2020).

Advantages

Pharmacy refill measures are objective and inexpensive (Rickles & Svarstad, 2007; Yildirim et al., 2019). They offer the advantage of measuring adherence over longer periods and across multiple medications, which has the potential to capture natural fluctuations in adherence over time (Anghel et al., 2019; Yildirim et al., 2019). This type of adherence measure also is non-invasive; that is, it does not require a patient to attend clinic (Yildirim et al., 2019), and the patient likely is less aware on a

day-to-day basis of being monitored (Anghel et al., 2019). Moreover, some data are stored in large databases [e.g., Medical Outcomes Research for Effectiveness and Economics (MORE) registry; Wu et al., 2018], which makes it more readily accessible. Finally, pharmacy refill measures do not require the patient or family to have sufficient reading or cognitive skills, like self-report measures do (Yildirim et al., 2019).

Disadvantages

In contrast to these advantages, there are some key limitations to consider when using pharmacy refill data as an adherence measure. First and most obvious, refilling a medication does not necessarily translate to medication-taking behavior (Al-Hassany et al., 2019; Anghel et al., 2019). Patients may stockpile or share medications with family members (Genn et al., 2019). For example, patients also may have an electronic prescription service that automatically refills their medication. Therefore, results may overestimate or underestimate a patient's nonadherence. Also, data collection and coding procedures can be complex and are not standardized (Yildirim et al., 2019), leading to different estimates of adherence rates. Thus, methodological transparency is important when using this type of assessment in research (Al-Hassany et al., 2019). Moreover, adjustments in physician dosing may not be reflected in the data obtained (Al-Hassany et al., 2019). Lastly, pharmacy refill measures do not provide information on barriers or variables related to nonadherence (Anghel et al., 2019) or patterns of nonadherence.

Pill Counts

Description

Pill counts have a long tradition in adherence assessment as indirect, objective measures and are relatively straightforward. For example, like Fig. 5.1, consider that someone has been prescribed to take two pills a day. They have 14 pills in their bottle at Time 1. When they return to clinic 2 weeks later (Time 2), they have four pills remaining. Adherence is calculated as [# of pills removed ÷ # of pills prescribed × 100], which in this example would be $10 \div 14 \times 100 = 71\%$.

Liquid medications can be similarly "counted" by measuring the volumes of medications at times 1 and 2. Another variation for inhaled medications is to weigh canisters at different time points (e.g., Bender et al., 2000), though this method has been rarely used with the advance of routine integrated dose monitors on inhalers (which can function like a pill count) as well as more recent technological innovation with electronic monitoring. By example, Reznik and Ozuah (2012) measured inhaled corticosteroid adherence in inner city, youth of color with persistent asthma using parent report, and the integrated dose monitor. Parent report of adherence was significantly higher than the more objective dose counter.

Advantages

Pill counts are uncomplicated, low-cost (if not requiring a home visit), and relatively feasible for use in clinical settings (Lam & Fresco, 2015). Their feasibility has been enhanced by obtaining pill counts from patients or family members by phone (e.g., Raymond et al., 2017). Because pill counts have been widely used in research, they can also be used to summarize and compare adherence rates across a variety of medication regimens and patient samples. Pill counts or measurements can also be used to validate other adherence assessment methods, such as patient, parent, or provider estimates.

Disadvantages

Pill counts, like electronic monitors and pharmacy refill data, cannot confirm ingestion. Most often, they overestimate adherence rates, which can occur if patients "dump" medications. Medications may also be shared with other family members. Pill counts reveal very little about variations in nonadherence, such as overdosing, underdosing, drug holidays, and the white coat effect. Sometimes, pill counts are not possible because patients do not bring medication containers to clinic visits, even when reminded by telephone calls prior to the visit. They also are not feasible to use when medication is prescribed on an as-needed (i.e., PRN) basis (Lam & Fresco, 2015). Furthermore, patients may dispense medications from more than one container or load them in pill reminder containers ahead of time, thus precluding an accurate count (Rudd, 1993).

Observation

Description

Direct observation of patient adherence is not commonplace in most pediatric psychology empirical studies (Wysocki, 2015), likely because most studies examine medication adherence, and other measures, such as assays, are firmly entrenched as the optimal way to assess medication ingestion. Nonetheless, observation measures, in the form of behavioral checklists, have been used to evaluate patient technique in performing skills necessary for adherence.

Behavioral checklists have been developed for assessing skills involved in insulin administration (Ortiz La Banca et al., 2022), factor replacement therapy (Sergis-Davenport & Varni, 1983), and inhaler technique (Naar-King et al., 2013; Sleath et al., 2011; Rodríguez-Martinez et al., 2017). These checklists need to be kept up to date with changes in medication delivery, as well as consistent across studies to lend results to comparison. Basheti et al. (2014) reviewed a wide range of checklists

available for powder inhaler technique and subsequently provided a recommended checklist for assessing skills in using turbohalers and diskus inhalers (see Table 2 in Basheti et al., 2014). National Jewish Hospital also offers on their website a series of videos and written instruction steps (which could be converted easily to a checklist) for proper use of each type of asthma medication device (see https://www.nationaljewish.org/conditions/medications/asthma-medications/devices). In addition, the CDC website offers videos demonstrating correct use of a variety of asthma inhalers (see https://www.cdc.gov/asthma/inhaler_video/default.htm). Sleath et al. (2011) found that only 8.1% of children (ages 8–16 years) correctly performed all the metered dose inhaler steps. Albeit a higher percentage, only 22% of youth performed all the diskus steps correctly. Similarly, when examining asthma medication device skills in high-risk African American adolescents (ages 12–16), Naar-King et al. (2013) found that only 5% of adolescents correctly displayed all skills in using their controller inhaler, while none of the adolescents demonstrated all rescue inhaler skills. Of course, observing and evaluating how patients execute these skills says nothing about how often or consistently they accurately perform them in their daily lives.

Some studies have utilized parent or sibling observations as a primary data source, with acceptable levels of agreement with independent observers (Lowe & Lutzker, 1979; Rapoff et al., 1984). Direct and unobtrusive observations in camp settings have also been used to measure dietary adherence (Wolanski et al., 1996) and to demonstrate concurrent validity of 24-h recall interviews (Reynolds et al., 1990).

Advantages

Unlike other strategies, observational measures are direct measures of regimen-related behaviors (Wysocki, 2015). They are automatically valid, in the sense that they measure what they intend to measure (Johnston et al., 2019). By directly measuring behavior, observational measures avoid subjective and potentially misleading judgments about behavior inherent in patient, family, and provider ratings of adherence. Observational measures also assess important dimensions of adherence behaviors, such as frequency (e.g., how often patients monitor blood glucose levels), duration (e.g., the amount of time patients' exercise), and how accurately the behavior was performed (e.g., correct steps to using a metered dose inhaler). Finally, by focusing on public behaviors, observational measures can also reveal contemporaneous controlling variables (antecedents and consequences) related to adherence that may be amenable to intervention (Youngstrom & Prinstein, 2020). Yet, if observational measures have so much to offer, why are they so infrequently used in medical adherence research and, even less so, in clinical practice?

Disadvantages

The major problem with observational measures is that clinicians have limited samples of behavior that may not reflect how patients typically behave in relation to prescribed regimens. Also, using observational measures can be labor-intensive, as they require extensive training, monitoring, and recalibration or retraining of observers (Youngstrom & Prinstein, 2020). An oft cited disadvantage of observational measures is their potential for reactivity (Wysocki, 2015). That is, when patients are being observed, they may behave in ways that may not be typical and usually in a socially desired direction (e.g., they may be more adherent). However, reactivity is a potential problem with all measures of adherence. Another type of reactivity is pertinent to those conducting observations of adherence. Specifically, when observers are being monitored, the quality of their observations may be higher than when they are not being monitored (Wildman & Erickson, 1977). Observer reactivity may be particularly critical when using participant observers, such as parents, who have a direct interest in what is being measured.

Another concern with observational measures for researchers is observer "drift" or variations in how paired observers record behavior across time. Over time, paired observers tend to develop a consensus about how behaviors are defined and recorded, which may substantially change or drift from the original coding definitions (Wildman & Erickson, 1977). Checking interobserver agreement between pairs of observers will not detect this problem because drift produces adequate agreement but with a corresponding decline in accuracy over time (Foster et al., 1988). Fortunately, there are many ways to minimize drift, including rotating pairs of observers, videotaping observation sessions and scoring them in random sequences, and retraining (Foster et al., 1988; Kazdin, 1977). There are a host of other observer, instrument, and subject variables to consider when conducting behavioral observations (see Bellack & Hersen, 1998; Kazdin, 1977; Youngstrom & Prinstein, 2020).

Provider Estimates

Description

Provider estimates generally involve global ratings by physicians or nurses of the degree to which their patients are adherent to a particular regimen. For example, in one study (Gudas et al., 1991), physicians were asked to rate adherence to medications, chest physiotherapy, and diet for children with cystic fibrosis using a five-point Likert-type scale, with the endpoints being 4 "almost always (95% of the time)" and 0 "rarely (5% or less of the time)." In another study involving adolescents with type 1 diabetes (Kichler et al., 2012), providers used information obtained from their clinical encounter and medical chart review to estimate each adolescent's average daily frequency for using their blood glucose meter. Thus, provider ratings can take various forms in research and clinical work.

Advantages

Provider estimates are fast, simple, and inexpensive, which makes them very feasible for use in clinical practice. There is some evidence that provider estimates are better than global estimates obtained from patients or family members (Rapoff & Christophersen, 1982).

Disadvantages

Provider estimates are not very accurate compared to other measures, such as assays (Rudd, 1993). Indeed, in the Kichler et al. (2012) study described above, provider rating of average daily blood glucose checks was not significantly related to glycemic control, unlike other measures employed in this research (e.g., electronic monitoring from blood glucose meter; self-report on questionnaire and in 24-h recall interview).

Furthermore, providers are imprecise in a specific way. Although they are generally accurate in identifying adherent patients, they often fail to recognize nonadherent patients. This is nicely illustrated in one study where pediatric providers (nurses and pediatricians) were asked to predict which of their patients would be adherent to an antibiotic regimen for otitis media (Finney et al., 1993). Providers were asked, "Do you think this family will administer most of the prescribed medication?" and their responses were dichotomized as "will adhere" or "will not adhere." The investigators gathered a pill count/liquid measurement in the patients' homes as an objective criterion for classifying patients as nonadherent (i.e., <80% of medicine removed). The *sensitivity* of provider predictions (the proportion of patients nonadherent by assay who were predicted to be nonadherent) was quite low (28%); the *specificity* of provider predictions (the proportion of patients identified as adherent by assay who also were predicted to be adherent by the provider) was perfect (100%); and the overall *accuracy* of provider predictions (proportion of all predictions, both positive and negative, that were correct) was moderate (65%). These results illustrate that overall accuracy does not capture the type of prediction errors made by providers. Most importantly, it shows that a fair number of patients who could benefit from interventions to improve adherence would not be identified by their providers.

The inaccuracy of predictions or clinical judgment should come as no surprise to behavioral scientists and clinicians. Clinical judgments can be biased in several ways (Groopman, 2007; Rock et al., 1987). Clinicians may hold on to or become "anchored" to their initial judgments even when faced with new and differing evidence (the "anchoring" bias). They may also base judgments on their inferred relation of certain factors with adherence, such as characteristics of the patient (e.g., cognitive abilities, health or disease status, perceived attention during clinical visit, accuracy of responses to provider questions) and family (e.g., socioeconomic status, strain or dysfunction, parental questions about treatment regimen). Moreover, clinicians may believe that judgment accuracy increases as they gain more clinical

experience (the "overconfidence" bias). Finally, there is the "correspondence" bias, which is the generalized tendency for people to attribute other's behavior (but not their own behavior) to unique dispositional determinants (e.g., "laziness," "lack of motivation"), while ignoring important situational determinants (see Gilbert & Malone, 1995, for an excellent review). All these biases have the potential of reducing the precision of clinical judgments and thus provider estimates of adherence.

Patient and Caregiver Reports

Description

Consistent with the emphasis on history taking in clinical practice, it is not surprising that patient and/or family reports are often used to assess adherence. Indeed, patient-reported outcomes (PROs) are the most used method for measuring adherence in both clinical and research settings. Reporting formats include *global ratings*, *questionnaires*, *structured interviews*, and *daily diaries*. There has been a proliferation of global and disease-specific patient and parent report adherence measures. Following PRISMA guidelines and applying Hunsley and Mash's (2018) criteria for evidence-based assessment across several psychometric domains (e.g., content validity, treatment sensitivity), Plevinsky et al. (2020) conducted a systematic review of patient-reported outcomes for pediatric adherence and self-management. This article is a valuable resource with its detailed results on 50 PROs across a range of pediatric conditions.

Global ratings, like provider estimates, require that patients or parents rate adherence over unspecified or varying (and sometimes lengthy) time intervals. For example, parents might be asked, "How often does your child miss taking their pills?" as a means of estimating overall adherence. Parents might also be asked to rate their child's adherence on a weekly basis using a Likert-type scale, with 1 being "very nonadherent" to 5 being "very adherent," nor youth can be asked to rate their adherence using a visual analog scale (e.g., Schaefer et al., 2019). In general, patients find it easier to rate general adherence than to state a specific number of doses they have missed (Garfield et al., 2011).

To enhance the veracity of parent and patient report, staff who ask for global ratings of adherence ideally should be different from care team members who deliver adherence support (Stirratt et al., 2015). Also, using a specific recall period that is long enough (e.g., past 30 days) to avoid ceiling effects, but not too long to lead to problems with recall, should strengthen the accuracy of self-report (Stirratt et al., 2015), for example, responses to a simple question asking parents and children whether they missed a dose of antiretroviral therapy medication since the previous visit was strongly associated with the development of virologic failure in a sample of children with HIV (Intasan et al., 2014). Finally, when asking for estimates or ratings of adherence, using a nonjudgmental stance and normalizing nonadherence when phrasing the question can help reduce social desirability in responding (Stirratt

et al., 2015). Taking this approach, an example in a patient with cystic fibrosis might sound like this: "Many patients tell me that they often forget to take their enzymes when they should. How many times in the past week would you say you forgot to take yours?" Unfortunately, providers may not realize that their approach to questioning encourages defensive or inaccurate disclosures, as in this example (said with a disapproving facial expression): "Mrs. Smith, Sam doesn't seem to be any better. Did you give her ALL the medicine I prescribed?" A more effective tactic (said in an empathic, but not patronizing manner) would be "Mrs. Smith, Sam doesn't seem to be feeling any better. This can happen for many reasons. Sometimes a different or stronger medicine is needed. Sometimes a child doesn't get enough of the medicine. Many parents have problems giving medicines to their children. In fact, I sometimes forget to give our son his medicine when he's sick. I wonder if you have had any problems giving Sam her medicine for one reason or another?" This conversational style would more likely elicit complete and accurate reports and lead to a dialogue about obstacles to adherence.

Over the past few decades, significant progress has been made in the development of *questionnaires* and *structured interviews* for assessing adherence in children, adolescents, and young adults. Using pediatric patients and/or their caregivers as informants, these self-report measures assess the child's adherence to regimens generically or specifically for a variety of health conditions (e.g., asthma, cystic fibrosis, diabetes, solid organ transplantation) (see Plevinsky et al., 2020, for a recent systematic and detailed review of evidence-based questionnaires and interviews and Al-Hassany et al., 2019, for a table of validated questionnaires and their specifications). These tools also can be helpful in assessing factors that directly impact adherence and thus may be important to target in interventions, such as barriers to adherence (e.g., Cushman et al., 2020) and child skills in completing regimen tasks (e.g., Ortiz La Banca et al., 2022). For example, children and caregivers can be interviewed with the Family Asthma Management System Scale (FAMSS), which assesses eight aspects of asthma management (e.g., symptom assessment, child response to exacerbations, medication adherence) using a family systems perspective (Klinnert et al., 1997) and has demonstrated reliability and validity (Celano et al., 2011; McQuaid et al., 2005). Questionnaires can be administered in person, over the telephone, or via a computer program.

Daily diaries require patients or parents to record specific adherence behaviors over varying lengths of time using standard forms or are obtained by phone interviews. These self-report diaries can however be unreliable if the patient does not return them or completes them fully just prior to their appointment (Lam & Fresco, 2015). Portable hand-held computers (i.e., ecological momentary assessment) can enhance the veracity of these data by allowing patients to record adherence events (e.g., Van Diest et al., 2016), motivation toward adherence (e.g., Psihogios et al., 2021), and other clinically relevant parameters, like pain levels (e.g., Palermo et al., 2004), in real time. These data are captured as they occur or when prompted (Plevinsky et al., 2020; Wu & Hommel, 2014; see Heron et al., 2017, for recommendations in using EMA with youth).

An excellent example of a daily dairy method is the extension and validation of the 24-h recall interview (a standard dietary assessment technique), which Suzanne Bennett Johnson and colleagues have refined to investigate adherence to diabetes regimens (see Johnson, 1995 for a review). This method involves assessing and quantifying adherence to 13 standard components of a diabetes regimen. Interviews are conducted separately with patients and parents over the phone. They report all the day's events in temporal sequence, from the time the child awakens in the morning until going to bed, but the interviewer records only diabetes-related activities. To ensure representativeness, three separate interviews are conducted over a 2-week interval, on 2 weekdays and 1 weekend day. Interviews are restricted to the previous 24 h to minimize recall errors. Each interview takes about 20 minutes to complete (Freund et al., 1991). Scores are obtained for each of the 13 adherence measures; higher scores indicate relative nonadherence, and scores close to zero indicating relative adherence. For example, *glucose testing frequency* is calculated based on an ideal frequency of four times per day, for a total possible frequency of 12 over the 3 interview days. The number of glucose tests reported is divided by the ideal and multiplied by 100 (e.g., $4 \div 12 \times 100 = 33$). This product is then subtracted from 100 (e.g., $100 - 33 = 67$), so that high scores indicate few glucose tests and low scores indicate frequent tests (e.g., a score of 67 indicates the patient reported four glucose tests being conducted over 3 days). This measure has also been adapted for assessing adherence to regimens for HIV (Marhefka et al., 2006; Naar-King et al., 2005), celiac disease (e.g., Mager et al., 2018; Dowhaniuk et al., 2020), enuresis (Baeyens et al., 2009), and cystic fibrosis (Ricker et al., 1998). Strong stability coefficients, good parent-child agreement, and associations between adherence and glycemic control in diabetes and viral load in HIV have been reported for the 24-h recall interview (Quittner et al., 2008).

Another cued-recall daily diary method is the Daily Phone Diary (DPD) which was originally developed to assess daily activities of mothers and children with cystic fibrosis (Quittner & Opipari, 1994). Like the 24-h recall interview, parents and children are asked to reconstruct their previous day, and each activity is recorded by an interviewer on a computer screen with clock hands that rotate through a 24-h clock, a set of activities, companions, and a rating scale for mood. Interviews are conducted on multiple (2 or 3) days with the primary caretaker and adolescent. The DPD has been adapted to assess adherence to regimens for asthma, cystic fibrosis, muscular dystrophy, and HIV (e.g., Grossoehme et al., 2016; Modi & Quittner, 2006; Naar-King et al., 2014; Pascoe et al., 2017; Wiener et al., 2004). The DPD has yielded high levels of interrater reliability and strong to modest convergence with self-report and electronic monitoring of adherence and has been negatively correlated with viral load in HIV (Quittner et al., 2008). Daily diaries have also been used to simply ask youth to record whether they took medication (e.g., Van Diest et al., 2016).

Advantages

In general, patient or proxy (such as parents) reports are relatively simple, convenient, inexpensive, and highly feasible in clinical practice (Al-Hassany et al., 2019; Lam & Fresco, 2015). They also address the problem of accessibility to patient behaviors over time and in ecologically relevant contexts (such as home and community). Thus, they are frequently used, particularly in the form of global ratings or responses to clinician questions. As noted earlier, how patients or family members are questioned about adherence may be critical in the quality of data obtained by reports. Questions that are nonjudgmental, specific, and time limited are likely to yield more accurate information about adherence, as they are less apt to generate evasive and defensive reactions and are less subject to recall errors or misunderstanding (Kaplan & Simon, 1990; Klinnert et al., 1997; Rand, 2000; Stirratt et al., 2015).

Diary and structured interviews offer additional advantages of providing detailed and comprehensive information on adherence patterns, the types of problems or obstacles encountered, and the temporal relation of adherence behaviors to disease symptoms or outcomes. They can also be integrated into disease management programs which facilitate patient and family involvement in healthcare (Rand & Wise, 1994). Structured interviews may be the best of the patient or family report measures because they are less labor-intensive for patients and families, as compared to completing daily diary forms, yet still comprehensive. Indeed, asking patients and families to reliably complete daily diary cards on adherence is demanding, and logically those individuals who are challenged to remember their medication will struggle to complete a diary card each day. Consequently, it is common that return rates for daily diary cards decline significantly over time, even within a few weeks (e.g., Butz et al., 2005).

Evidence-based assessments of adherence measures have been reported using the criteria of "promising" (the measure is presented in at least one peer-reviewed article and is sufficiently described and available from the authors, and some vague or moderate statistics are presented on reliability and validity), "approaching well-established" (the measure is presented in at least two peer-reviewed articles and is sufficiently described and available from the authors, and some vague or moderate statistics are presented on reliability and validity), and "well-established" (the measure is presented in at least two peer-reviewed articles by different investigators and is sufficiently described and available from the authors, and statistics are presented indicating good validity and reliability in at least one peer-reviewed article) (Cohen et al., 2008). The psychometric properties of the 24-h recall interview and DPD are strong and have led to the conclusion that they are "well-established" instruments for assessing adherence (Quittner et al., 2008). However, more work needs to be done to establish the psychometric properties of structured interviews, as they range from "promising" to "well-established" instruments for assessing adherence (Quittner et al., 2008).

Disadvantages

Patient or family reports tend to overestimate adherence, most notably, by minimizing doses that have been missed (Al-Hassany et al., 2019). This is likely to be truer for global estimates versus diaries or structured interviews. Global estimates can tax the person's memory for adherence events and lead to errors in self-reports (Tourangeau, 2000). Unless they are actively rehearsed, memories fade within a short period of time. The "outer limits" of recall for events are generally less than 2 weeks (Rudd, 1993). Also, people tend to remember unique events (ones that are stimulating or emotionally laden) and generally remember events in chronological order for up to 10 days and thereafter, in relation to other major events, such as holidays and birthdays. Diary methods can obviate the need for remembering events if patients complete them close in time to the behavior being monitored. Though about 50% of patients keep complete diary records (Johnson, 1993), one cannot ascertain when and where they were completed.

Report measures are also sensitive to demand or social desirability effects (Al-Hassany et al., 2019). That is, patients or families may tell providers what they want to hear, which could lead to overestimates or outright deception about adherence (Johnson, 1993). In this way the patient or family "protects" their relationship with the provider or at least avoids their disapproval. Indeed, few self-report questionnaires can distinguish intentional or volitional nonadherence from nonintentional nonadherence (Garfield et al., 2011).

Proxy informants (such as parents) do not always have access to relevant behaviors, especially during adolescence. For example, only about 50% of diabetes-related activities are observed by parents (Johnson, 1995). Obviously, parents can only report on that which they see. However, parents and patients can be interviewed separately to obtain more representative samples of adherence behaviors. Further work is needed to corroborate diary and structured interview methods by more direct measures such as observations, assays, or electronic monitoring.

Comparative Performance of Adherence Measures

Numerous studies have compared different approaches to measuring pediatric adherence. The "classic" comparative assessment study in the pediatric literature was reported over 50 years ago by Gordis et al. (1969). They compared patients' and their mothers' reports of adherence to penicillin prophylaxis for rheumatic fever with urine assays obtained during clinic visits. Children were classified into categories, with 69–73% of patients classified as compliers by patient/parental report, in contrast to 33–42% by urine assays. The major conclusion of this study was that patient or parental reports of adherence were "grossly inaccurate."

Many researchers have compared adherence rates obtained by electronic monitors to other measures of adherence. A consistent finding is that adherence rates are lower as assessed by electronic monitors versus rates obtained by pill counts,

canister weighing, and parent or patient report (e.g., Alili et al., 2016; Butz et al., 2005; Craker et al., 2019; Lawani et al., 2018; Martin et al., 2009; Modi et al., 2011). When dosing intervals are considered in defining adherence, rates are even lower for electronic monitoring (e.g., Freedman et al., 2012). Another consistent finding in comparative studies is that self- or parent report of adherence is significantly higher than that obtained from more objective measures including pill count and electronic monitoring (e.g., Schaefer et al., 2019). Having obtained this same finding in a sample of youth with new-onset epilepsy, Modi et al. (2011) identified a correction factor to apply to parent report adherence to adjust for this discrepancy, given that self- or parent report measures tend to be more clinically feasible than electronic monitoring. Table 5.2 summarizes some details from a sample of recent studies across a range of health conditions and comparative measures of regimen adherence in pediatric medicine.

Table 5.2 Sample of recent studies comparing different measures of adherence in pediatric medicine

Reference	Sample/regimen	Comparison	Aware of EM?[a]	Results	Comments
Lawani et al. (2018)	*N* = 319 (ages 12–45) with an asthma diagnosis	4-item self-report questionnaire vs. single question (SQ) developed by the study team vs. medication possession ratio (MPR)	N/A	4-item self-report questionnaire mean adherence = 16% SQ mean adherence = 43% MPR mean adherence = 9.1%	Rates of MPR adherence were higher among males, those with 3 or less prescribed medications, and those from a lower SES background
Craker et al. (2019)	*N* = 66 (ages 16–26) with a diagnosis of HIV	Youth self-reported adherence vs. Wisepill electronic monitoring (EM) device	Not reported	Youth self-reported adherence was higher than the EM adherence Youth self-reported adherence remained consistent across all time points (~90%) EM adherence declined from the first time point to the last time point (64% to 34%)	Increase in missing data due to EM device malfunctions 19% of youth reported not using the EM device for an unspecified period

(continued)

Table 5.2 (continued)

Reference	Sample/regimen	Comparison	Aware of EM?[a]	Results	Comments
Hommel et al. (2008)	*N* = 36 (ages 13–17) with a diagnosis of Crohn's disease or ulcerative colitis	Biological assay vs. caregiver and youth self-reports (via semi-structured interviews) vs. pill counting	N/A	6-MP mean adherence: Self-report = 93.71% Pill count = 62.62% 5-ASA mean adherence: Self-report = 96.99% Pill counting = 51.56%	80.56% of the adolescents had subtherapeutic 6-TGN levels (determined from the biological assay)
Inoue et al. (2016)	*N* = 19 (ages 2–21) with a diagnosis of SCD	MPR (from pharmacy refill records) vs. EM-Glow Cap	Yes	Mean EM-Glow Cap adherence = 78% Mean MPR adherence = 86%	There was a statistically significant association between part-time/full-time employment and lower EM-Glow Cap adherence rate (when compared to unemployment)
Intasan et al. (2014)	*N* = 207 (ages 1–12) Thai and Cambodian children diagnosed with HIV	Pill counting vs. caregiver and youth self-reports	N/A	88.3% of youth had "good" adherence according to the caregiver reports, and 8.6% had "poor" adherence 89.8% of youth had "good" adherence according to youth self-reports, and 8.3% had "poor" adherence Mean adherence by pill count for children with virological failure (VF) = 13.5% Mean adherence by pill count for children without VF = 2.9%	The most cited reasons for poor adherence were child refusal, delayed clinic visits, and forgetting to take the medication

(continued)

Table 5.2 (continued)

Reference	Sample/regimen	Comparison	Aware of EM?[a]	Results	Comments
Kichler et al. (2012)	$N = 76$ (ages 12–17) with type 1 diabetes	Diary (via 24-h recall interview) vs. EM-Blood Glucose Meter (BGM) vs. youth self-report vs. healthcare provider rating	Not reported	Scores across all 4 adherence measures were interrelated at medium-large effect sizes ($r = .24–.48$) (Note: means were not reported)	Caucasian youth had higher adherence levels on both the 24-h recall and the BGM than non-Caucasian youth Females had higher adherence levels than males on the 24-h recall
Landier et al. (2017)	$N = 416$ (ages ≤ 21) with a diagnosis of acute lymphoblastic leukemia (ALL) in remission	Caregiver and youth self-report vs. EM-Medication Event Monitoring System (MEMS) Track Cap	Yes	Mean total adherence = 91% Mean self-report adherence = 92.6% Mean EM-MEMS Track Cap adherence = 83.7%	For individuals aged ≤ 11, their caregivers completed the self-report For those aged 12–17, both the adolescent and their caregiver provided a report of adherence For young adults aged 18–21, their caregivers did not provide a report of adherence Participants were classified as either perfect reporters, over-reporters, or under-reporters
Mikesell et al. (2017)	$N = 85$ (ages 6–24) with cystic fibrosis	EM device embedded in a high-frequency chest wall compression (HFCWC) vest vs. caregiver and youth self-reports (via telephone interviews)	Not reported	Mean adherence = 69% Caregivers of teens overestimated adherence by 52.2% Caregivers of pre-teens overestimated adherence by 19.2%	Adherence significantly decreased as prescribed therapy time increased Individuals receiving assistance with therapy had higher adherence Adherence was found to be the highest in children

(continued)

Table 5.2 (continued)

Reference	Sample/regimen	Comparison	Aware of EM?[a]	Results	Comments
Pai et al. (2012)	*N* = 48 (ages 10–25) with a diagnosis of nephrotic syndrome or who underwent a kidney transplantation	Self-report vs. EM-MEMS Track Cap	Not reported	Mean self-reported adherence = 96.58% Mean EM adherence = 79.51%	The study highlights the need for medication-specific adherence models, especially when considering differences that exist in the dosage and side effects of certain medications
Schaefer et al. (2019)	*N* = 54 (mean age = 19.13 years old) undergraduates diagnosed with ADHD	Subjective measure (visual analog scale) vs. objective measure (pill counting and EM)	Yes	Subjective measure: 25% of missed doses were reported Objective measures: 40%–43% of missed doses were reported	Individuals with ADHD are prone to overestimating their medication adherence when self-reporting
Siracusa et al. (2015)	*N* = 12 (ages 6–48) with cystic fibrosis	EM-MEMS Track Cap vs. self-report vs. MPR	Yes	Mean EM adherence = 61% Mean self-report adherence = 100% Mean MPR adherence = 84%	Adherence among the participants decreased over time (by 1.93% each week)
Van Diest et al. (2016)	*N* = 56 (ages 11–17) with a primary diagnosis of migraine	Youth self-report (via mobile application) vs. MEMS Track Cap	Not reported	Mean self-report adherence = 64% Mean MEMS Track Cap adherence = 75%	Medication adherence rates decreased for both self-report and MEMS as the number of medications prescribed increased

[a]Were participants informed about electronic monitoring capabilities?

Collectively, these studies and previous reviews of the literature suggest that assays or electronic monitors are superior measures of medication adherence compared to patient, parental, or provider reports and pill counts. However, there is no error-free way to assess adherence. All adherence measures share some common methodological problems that clinicians and researchers need to address or consider when choosing an approach (Lam & Fresco, 2015). Ideally, researchers and

clinicians should use multiple methods for assessing adherence to obtain a more comprehensive and accurate understanding of behaviors (e.g., Al-Hassany et al., 2019; Cain et al., 2020; Lam & Fresco, 2015; Lehmann et al., 2014; Quittner et al., 2008). When interpreting results from these multiple measures, it is important to consider the relative strengths and weaknesses of each assessment approach. As an illustration of this suggestion, Rohan et al. (2017) used pharmacological (i.e., metabolite concentrations) and behavioral (i.e., electronic monitoring) measures of adherence to 6-mercaptopurine (6MP) in pediatric cancer patients (ages 7–19 years). These researchers noted that the former assessed intake of medication, while the latter measured patterns of adherence; they concluded that using multiple measures of adherence provides a more complete description and thereby better informs clinical care (Rohan et al., 2017).

Methodological Issues and Recommendations for Adherence Measurement

Reactivity

All adherence measures are potentially subject to reactivity effects – that is, a person changes their behavior due to the presence of an observer. If patients are informed about why someone is drawing their blood, watching them, asking them to use a special container with microelectronics, counting their pills, or asking them direct questions about adherence, they are more likely to behave in a socially sanctioned or desirable manner. This effect likely contributes to consistent findings that self-report or proxy-report of adherence is higher than more objective measures, like electronic monitoring (e.g., Mikesell et al., 2017). Although reactivity can contribute to measurement error, it turns out to be useful in helping patients change their behavior, as with self-monitoring strategies to increase adherence. Fortunately, the behavioral observation literature would suggest that reactivity effects are either nonexistent or short-lived and can be minimized (Gittelsohn et al., 1997; Johnston et al., 2019). Clinicians and researchers can try to:

- Make measurements as unobtrusive as possible. Observers should minimize discussions and eye contact with patients while conducting observations. Alternatively, participant observers, such as parents or older siblings, can be asked to make observations.
- Allow patient's time to adapt to measurement conditions, just as a physician has a patient rest for 5 minutes before taking their blood pressure. This might involve disregarding information collected during the initial assessment period.
- Collect repeated measurements for an individual across time, and consider discarding data from the initial periods (e.g., first day of observational data) to control for reactivity.

Representativeness

Obtaining representative samples of behavior is also a problem shared by all adherence measures, particularly when assessing adherence to chronic disease regimens. Regimen-related behaviors are required at specific times, and one may miss many of these opportunities to record what the person is doing. To obtain more representative samples of adherence behavior, clinicians and researchers should:

- Measure as long and often as possible (Johnston et al., 2019).
- Use methods that are more likely to yield representative samples of behavior. For example, electronic monitors are better at this than periodic drug assays. They minimize the effect of clinic-related behavior changes and reflect data from the natural environment (e.g., home), which helps improve the accuracy of measurement (Mikesell et al., 2017).
- Compare continuous and discontinuous methods to determine if much is lost by using the more feasible, discontinuous method. For example, one could do six structured interviews and compare the results obtained with three interviews.

Directness

A direct measure is one that measures a phenomenon in a way that captures the essence of that phenomenon. Because the focus of adherence assessment is behavior, this means directly observing behavior at the time and place of its natural occurrence (Wysocki, 2015). Because this is not usually feasible, all methods for assessing adherence will vary in their degree of directness. Asking patients to report retrospectively and globally about their adherence is much more indirect than electronic monitoring or directly observing them. The issue of directness can be addressed in several ways by clinicians and researchers:

- When possible, use the most direct method available. For example, one could ask patients or family members to monitor adherence behaviors as they occur versus asking them to rate adherence retrospectively.
- Define and refine, as needed, behavioral response classes so they are more easily understood and used by observers, including patients and families. This requires that medical providers be very specific about the nature of their recommendations. For example, vague recommendations such as “exercise regularly” or “let your body tell you what you can do” are too vague and need some operational work.
- Compare different methods that vary in directness, and empirically determine if the more indirect method converges with the more direct one (e.g., correlate pill counts with assays).

Measurement Standards

All measures of adherence vary in terms of how well they meet minimal scientific standards of measurement, including reliability, validity, and accuracy. *Reliability* refers to the consistency or reproducibility of measures (Crocker & Algina, 1986). *Validity* refers to the extent that a measure represents the phenomenon of interest or measures what it purports to measure (Anastasi, 1988). *Accuracy* (though often confused with reliability) refers to the extent that a measure reveals the "true" state of nature (Johnston et al., 2019). The way these standards are addressed depends on the type of measure. For example, the reliability of interview measures is often tested by correlating data obtained at two points in time (test-retest reliability), while the reliability of observational measures is tested by determining agreement between two independent observers watching the same person (interobserver agreement).

Accuracy is a much more difficult standard because it assumes that there is a way or an "incontrovertible" standard for judging the true state of nature (Sharp et al., 2006). In a very important sense, we cannot know what is "really there" because by measuring it, we change what is there. So, what should be done? Clinicians and researchers should:

- Obtain consensus among experts about the "best" measure or combination of measures for a particular type of regimen-related behavior (e.g., assays plus electronic monitoring appears to be the best way to assess medication adherence). The chosen measure then becomes the "nearly incontrovertible" standard by which all measures are compared.
- Depending on the measure, obtain appropriate reliability indices, such as test-retest and internal consistency for interview measures and interobserver agreement for behavioral observations.
- Depending on the measure, obtain appropriate validity indices, such as criterion- or construct-related validity. For example, predictive validity can be demonstrated by correlating adherence with disease or health status, or construct validity can be demonstrated by correlating one measure of adherence with another (more established) measure.

Interpretation or What's in a Number?

Most data are not meaningful on their own. Rather, data are interpreted, in part, by assigning numbers or specifying the unit of analysis. There are a number of dimensions to adherence behaviors that may be of interest, including frequency (e.g., the number of pills consumed), duration (e.g., time spent exercising), rate or the frequency per some time dimension (e.g., the frequency of exercising per week), percent of opportunities to engage in the behavior (e.g., the percent of opportunities when PRN medications were taken when it was apparent by symptom monitoring

that it was appropriate to use the medication), and accuracy of medication-taking skills (e.g., inhaler technique). Because taking medications is the most common regimen-related behavior in the management of acute and chronic diseases, the following units of analysis and formulas are recommended (Kastrissios et al., 1996):

- *Fraction of Doses* (Fr), where Fr is the number of doses taken divided by the number of doses prescribed. This is the metric derived from pill counts, and the product is multiplied by 100 to obtain a percentage.
- *Daily Count Index* (DCI), where DCI is the number of days on which the prescribed number of doses was taken divided by the number of days of monitoring. Again, the product is multiplied by 100 to obtain a percentage. This can be derived from electronic monitoring but not usually pill counts (unless they are done daily, which is unlikely).
- *Prescribed Intervals Method* (PI), where PI is the number of prescribed dosing intervals (± some "forgiveness" interval, such as 2 h) divided by the total number of possible intervals. This can be derived from electronic monitoring, and the product is multiplied by 100 to obtain a percentage.
- *Exact Daily Adherence* (EAC), where EAC is the number of days when doses were taken as prescribed (including at the recommended dosing interval ± a forgiveness interval) divided by the total number of days of monitoring. Again, this can be derived from electronic monitoring and the product is multiplied by 100 to obtain a percentage. This index can employ the DCI or PI method and is the most stringent of all the indices. Indeed, when dosing interval is considered in defining adherence, rates typically are lower than adherence defined without time specifications (beyond the day it was taken) (e.g., Freedman et al., 2012). Pritchard and Nicholls (2015) refer to this as "true adherence" and illustrates in Fig. 1 (page 70) how inhaler competence can be considered in addition to medication taking when measuring "true adherence."
- *Therapeutic Coverage* (TC), where TC is the number of hours of therapeutic coverage divided by the total number of hours monitored. Again, the product is multiplied by 100 to obtain a percentage. TC can only be approximated by electronic monitoring (with knowledge of a drug's half-life). Direct assessment of TC requires pharmacokinetic studies using assays.

Once a number is assigned to the data, clinicians and researchers must make sense of these numbers or compare them to some standard. The ideal standard would be "biologic" or the level of adherence necessary to achieve a therapeutic response (Haskard et al., 2009). Typically, however, standards have been arbitrary, such as defining adequate adherence as taking greater than 80% of medication. Other approaches could include within-subject comparisons (where the patient serves as his or her own comparative yardstick) and between-subject comparisons (comparing a patient to an appropriate reference or normative group). It is important to note that when using adherence in regression models, it is best to measure it continuously and analyze without categorizing those data (e.g., adequate vs. inadequate adherence) to enhance statistical power and reduce statistical bias (Tueller et al., 2016).

Clinical and Treatment Utility

Measures of adherence vary in terms of cost and feasibility for use in clinical settings. The measures that are considered more "objective," such as electronic monitoring or direct observation, are also the most expensive and resource-intensive and the least practical for use by clinicians. Another neglected dimension of assessment is *treatment utility* or the degree to which assessments contribute to beneficial treatment outcomes (Hayes et al., 1987) or predict significant morbidities, such as increased healthcare utilization (McGrady & Hommel, 2013). For the most part, this has not been investigated for any of the adherence measures. For example, it is conceivable that assessment methods yielding data on adherence patterns and obstacles would be more useful in planning and executing interventions to improve adherence. Clinical and treatment utility issues can be addressed by:

- Reducing the complexity and cost of measurement procedures to increase their clinical utility. Time efficiency is key. For example, structured interviews could be simplified and tested in clinical settings (Wu et al., 2013). Given the challenge of reaching families by phone, conducting interviews within the medical environment may be more feasible. Nonetheless, clinicians need to recognize that social desirability likely will impact responses to interview questions in this context (Martin et al., 2009).
- Improving on what clinicians already do to assess adherence informally, such as testing different ways to phrase questions to patients (e.g., reducing judgmental tendencies and enhancing empathy by normalizing adherence challenges).
- Addressing treatment utility by empirically comparing different adherence measures in terms of their relative ability to produce beneficial effects, such as improved adherence and better medical outcomes (Wu et al., 2013). From a clinical perspective, treatment utility may be the most important dimension of assessment.

Summary

Assessment is the cornerstone of understanding adherence behavior. There are many reasons why adherence behaviors are assessed, as well as different ways to approach assessment. Choosing and defining target behaviors is a critical first step. Selecting appropriate measures for assessment is the next step, recognizing that some measures are direct and/or objective, while others are indirect and/or subjective. Selecting an assessment approach requires careful consideration of the respective strengths and limitations, feasibility, and clinical utility of the various strategies available. Because there is no perfect measure of adherence, plans should be made to minimize potential impact of issues such as reliability, reactivity, representativeness, etc. to obtain the best data possible.

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Chapter 6
Assessing Disease and Health Outcomes

Disease and Health Status Measures

Disease and health status parameters are initially monitored to establish a medical diagnosis. Once a diagnosis is made and a treatment plan implemented, these parameters are useful for monitoring changes in patients' status over time and informing physicians about when and how to alter the initial treatment plan. In clinical trials, outcomes are needed to demonstrate the relative efficacy of various treatments and for monitoring unintended (iatrogenic) effects of medical treatments. Assessing outcomes, in parallel with adherence assessments over time, can also guide decisions about when and how to intervene to improve adherence and outcomes.

Rapoff (2000) introduced the term "clinically significant nonadherence" to refer to "inconsistencies in following a particular regimen that may result in compromised health and well-being for particular patients with particular diseases" (p. 339). He recommended primary prevention adherence interventions for patients without clinically significant nonadherence (CSN), secondary prevention adherence interventions for patients with CSN identified early on in their treatment course, and tertiary prevention adherence interventions for those with an ongoing pattern of CSN. Pai and Drotar (2010) coined the term "treatment adherence impact (TAI)" which referred to the "quantification of the effects of adherence behaviors on medical, psychological, or social outcome" (p. 384). Borrowing from Bronfenbrenner's (1979) ecological systems theory, Pai and Drotar classified TAI outcomes on the patient, micro-, meso-, and macro-level. We will use this classification system to describe outcomes.

M. A. Rapoff et al., *Adherence to Pediatric Medical Regimens*, Issues in Clinical Child Psychology, https://doi.org/10.1007/978-3-031-27484-8_6

Patient-Level Outcomes

Traditional medical outcomes have included clinical signs and symptoms and laboratory and diagnostic studies. For example, in asthma management, physicians are encouraged to have patients monitor their peak flow rates using a meter and record their symptoms such as coughing, and physicians are to obtain measures of lung function by spirometry in their offices or clinics (Aronson et al., 2001) and to take into consideration ethnic differences in lung function with pulmonary function testing (Lum et al., 2015). Hemoglobin A1c lab values are the best measure of glycemic control in youth with type 1 diabetes. In a meta-analysis of 21 studies involving 2492 youth with type 1 diabetes, Hood, Peterson, Rohan, and Drotar (2009) found that the mean effect size of correlations between adherence and hemoglobin A1c values was −.028 (medium effect), such that as adherence increases, A1c values decrease.

Patient and caregiver ratings of disease activity have also been assessed to measure treatment outcomes. In pediatric rheumatology, patient, parents, and physician ratings of disease activity have been examined. In one study, concordance between physician and parent ratings of "inactive" disease in children with juvenile idiopathic arthritis was seen in 40% of clinic visits. Parents tended to disagree with physicians if their child had pain or functional impairment, while physicians disagreed with parents if the child had active joint symptoms (Consolaro et al., 2007). One study examined interrater reliability of physician ratings of global disease activity in youth with dermatomyositis (Rider et al., 1997). Physicians rated global disease activity on a 5-point Likert scale (0 = no evidence of disease activity, 1 = mild disease activity, 2 = moderate disease activity, 3 = severe disease activity, 4 = extremely severe disease activity). Interrater reliability among the physicians was substantial with mean percent agreement = 89.8%, mean Kappa coefficient = 0.67, and Cronbach's alpha = 0.98. Parent and physician ratings of disease activity have been compared. In one study (Rapoff et al., 1991), involving parents of children with juvenile arthritis, parental ratings of morning stiffness (0 = no stiffness to 3 = severe stiffness, dressing and moving with great difficulty) significantly correlated with physician ratings of active joint counts (0.57, $p \leq 0.01$); parental ratings of activity limitations (0 = normal activity to 2 = very little activity, resting often) significantly correlated with physician ratings of active joint counts (0.54, $p \leq 0.01$); and parental ratings of pain complaints (0 = no complaints to 2 = complaints frequent and throughout the day) significantly correlated with physician ratings of active joint counts (0.46, $p \leq 0.02$). Internal consistency of parental ratings was moderately high (0.82), but test-retest correlations were 0.62 for morning stiffness, 0.25 for activity limitations, and 0.51 for pain complaints, which might be explained by the fluctuations in symptoms of juvenile arthritis over time.

Technological advances now allow patients and their families to monitor disease activity electronically and in real time. For example, continuous glucose monitoring devices are now routinely used in clinical practice for youth with type 1 diabetes to monitor blood glucose levels and, in conjunction with insulin pumps, can lead to better control of diabetes (Galderisi & Sherr, 2019). The magazine, *Diabetes*

Forecast, publishes an annual consumer guide for reviewing and comparing devices (http://www.diabetesforecast.org).

However, there is a consensus in medicine that assessment of medical outcomes needs to expand beyond traditional methods. Medical providers and researchers are beginning to appreciate that patients and their families have a unique perspective on how diseases affect important aspects of their lives or health-related quality of life (HRQOL) (Blue & Colburn, 1996; Hall et al., 2019; Johnson, 1994; Kourkoutas et al., 2010). For example, Kaplan (1994) referred to this perspective as the "Ziggy Theorem." In one of the Ziggy cartoons strips, Ziggy asks a wise old man about the meaning of life, and the wise man replies "doin' stuff." Kaplan argued that the purpose of healthcare is to help people live longer and better and that HRQOL is defined primarily by behavioral functioning or being able to "do stuff."

Outcome assessments, particularly HRQOL measures, can help identify the psychosocial as well as physical consequences of chronic diseases. These can help in identifying subgroups of patient populations at risk for psychosocial adjustment problems (Spieth & Harris, 1996). They can also help evaluate the quality of medical care and inform healthcare policy (Kaplan, 1994). Decisions about allocation of medical resources and services can be better made when evaluated by outcomes that reflect both the quantity and quality of life.

Disease and health status indicators also need to be assessed to determine the relationship between adherence and outcome, which is either imperfect or unknown (Johnson, 1994). The whole enterprise of assessing, predicting, and improving adherence is predicated on developing reliable and valid measures of adherence and treatment outcome. HRQOL measures may be particularly useful in determining if higher adherence has positive or negative consequences for patients and their families. Measures of disease and health outcomes, such as hemoglobin A1C in diabetes, are not and should not be used as proxy measures of adherence. They need to be assessed separately and concurrently with adherence measures to determine the relationship between these two sets of variables and to determine if interventions to improve adherence also improve disease and health outcomes.

There is consensus in the literature that HRQOL is a multidimensional construct that should include at least *four core domains* (Aaronson, 1989; Palermo et al., 2008; Spieth & Harris, 1996):

- *Physical symptoms* (pain and fatigue)
- *Functional status* (ability to perform age-appropriate daily activities)
- *Psychological functioning* (affective states, adjustment indices, and self-esteem)
- *Social functioning* (the number, type, and quality of social contacts and relationships)

Another significant domain includes cognitive functioning and school-related performance (Palermo et al., 2008; Spieth & Harris, 1996). This domain is relevant for certain diseases (e.g., epilepsy) and treatments (e.g., cranial radiation) that affect the central nervous system. Also, chronically ill children and adolescents often have brief, but frequent absences from school that can adversely affect academic performance.

There have been significant advances made in the measurement of HRQOL in children and adolescents in the past decade (Eiser & Morse, 2001). There are now "well-established" generic HRQOL measures for children and adolescents (Palermo et al., 2008), such as the Child Health and Illness Profile (Starfield et al., 1999), the Child Health Questionnaire (Landgraf et al., 1996; the Pediatric Quality of Life Inventory (Varni et al., 1999), and the Youth Quality of Life (Patrick et al., 2002). The generic measures of HRQOL are useful in comparing HRQOL between children who have different diseases and with healthy children. There are also a number of "well-established" disease-specific HRQOL measures (Palermo et al., 2008), such as the Child Health Assessment Questionnaire for juvenile arthritis (Singh et al., 1994), the Cystic Fibrosis Questionnaire Revised (Quittner et al., 2005), the Juvenile Arthritis Functional Assessment Report (Howe et al., 1991), the Pediatric Asthma Quality of Life Questionnaire (Juniper et al., 1996), and the Pediatric Oncology Quality of Life Scale (Goodwin et al., 1994). Disease-specific HRQOL measures address unique challenges posed by specific illnesses and may have greater clinical relevance for patients and their families (Palermo et al., 2008).

By far, the most commonly used measure of generic and disease-specific quality of life is the PedsQL developed and validated by James Varni and his colleagues. The generic version, the PedsQL 4.0, is a 23-item measure of health-related physical, emotional, social, and school functioning. There are parallel child self-report (ages 5–7, 8–12, and 13–13 years) and parent proxy report forms (ages 2–4, 5–7, 8–12, and 13–18 years). In one study, the PedsQL 4.0 was administered to 10,241 families newly enrolled in the California State's Children's Health Insurance Program (Varni et al., 2003). The scales demonstrated excellent internal consistency reliabilities (Cronbach's coefficient alpha = .89 for child and .92 for parent reports) and construct validity with significantly lower total scores for children with a chronic health condition versus healthy children. The measures were also deemed to be feasible as only 1.8% of child report and 2.4% of parent report items were missing. Also, Varni et al. (2003) found that a 4.4 change in the PedsQL 4.0 total score for the child self-report and a 4.5 change in the parent total score were the "minimal clinically important difference." Another study found that children as young as 5 years of age can reliably and validly report their HRQOL using the PedsQL 4.0 (Varni et al., 2007). A meta-analysis reviewed 66 studies involving 34 countries and 67,805 subjects where the PedsQL 4.0 was used as a measure of HRQOL (Ow & Mayo, 2020). Youth below the age of 7 years and above 12 years of age had higher total scores. Also, females had lower scores than males. The authors suggested that this meta-analysis provides normative comparisons of HRQOL across different countries.

Varni and colleagues have also published studies on reliability and validity of disease-specific HRQOL measures including ones for youth with asthma (Varni et al., 2004), cancer (Varni et al., 2002a, b), cardiac disease (Uzark et al., 2008), epilepsy (Modi et al., 2017), gastrointestinal diseases (Varni et al., 2015), renal disease (Goldstein et al., 2008), rheumatic disease (Varni et al., 2002a, b), sickle cell disease (Panepinto et al., 2013), transplantation (Weissberg-Benchell et al., 2010), and type 1 diabetes (Varni et al., 2018) and type 2 diabetes (Varni et al., 2019)

Micro-level Outcomes

Outcomes at this level include family functioning, social functioning, school attendance, and missed work/wages for caregivers (Pai & Drotar, 2010). The Living with a Chronic Illness (LCI) Scale was designed by Adams and colleagues to specifically measure social difficulties related to chronic disease (Adams et al., 2002). There is a parent version which was administered to 108 parents of children with a chronic disease and a child version which was administered to 115 children, 9–18 years, with a chronic disease. Internal consistency was satisfactory for both versions, and they demonstrated convergent and divergent validity. The authors suggest that there is initial evidence that the LCI can distinguish illness versus non-related illness social difficulties for children with a variety of chronic illnesses.

Tracking school attendance among chronically ill children can be a useful measure of outcomes at the micro level. Youth with chronic illness are absent from school, on average, 16 days a year compared to about 3 days for healthy children. Absences also vary by diseases, with children being treated for leukemia missing an average of 40 school days during their initial stages of treatment whereas children with type 1 diabetes missing school at an average of 14 days per year (Shaw & McCabe, 2008). Disease symptoms and treatment side effects can negatively impact academic performance and motivation.

Meso-level Outcomes

Outcomes at this level include clinic treatment success rates and clinic flow rates, such as the number of patients seen per day (Pai & Drotar, 2010). Adherence can significantly impact treatment success. For example, Modi, Rausch, and Glauser (2014) electronically monitored adherence to antiepileptic drugs (AEDs) in a prospective longitudinal study of 124 children with newly diagnosed epilepsy. They found that children who were nonadherent to AED therapy in the first 6 months of treatment were 3.24 times more likely not to be seizure-free for ≥1 year at the 4 years postdiagnosis endpoint. Only 12% of the children who were adherent versus 31% who were nonadherent continued to experience seizures at the 4-year mark. Another study electronically monitored adherence to oral mercaptopurine over a 6-month period in 327 children with acute lymphoblastic leukemia (ALL). The researchers found that there was a decrease in adherence over time (94.7% at month 1 and 90.2 the end of month 6) and a progressive increase in disease relapses with decreasing adherence (Bhatia et al., 2012).

Macro-level Outcomes

Outcomes at this level include healthcare costs and utilization (Pai & Drotar, 2010). In a population-based study of medical expenditures involving youth with five different medical conditions, there was an additional $1377.60 to $9059.49 annual medical costs for youth with asthma, diabetes, or epilepsy compared to youth who did not have these conditions (Miller et al., 2016). Another study monitored oral medication adherence and physician and hospital charges for 99 patients 2–21 years with inflammatory bowel disease and found that patients with increasing nonadherence demonstrated significantly higher medical costs than those with stable or decreasing adherence (Hommel et al., 2017). A systematic review of medication adherence and healthcare utilization found that nine of the ten studies reviewed demonstrated that nonadherence increased healthcare usage, including emergency room visits, outpatient visits, and hospitalizations (McGrady & Hommel, 2013).

Methodological Issues and Recommendations for Assessing Disease and Health Measures

Both traditional and HRQOL measures are required to conduct a comprehensive assessment of disease and health status. They are complementary and help determine the impact of adherence to medical regimens on the physical, social, and psychological functioning of children with acute and chronic health problems. As with all measures, there are several methodological issues that need to be addressed.

Choice of Informants

The choice of informants varies depending on the type of disease and health status measure chosen. Laboratory and diagnostic procedures require highly trained and skilled healthcare professionals. Some traditional measures require taking a history or obtaining reports of symptoms from patients, their parents, or both. HRQOL measures are almost exclusively based on ratings obtained from patients or their parents. The perspectives of patients and their parents may differ from providers, which is the major justification for obtaining HRQOL measures. Patients may also offer different perspectives than their parents (Hall et al., 2019; Rosenbaum et al., 1990). The term for this in the psychological assessment literature is "cross-informant variance" (Achenbach et al., 1987). Because of this variance, reports should be obtained from multiple informants as they have unique and non-overlapping perspectives. Clinicians and researcher should:

- Utilize multiple informants including healthcare providers, patients, parents, teachers, and other significant people in the lives of children to obtain a comprehensive assessment of disease and health status.
- Develop and validate traditional and HRQOL measures that can be rated by patients (Rosenbaum et al., 1990). The pediatric pain assessment literature shows that if children are given the opportunity and a developmentally appropriate instrument, they can rate their own symptoms in a psychometrically sound way as adults (Cohen et al., 2008; McGrath, 1990).

Representativeness

This issue concerns when and how often disease and health status assessments are obtained. Ideally, patients would be assessed frequently enough to determine their current disease and health status and to document clinically significant changes in their status from previous assessments. However, for children with chronic health problems, there are limited opportunities for obtaining measures of disease and health status, unless patients are hospitalized or seen frequently in outpatient clinics. This can create a "severity bias" in studies designed to assess the overall impact of chronic diseases. That is, patients available for assessment are those who have the most contact with the healthcare system because their disease is less well controlled. The upside of this bias would be that those patients in poor disease control might also be poorly adherent and could be offered interventions to improve their adherence. Clinicians and researchers should:

- Assess patients as often as possible to adequately characterize disease and health status.
- Continue to develop and validate patient and/or parental measures of disease symptoms (such as automated formats) and HRQOL, which can be completed by phone, online, or in home, school, or community settings.
- When feasible, use automated instruments to record symptoms and physiological indices, such as glucometers to record blood glucose levels and peak flow meters to record pulmonary function. Patients and their parents will need specific training and recalibration to obtain reliable and valid data for clinical and research purposes.
- The 24-h recall interview methodology for assessing adherence could be adapted to assess disease and health status. These interviews are clinically feasible as they can be done briefly by phone.

Generic Versus Disease-Specific Measures

This issue is most relevant to HRQOL measures. Both generic and disease-specific measures have their place in assessing disease and health status. Generic measures are most useful for documenting health-related disability and limitations for patients with a variety of chronic diseases. Disease-specific measures have greater clinical sensitivity and utility as they capture unique physical and psychosocial sequelae of specific diseases. Clinicians and researchers should:

- Utilize both generic and disease-specific HRQOL measures, as they complement each other and provide a more comprehensive approach to assessing outcomes.
- Although specific traditional outcome measures can be used with different patient groups (e.g., pulmonary function testing being useful for patients with asthma and CF), there is a need for a global and generic disease severity index that can be used for children and adolescents with various health problems. For example, the global severity scheme (mild intermittent, mild persistent, moderate persistent, and severe persistent) applied to patients with asthma is like other global severity indices (e.g., mild, moderate, and severe categories applied to patients with rheumatic diseases). Clinicians and researchers could agree on such a global rating format and develop unique criteria (based on traditional measures of disease activity) to operationalize severity categories for specific diseases.

Psychometric Standards

Measures of disease and health status must be scientific standards for reliability, validity, sensitivity, and specificity. Therefore, clinicians and researchers should:

- Obtain interobserver or interrater reliability indices for measures generated by providers through direct physical examination, observation of the patient, or interpretation of laboratory and diagnostic studies. Interrater reliability of adult proxy reports of patients' symptoms and HRQOL also needs to be assessed. Internal consistency reliability would be important to assess for questionnaires and rating scales that tap specific constructs or dimensions (such as functional status). Test-retest reliability may or may not be useful depending on the interval between assessments and whether the symptom or construct would be expected to be stable over a particular interval. Many symptoms of chronic disease (such as pain or fatigue) are variable or episodic, and one may not expect consistency between assessment occasions.
- Obtain appropriate validity indices. Construct validity would be particularly important for HRQOL measures that seek to assess multidimensional constructs such as physical, social, and psychological functioning. Newly developed measures need to demonstrate concurrent validity with existing or standard instruments. Discriminant validity is relevant to demonstrating differences in disease

and health status between healthy and ill children and among chronically ill children who are at different stages of treatment and have different disease courses.
- Ensure that traditional and HRQOL measures of disease and health status meet standards for sensitivity and specificity (Fletcher et al., 1988; Mandrekar, 2010). This is particularly crucial for diagnostic or screening tests. Test results can be either positive or negative for the presence of a disease state, for abnormal versus normal test results, or for different levels of disease severity. For example, a HRQOL screening instrument should correctly classify patents as having lower or higher HRQOL based on more extensive traditional or HRQOL measures.

Limiting "Physiogenic Bias"

In assessing HRQOL, investigators sometimes use a "battery" approach where a variety of psychological tests and scales are used to assess various psychosocial domains, such as affective distress and behavior problems (Spieth & Harris, 1996). These instruments were not specifically designed to assess HRQOL, and they have not been normed on children and adolescents with chronic disease. Of particular concern is what has been termed "physiogenic bias" (Wells & Strickland, 1982). This means that items on psychological instruments may be tapping disease or treatment-related symptoms rather than psychological symptoms. For example, the Child Behavior Checklist (Achenbach & Rescorla, 2001) is one of the most used questionnaires to document internalizing (e.g., depression) and externalizing (e.g., aggression) disorders in children with chronic disease (Lavigne & Faier-Routman, 1992). Cautions have been raised about using the Child Behavior Checklist with chronically ill children because some of the items may reflect physical rather than psychological symptoms (Perrin et al., 1991). Examples include "stares blankly" (which may indicate seizure activity), "constipated" (which accompanies spina bifida), and "feels dizzy" (which may be a symptom of hypoglycemia). Though respondents are cautioned that these items are to be considered "physical symptoms without known medical cause," they may not be rated consistent with this caveat, or the opposite pattern can occur when respondents may erroneously attribute psychological symptoms to a child's illness (Perrin et al., 1991). To minimize physiogenic bias, clinicians and researchers could:

- Delete somatically loaded items but this creates problems in scoring and interpreting standardized scales.
- Make sure that respondents understand that they are being asked to rate symptoms that do not relate to disease or treatment-related symptoms.
- Develop separate norms for children and adolescents with various chronic diseases.
- Conduct studies to assess whether physiogenic bias affects standardized measures of psychological functioning for children and adolescents with chronic illness. This has been done with chronically ill adults and would be an important contribution to the pediatric literature.

Clinical Feasibility, Utility, and Relevance

Measures of disease and health status may be reliable and valid and yield clinically useful information but may be underutilized because they are not feasible. Clinical feasibility, utility, and relevance can be enhanced by:

- Making instruments and scales understandable and easy to use for providers, patients, and parents. Because there is a limited amount of time during routine clinic visits, instruments should not overburden respondents or assessors. In outpatient subspecialty clinics, routine follow-up visits are often limited to 15 minutes and less, and priority is given to essential and traditional measures of disease activity (e.g., physical examination and laboratory tests). This means that administration time for HRQOL measures needs to be 10 minutes or less. Unfortunately, most HRQOL measures do not meet this standard. Research is needed to shorten and re-validate current HRQOL measures.
- Specifying a time interval (e.g., the past week) when asking patients or proxies about symptoms and HRQOL dimensions. The time interval should be short enough to limit distortion and bias due to memory, which usually means over the past month or less.
- Providing patients or proxies a comparative reference point for symptom and HRQOL ratings, such as how they are functioning compared to before diagnosis, treatment, or since their last visit (Aaronson, 1989).
- Allowing patients or proxies to assess the importance as well as the severity of problems in various HRQOL domains (Gill & Feinstein, 1994). For example, chronic illness may limit children's participation in organized sports, but depending on their pre-illness history, this dimension may or may not be important to a particular child.
- Augmenting standard or supplied items on HRQOL instruments with open-ended supplemental items that allow patients or proxies to add unique opinions and reactions. In short, clinicians need to give patients and their parents the opportunity to communicate information they did not think to ask about.

Clinical Implications of the Adherence-Outcome Relationship

There is a conditional relationship between adherence and disease and health status outcomes of medical treatments that is not simply a one-to-one linear relationship. Figure 6.1 is a 2×2 contingency table that illustrates potential clinical implications and potential relationships between adherence and outcomes. As can be seen in quadrant **A**, this would be the best possible outcome; the patient is adherent, and the medical treatment is effective. Patients in quadrant **B** and their families need to advocate for more effective treatments with their providers. Those in quadrant **C** do not need an adherence intervention, but providers need to try to figure out why they are improving even though they are poorly adherent. They may be receiving

Adherence \ Health/Disease/Quality of Life Outcomes	GOOD	POOR
GOOD	**A** Best possible outcome. Patient is sufficiently adherent to achieve favorable outcomes with minimal or no negative side effects of treatment. Action: Continue to encourage good adherence.	**B** Patient is sufficiently adherent, but the treatment is not effective or is not potent enough. Action: Change treatment or add additional elements
POOR	**C** Patient is nonadherent but has good outcomes because of spontaneous remission, they are adherent enough to achieve good outcomes, or other factors (outside of the prescribed treatment) are helping to obtain good outcomes. Action: Do nothing about adherence but monitor outcomes.	**D** Patient is nonadherent and has poor outcomes, presumably due to lack of adherence or some other factors (like the lack of efficacy of prescribed treatment). Action: Addressing nonadherence should be a prime target to improve outcomes.

Fig. 6.1 The potential relationships between adherence and medical outcomes

unnecessary treatments. Patients in quadrant **D** and their families are prime candidates for adherence interventions.

For these scenarios to play out, we need standard definitions of what "good" and "poor" adherence and medical outcomes mean. These issues are discussed in Chaps. 1 and 9.

Conclusions

Much work still needs to be done to develop reliable, valid, accurate, and clinically useful measure of adherence, disease status, and HRQOL. Healthcare professionals need all these measures to show that interventions that enhance adherence also result in improvements in disease outcomes and HRQOL. A critical issue is the developmental level, particularly cognitive maturity, of children asked to report on their disease and health status. For example, pain has been reliably and validly rated by children as young as 3 years of age, if they are given an age-appropriate measure

(Stinson et al., 2006). HRQOL measures, such as the PedsQL 4.0, have been reliably and validly rated by children as young as 5 years of age, and for those younger than 5, parent proxy measures are available for children as young as 2 years of age (Varni et al., 2007). However, we must be careful not to use age as a proxy measure of cognitive maturity but directly assess whether children understand and can use measures we have developed.

Another issue relevant to adherence and disease/health status measures is establishing standards for "meaningful or clinically significant improvement" on the measures we develop. For example, with a generic HRQOL, would the standard be that we help patients achieve a level of HRQOL that is in the average range of scores (plus or minus one standard deviation) for appropriate normative groups of healthy children and adolescents? Norman, Sloan, and Wyrwich (2003) reviewed 38 studies that computed a "minimally important difference" index and found that all were close to a half a standard deviation. For self-report measures of pain, a 30% reduction in the rating of pain intensity has been suggested for defining clinically significant improvement on this symptom (Rowbotham, 2001). As standards evolve, we will be able to demonstrate to patients, families, healthcare providers, politicians, and insurance carriers that our adherence interventions produce clinically meaningful improvements in the lives of chronically ill children and adolescents.

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Chapter 7
Review of Adherence Intervention Studies

Intervention Studies on Improving Adherence to Regimens for Chronic Pediatric Diseases

The number of intervention studies that aim to improve adherence in children with chronic diseases has dramatically increased over the past 10 years. Enough published intervention studies exist to warrant systematic reviews for pediatric asthma, cystic fibrosis, epilepsy, HIV/AIDS, type I diabetes, sickle cell disease, and organ transplant. However, intervention studies aiming to improve adherence are noticeably lacking in pediatric cancer, GI disorders, spina bifida, and rheumatic diseases. The largest proportion of systematic reviews focused on adherence to regimens for asthma (n = 11 reviews) or diabetes (n = 7 reviews). The majority (39/45, 87%) of systematic reviews and individual studies focused on adherence to medications, which is understandable given the primacy of medications in the treatment of chronic diseases. Common secondary outcomes included healthcare utilization, number of emergency department visits or hospitalizations, disease parameters (e.g., HbA1C level), and psychological well-being (e.g., quality of life, depression).

The methodology for measuring adherence varied greatly among studies. Single intervention studies largely relied on patient and/or parent self-report of adherence to medications, diet, exercise, or monitoring regimens. Patient and parent self-report measures ranged from single author-generated items to medication diaries to validated adherence measures (e.g., Family Asthma Management System Scale). Chart review for healthcare utilization, prescription refill records, and blood assays were often utilized as more objective measures of medication adherence. The majority of studies reported a combination of adherence outcomes (e.g., blood assays plus patient and parent report). However, the use of disease outcomes or healthcare utilization to measure medication adherence has inherent limitations when medical regimen adherence does not always directly correlate to disease or healthcare utilization outcomes (e.g., Kluthe et al., 2018; Russell-Minda et al., 2009; Sun et al., 2019). In

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terms of study design, randomized controlled trials were the most common intervention study design, with pre-post interventions as the second most common study design. Single-subject design studies have been used less often in recent years and were not included in recent systematic reviews.

Adherence interventions ranged from clinic-based behavioral interventions to family-based therapy to mobile health interventions (e.g., text reminders, apps). Multicomponent education, behavioral, and monitoring strategies continue to be the primary interventions tested. Educational strategies are rarely attempted in isolation but usually combined with behavioral strategies, such as monitoring and positive reinforcement. While a few studies have shown benefits of educational interventions (Al-Aqeel & Al-Sabhan, 2011; Bagnasco et al., 2016), educational strategies alone tend to have limited impact on improving adherence (Al-Aqeel & Al-Sabhan, 2011; Dobbels et al., 2010; Favier et al., 2018; Lewis et al., 2015). The primary clinical/organizational strategy employed to improve adherence has been simplifying treatment regimens. Research has demonstrated mixed results for simplifying or individualizing treatment plans. Similar to education only, some individuals obtain benefit from simplified or individualized treatment plans (Rapoff et al., 2002; Tinkelman et al., 1980); however, the overall evidence for simplifying or individualizing treatment plans in increasing adherence is limited (e.g., Bain-Brickley et al., 2011; Fortin et al., 2018; Lewis et al., 2015; Rooks-Peck et al., 2019; Toelle & Ram, 2004).

The most frequently tested and effective strategies have been behaviorally based. Common behavioral adherence interventions include increased medication monitoring (e.g., Eney & Goldstein, 1976; Macedo et al., 2021), explicit training and feedback (e.g., Epstein et al., 1981; Cox et al., 2013), disease management training (Mosnaim et al., 2016; Stinson et al., 2010; Wagner et al., 2017), contracting (e.g., Gross, 1983), and reward systems (e.g., Stark et al., 2005). Researchers have also evaluated different psychotherapy interventions, including layperson-led peer support groups (Kew et al., 2017), family-based therapy (Feldman et al., 2018; Hood et al., 2010), motivational interviewing in adults (Wagoner & Kavookjian, 2017), and counseling (Mathes et al., 2017; Velloza et al., 2021; Viana et al., 2016). Peer support groups were not effective in improving adherence outcomes. However, family-based therapy and psychotherapy interventions tended to be beneficial in improving adherence outcomes across different pediatric chronic disease populations. Multicomponent family systems-based interventions that focus on the entire family and involve communication training, problem-solving cognitive restructuring, and behavioral contracting consistently appear helpful for improving adherence outcomes (e.g., Feldman et al., 2018; Hill-Briggs & Gemmell, 2007; Wysocki & Gavin, 2006).

In recent years, behavioral interventions have increasingly been implemented via mobile health and electronic health technologies. For instance, traditional behavioral interventions are now delivered via telehealth with positive impacts on adherence (e.g., Velloza et al., 2021). Systematic reviews of mixed mobile health and electronic health adherence intervention studies demonstrate an overall positive impact on medication and medical adherence (Ramsey et al., 2020; Russell-Minda

et al., 2009; Wang et al., 2020). Reviews that have narrower search criteria and are more targeted demonstrate more mixed results. In the past decade, researchers have developed mobile applications (apps) that can be downloaded on smartphones for patient use in the home setting. App content and programing vary widely between studies, but the majority of smartphone apps provide medication reminders and/or medication monitoring (Alquran et al., 2018; Linder et al., 2019; Sun et al., 2019). Mobile app studies demonstrate mixed results, with some studies demonstrating improved adherence (Alquran et al., 2018; Sun et al., 2019) and other studies demonstrating no effects on adherence (Linder et al., 2019; Sun et al., 2019). Another common mobile health technology intervention is text reminders (Mehra et al., 2021; Miloh et al., 2017; Ting et al., 2012). Multiple studies evaluating the impact of text reminders on adherence found positive results for increasing either clinic visit adherence or medication adherence. However, a meta-analysis in pediatric HIV/AIDS found that text message reminders did not significantly improve adherence outcomes (Mehra et al., 2021). Other studies have developed and evaluated web-based interventions that are more comprehensive and provide education regarding disease self-management (Stinson et al., 2010; Virella Pérez et al., 2019). Results of these studies are also mixed with about half of the studies demonstrating improvements in adherence and the other half showing no benefits on adherence.

Cochrane review examined school-based self-management interventions for asthma in children and adolescents (Harris et al., 2019). School-based interventions all attempted to improve knowledge of asthma and its triggers and teach youth the importance of regular follow-up with their asthma medical provider. There was variability in how interventions were delivered in schools, with some being delivered via electronic games and some being in-person instruction. Instructional sessions ranged from 1 to 16 across studies. School nurses and parents were involved in some of the studies. Authors concluded that school-based asthma self-management interventions reduce hospital admission by an average of about 0.16 admissions per child over 12 months. School-based interventions may also slightly reduce Emergency Department visits from 7.5% to 5.4% over 12 months. School-based interventions may also reduce the number of days that children experience asthma symptoms and probably lead to small improvements in asthma-related quality of life. Many of the studies reviewed tested school-based interventions in younger children from socially disadvantaged populations, targeting a high-risk population for severe asthma symptoms. Authors noted that interventions that used a theoretical framework engaged parents in the intervention and were implemented during school hours were more successful regarding implementation. Although most study effect sizes were small, implementing interventions within the school allows for clinicians to reach a large number of children.

Of the 53 meta-analyses, reviews, and single studies (when reviews were not available) in Table 7.1, 42 (79%) reported positive effects on enhancing adherence. Of these 42 reviews and studies, 12 (28%) showed mixed results, with some adherence outcomes improved and no effect observed on other adherence outcomes. In two available meta-analyses in pediatric asthma (Fidler et al., 2021; Wu & Pai, 2014), improved adherence outcomes decreased over time, while improved

Table 7.1 Adherence intervention studies for chronic pediatric diseases: systematic reviews and meta-analyses

Intervention	Reference	Article type	No. studies	No. children	Outcome	Effect size	Notes
Asthma							
Behavioral interventions for inhaled steroids	Fidler et al. (2021)	Meta-analysis	33	4469	+ Significant increase in adherence of inhaled steroids	Small, $g = 0.39$	Long-term follow-up not significant, $g = 0.38$
Smartphone applications	Alquran et al. (2018)	Systematic review	8	105	+ Positive effect of smartphone apps on medication adherence	N/A	
Behavioral interventions for severe asthma	Boutopoulou et al. (2018)	Systematic review	7	508	+ Adherence rates significantly increased from 28–67% to 49–81%	N/A	
School-based	Harris et al. (2019)	Systematic review	55	14,174 in qualitative analysis 12,623 in randomized trials	+ Reduce hospitalizations over 12 months + Reduce unplanned hospital/primary care visits from 26% to 21% + May reduce ED visits from 7.5% to 5.4% over 12 months	N/A	Interventions with theoretical framework, engaged parents, and were run outside of children's free time were more successful
Lay-led and peer support	Kew et al. (2017)	Systematic review	5	1146	− No effect on adherence	N/A	
Mixed interventions	Knibb et al. (2020)	Systematic review	27	N/A	+ eHealth interventions significantly improved adherence	N/A	Mixed interventions
Pharmacists' interventions	Macedo et al. (2021)	Systematic review	5	N/A	N/A	N/A	
Behavioral interventions	Mosnaim et al. (2016)	Systematic review	24	N/A	+ Increase asthma self-management skills	N/A	

Digital intervention	Ramsey et al. (2020)	Systematic review	15	3739	+ 87% of the digital interventions demonstrated improved adherence	N/A	
Written individual plans	Toelle and Ram (2004)	Systematic review	7	N/A	− No consistent evidence that written plans improved adherence	N/A	
Cancer[a]							
Barrows Cards educational intervention	Bagnasco et al. (2016)	Single study	1	17	+ Improved adherence to immunosuppressive medication and reduced hospital readmissions	N/A	Problem-solving theory
Medication reminder app	Linder et al. (2019)	Single study	1	23	− No improvement in overall adherence		
Direct observation of vitamin D supplementation	Orgel et al. (2017)	Single study	1	51	+ Improved adherence/ therapeutic vitamin D level	N/A	
Cystic fibrosis							
Exercise training to promote physical activity	Cox et al. (2013)	Cochrane review	4	199	+ Improvements to physical activity adherence for interventions more than 12 months − No improvement in adherence to physical activity for interventions less than 6 months	N/A	One study included adults

(continued)

Table 7.1 (continued)

Intervention	Reference	Article type	No. studies	No. children	Outcome	Effect size	Notes
Behavioral interventions	Goldbeck et al. (2014)	Cochrane review	17	556	+ Some evidence that behavioral interventions improved energy expenditure adherence − No evidence that cognitive behavioral interventions, motivational interviewing, or parent-child intervention improved adherence	N/A	Two adult studies
Diabetes (type I)							
Psychotherapy, family therapy, and behavioral interventions	Hood et al. (2010)	Meta-analysis	15	997	+ Multicomponent interventions and those that targeted emotional, social, or family processes improved HbA1c control	Small, $ES = 0.11$	
Psychology, telehealth, and educational interventions	Viana et al. (2016)	Meta-analysis and systematic review	19	1782	+ Improved HbA1c after psychology intervention − No improvement after telecare or educational interventions	Small, psychology $MD = -0.310$	Mixed samples of children and adults
mHealth interventions	Wang et al. (2020)	Meta-analysis and systematic review	11	N/A	+ Improved adherence and HbA1c control	Small, $MD = -0.25$ to -0.48 for improved HbA1c	Mixed samples of teens and adults
Family-based interventions	Feldman et al. (2018)	Systematic review	25	2642	+ Generally improve HbA1c control	N/A	

Problem-solving	Hill-Briggs and Gemmell (2007)	Systematic review	52	508	+ Some studies showed improved global adherence, glucose monitoring, dietary behavior, and HbA1c level − Some studies showed no improvement in HbA1c level or glucose monitoring	N/A	
Health technologies	Russell-Minda et al. (2009)	Systematic review	4 (included TMDI)	204	+ Remote patient monitoring improved HbA1c maintenance, self-report adherence, and adherence to exercise	N/A	Mixed samples of type I and type II diabetes
Mobile apps	Sun et al. (2019)	Systematic review	14	823 (children and adults)	+ Improved adherence to glucose monitoring − Majority of studies did not improve HbA1c levels	N/A	Mixed samples of children and adults
Epilepsy							
Parent education intervention	Al-Aqeel and Al-Sabhan (2011)	Cochrane review	1	51	+ Improved adherence to medication as measured by blood serum	N/A	
Medical, behavioral, and educational interventions	Lewis et al. (2015)	Systematic review	9	572	− No improvement in medication adherence	N/A	
Self-management interventions	Wagner et al. (2017)	Systematic review	24	1569	+ Improved medication adherence and reduced seizure frequency	N/A	Only two studies examined adherence
GI disorders (celiac, IBD, Crohn's)[a]							

(continued)

Table 7.1 (continued)

Intervention	Reference	Article type	No. studies	No. children	Outcome	Effect size	Notes
Text message reminders	Miloh et al. (2017)	Single study	1	51	+ Improved medication adherence	N/A	
HIV/AIDS							
Text message reminders	Mehra et al. (2021)	Meta-analysis	7	987	− Not statistically significant but five of seven studies showed improved adherence	NS, *MD* = 0.05, (95% CI: −0.08 to 0.17)	
Medical and behavioral interventions	Bain-Brickley et al. (2011)	Cochrane review	4	232	+ Home-based nursing intervention improved adherence − Medication diaries, change in medial regimen, and peer support therapy did not improve adherence	N/A	
Medical regimen and behavioral interventions	Rooks-Peck et al. (2019)	Systematic review	5	N/A	+ Medical regimen interventions improved viral load − Medication diaries and one time interventions did not improve adherence	N/A	
Rheumatic diseases (JIA, lupus)[a]							
Ultrasound intervention	Favier et al. (2018)	Single study	1	8	− No improvement on adherence	N/A	
Educational and behavioral intervention	Rapoff et al. (2002)	Single study	1	34	+ Small improvement in adherence	N/A	

Behavioral intervention for calcium intake	Stark et al. (2005)	Single study	1	49	+ Increased adherence to calcium	N/A	
Internet self-management program	Stinson et al. (2010)	Single study	1	46	− No improvement on adherence	N/A	
Text message intervention	Ting et al. (2012)	Single study	1	70	+ Improved clinic visit adherence − No improvement in medication adherence	N/A	
Sickle cell disease							
Iron chelation interventions in sickle cell disease or thalassaemia	Fortin et al. (2018)	Cochrane review	16	1525	− Available data inconclusive	N/A	Compared adherence for different oral-chelating agents
eHealth interventions	Badawy et al. (2018)	Systematic review	16	747	+4 of 5 studies reported improvement in medication adherence	N/A	Only 5 of 16 articles targeted medication adherence
Multicomponent interventions	Shih and Cohen (2020)	Systematic review	9	236	+ Small to large effects on improved medication adherence	N/A	Combination of behavioral, educational, family-based, support, and technology elements
Spina bifida[a]							
eHealth and telecoaching intervention	Wingo et al. (2020)	Single study	1	50	− No effect on dietary intake or physical activity adherence	N/A	50% spina bifida, 24% other mobility limitation

(continued)

Table 7.1 (continued)

Intervention	Reference	Article type	No. studies	No. children	Outcome	Effect size	Notes
Organ transplantations							
eHealth interventions	Tang et al. (2020)	Meta-analysis	21	N/A	+ Overall improved medication adherence up to 12 months post-transplant − Nine studies reported harm	Modest, RR = 1.34	Adults and children
Education intervention	Dobbels et al. (2010)	Systematic review	1	29	− No effect on adherence	N/A	Kidney transplant
Educational, behavioral, and reminder interventions	Duncan et al. (2018)	Systematic review	10	307	+ Four studies showed improved adherence − Six studies showed no effect on adherence	N/A	
Educational and counseling interventions	Mathes et al. (2017)	Systematic review	2	N/A	+ Improved adherence		
Mixed chronic disease samples							
Educational, behavioral, organizational, and psychological interventions	Graves et al. (2010)	Meta-analysis	71	3077	+ Improved adherence across outcomes + Improved health across outcomes	Medium group studies, $d = 0.58$; Large singe subject studies, $d = 1.44$	Medium, at follow-up $d = 0.48$
Psychological interventions (educational, behavioral, psychosocial, technology-based)	Kahana et al. (2008)	Meta-analysis	70	5703	+ Improved adherence across outcomes; behavioral and multicomponent interventions most effective − Technology-based interventions did not improve adherence	Small, overall $d = 0.34$; range $d = 0.54$ to 0.08	

Behavioral interventions	McGrady et al. (2015)	Meta-analysis	20	2688	+ Decreased healthcare utilization – Additional eight studies did not improve adherence	Small, $d = -0.27$ to -0.38	
Psychological interventions	Pai and McGrady (2014)	Meta-analysis	23	3898	+ Improved adherence across outcomes	Small $d = 0.20$	Small, at follow-up $d = 0.29$
Healthcare provider-delivered	Wu and Pai (2014)	Meta-analysis	35	4616	+ Significant increase in adherence	Small, $d = 0.49$	Long-term follow-up effect size decreased, $d = 0.32$
Behavioral interventions for oral medications	Coyne et al. (2019)	Systematic review	24	3509	+ Most interventions had some benefit	N/A	
Organizational, behavioral, and multicomponent interventions	Lemanek et al. (2001)	Review	23	N/A	+ Behavioral and multicomponent interventions likely improve adherence – No interventions are "well-established"		
Theory-based health behavior interventions	Ng et al. (2018)	Systematic review	29	N/A	+ Positive association with increased adherence	N/A	Most studies (55%) based on social cognitive theory
Behavioral interventions	Salema et al. (2011)	Systematic review	17	2390	+ Multi-modal, family-based, and improving access to care increased adherence	Small to medium	

(continued)

Table 7.1 (continued)

Intervention	Reference	Article type	No. studies	No. children	Outcome	Effect size	Notes
Behavioral interventions	Velloza et al. (2021)	Systematic review	26	N/A	+ Adolescent-friendly clinics, peer-based counseling, and telehealth interventions increased adherence	N/A	
Mobile and web-based health apps	Virella Pérez et al. (2019)	Comprehensive review	6	336	+ 4 of 6 studies reported increased medication adherence	N/A	

N/A indicates that data was not available, *d* Cohen's *d* effect size, *ES* weighted least squares effect size, *g* Hedges' *g* effect size, *MD* mean differences between intervention and control groups, *RR* relative risk statistic

[a]Systematic reviews and meta-analyses were not identified. Thus, available single studies with multiple subjects were included

adherence outcomes were maintained at follow-up in two meta-analyses of mixed pediatric disease groups (Graves et al., 2010; Pai & McGrady, 2014). The remaining 11 studies (22%) showed no significant or obvious effect on adherence. One review of pharmacist interventions (Macedo et al., 2021) did not synthesize results enough to report an overall adherence outcome.

Meta-Analytic Reviews of Adherence Interventions for Pediatric Medical Regimens

Measuring Effectiveness

Qualitative reviews, as in the previous section of this chapter, cannot determine the quantitative power and effectiveness of adherence interventions. A meta-analysis is the best technique to provide such information (Rosenthal, 1991). Because adherence is a continuous variable, the recommended effect size (ES) estimate is the standardized mean difference effect size, also known as the *d* statistic (Lipsey & Wilson, 2001). The Cohen's *d* statistic is the difference between the means (M1-M2) divided by the pooled standard deviation. If M1 is the experimental group mean and M2 is the control group mean, then the difference is positive if it is in the direction of greater adherence in the experimental group. If *d* is equal to zero, then the distribution of scores for the experimental group overlaps completely with the distribution of scores for the control group. Cohen (1988) classified *d* statistics as follows:

• "Small," $d = 0.20$	(14.7% non-overlap)
• "Medium," $d = 0.50$	(33% non-overlap)
• "Large," $d = 0.80$	(47.4% non-overlap)

Hedges' *g* is another common measure of effect size. Similar to Cohen's *d,* Hedges' *g* measures the effect size for the difference between means, usually a difference between an experimental group and control group. Hedges' *g* statistic expresses the difference of the means in units of the pooled standard deviation. It is considered more accurate for smaller sample sizes (e.g., sample below 20). Effect size strength is interpreted the same as Cohen's *d* above.

Other measures of intervention effect include mean difference (MD) and relative risk ratio (RR; Hays, 1994). The mean difference measures the absolute difference between the mean values in two groups in a clinical trial. It estimates the average amount that the experimental intervention changes the outcome of interest, compared to the control group. The relative risk ratio is the ratio of risk of an event in one group (the exposed group) versus the risk of the event in another group (the non-exposed group). The relative risk ratio is used to measure the effect of a treatment to which people are exposed. The effect could be beneficial (from an

intervention or therapy) or harmful (from a hazard). Relative risk is the number of those having the outcome of interest (e.g., adherence to medication) divided by the total number exposed to the intervention or treatment. A relative risk ratio of 1 indicates no difference between the groups. A relative risk ratio greater than 1 indicates an increased probability of the outcome (e.g., adherence to medication) in the treatment group.

Meta-Analyses of Adherence Interventions for Chronic Pediatric Diseases

Eleven meta-analyses on interventions to promote adherence to regimens for chronic pediatric disease could be located for this review (see Table 7.1). Pediatric disease populations with meta-analyses included asthma (n = 1 article), diabetes (n = 3 articles), HIV/AIDS (n = 1 article), organ transplant (n = 1 article), and mixed chronic disease samples (n = 5 articles). Conclusions from meta-analyses will be discussed separately for each chronic disease population, as well as general conclusions across chronic disease populations.

Asthma

Fidler et al. (2021) examined interventions aimed at improving adherence to inhaled steroids in youth less than 18 years with asthma. Authors included 33 intervention study articles. The calculated aggregate effect size across all interventions was small but significant (n = 33, g = 0.39, 95% confidence interval [CI] = 0.24–0.54). The most common interventions included asthma education, technology feedback/electronic monitoring, text message-based asthma management reminders, spirometry/peak flow monitoring reports, parental support group meetings, written action plans, and multisystemic therapy. Unfortunately, a decay in treatment effect was observed at most follow-up time periods, with the aggregate effect size at follow-up being non-significant (n = 6, g = 0.38, 95% CI = 0.08–0.83). Method of adherence measurement and intervention format were significant moderators of intervention success in pediatric asthma. Specifically, interventions utilizing electronic measurements showed a significantly larger aggregate effect sizes (n = 13, Cohen d = 0.80, 95% CI = 0.41–1.19) than those using pharmacy refills (n = 6, Cohen d = 0.10, 95% CI = 0.20–0.40) and subjective report (n = 8, Cohen d = 0.24, 95% CI = 0.08–0.40). Although post hoc analyses indicated the intervention groups were not statistically different, technology only interventions (n = 11, Cohen d = 0.66, 95% CI = 0.38–0.93), as well as combined in-person plus technology interventions (n = 9, Cohen d = 0.43, 95% CI = 0.14–0.73), produced a larger aggregate effect sizes compared to in-person only interventions (n = 13, Cohen d = 0.17, 95% CI = 0.07–0.41). Taken together, behavioral, educational, technology-based,

and organizational interventions aimed at increasing adherence in pediatric asthma are generally effective, demonstrating small effect sizes. However, intervention effects decay over time. Electronic measurement of outcomes may be most effective in capturing improvements in adherence in pediatric asthma.

Diabetes

Adherence to medication and glucose monitoring is a significant concern for many youth with type 1 diabetes. Nonadherence can lead to hospitalization for diabetic ketoacidosis and long-term health complications. A large literature exists examining interventions aimed at increasing medical adherence in this population. In one of the first meta-analyses in type 1 diabetes, Hood et al. (2010) examined 15 studies with 997 youth with type 1 diabetes. Interventions included clinic-based interventions, diabetes video game, diabetes motivational game, problem-solving therapy, multisystemic therapy, and behavioral family systems therapy. The mean effect size for pre- to post-treatment change for the intervention versus control group (usually standard care) comparison was small at 0.11 (95% CI = 0.01–0.23). Authors noted the overall small effect size and very modest improvements in glycemic control. However, authors performed sub-analyses that identified multicomponent interventions that target emotional, social, or family processes as more potent in improving HbA1C than interventions just targeting a direct, behavioral process (e.g., increase in blood glucose monitoring frequency). Similarly, Viana et al. (2016) concluded that psychological approaches to improving adherence modestly improved HbA1C in studies with children and adults with type 1 diabetes, while telecare and education interventions did not change glycemic control. Viana et al. (2016) reviewed 19 articles for a meta-analysis, with data from 1782 pediatric and adult patients. The randomized controlled trials (2–24 months in duration) were divided into four groups according to type of intervention: psychological (7 studies; 818 patients), telecare (6 studies; 494 patients); education (5 studies; 349 patients), and psychoeducation (1 study; 153 patients). Improvement in HbA1C was observed after psychological (MD = −0.31; 95% CI = −0.59 to −0.02) but not after telecare (MD = −0.12; 95% CI = −0.27 to 0.02) or educational (MD = −0.001; 95% CI = −0.20 to 0.20) interventions.

In comparison to the above meta-analyses, a more recent meta-analysis by Wang et al. (2020) evaluated the effectiveness of mHealth interventions in diabetes care for adolescents and adults with type 1 diabetes. mHealth interventions were primarily mobile apps, text messaging, and self-monitoring. The effectiveness of mHealth interventions varied widely by study. Three clinical trials were available for meta-analysis of mHealth interventions and indicated a significant reduction in HbA1C from baseline to follow-up but with substantial heterogeneity in the pooled effect. Thus, authors concluded that mHealth interventions are promising but that there is limited evidence about their effectiveness in glycemic control at this time.

HIV/AIDS

Mehra et al. (2021) examined the effectiveness of phone text message reminder interventions to improve adherence to antiretroviral therapy among adolescents aged 10–19 years living with HIV. Seven studies were included in the authors' review, including five randomized controlled trials and two cohort studies. Four studies used only text messages as the intervention, while the other three studies included counseling or peer support as a part of both the intervention and standard of care groups. Five individual studies reported improved adherence with text messaging, while no difference was found in two studies between the intervention and control (standard of care) groups. Three randomized controlled trials were included in the meta-analysis. The pooled mean difference between the intervention and the control group was not significant at 0.05 (95% CI = −0.08 to 0.17). Subgroup analyses supported non-significant meta-analysis findings, where there was no difference between intervention groups for one-way text messaging, two-way text messaging, or a short follow-up time period. Thus, while results of individual studies were highly variable, current data does not support the effectiveness of text message interventions in increasing adherence to antiretroviral therapy in adolescents with HIV.

Organ Transplant

A meta-analysis in pediatric solid organ transplant (lung, liver, pancreas, heart, kidney, intestines, combined organ transplantation) examined the effectiveness of eHealth interventions for increasing medication adherence (Tang et al., 2020). eHealth interventions included telehealth, Internet, and computer-based education and counseling, as well as mobile health interventions (e.g., apps and text messaging), wearable sensors, and electronic pillboxes. Twenty-one trials from 6 countries involving 2114 participants contributed to this meta-analysis. Results suggest that eHealth interventions may improve medication adherence (risk ratio = 1.34; 95% CI = 1.12–2.56) and self-monitoring behavior (risk ratio = 2.58; 95% CI = 1.56–4.27) up to 12 months post-transplant, compared to standard care. However, authors note that the overall risk of bias was considered high or unclear in most clinical trials, and the quality of evidence for eHealth interventions improving adherence after pediatric solid organ transplant was low to very low for all outcomes. Additionally, authors noted that nine clinical trials reported harm to participants including technical failure of the intervention ($n = 5$), intervention burden ($n = 3$), intervention unappealing and lost interest ($n = 2$), concerns regarding privacy ($n = 1$), and anxiety and stress from being monitored by the intervention ($n = 2$). This assessment of harm reported by Tang et al. (2020) is important to consider when developing clinical interventions aimed at improving medical regimen adherence. Behavioral and educational interventions are often thought of as benign, yet some may cause increased distress in participants. Thus, careful considerations regarding participant burden, privacy, feedback, and monitoring of adverse events are recommended.

Mixed Chronic Disease

Four identified meta-analyses have examined adherence interventions in mixed samples of pediatric chronic disease groups. The first meta-analysis includes 70 studies (Kahana et al., 2008) with the following disease groups: 32 (45.7%) asthma, 16 (22.9%) diabetes, 10 (14.3%) cystic fibrosis, 2 each with JRA and obesity (2.9%, respectively), and 1 each for hemodialysis, hemophilia, HIV, IBD, PKU, seizures, sickle cell disease, and tuberculosis (1.4% each). Of the 70 studies, 29 (41.4%) were identified as randomized controlled trials, and 42 (60%) reported effect sized based on an experimental versus control group design, while 19 (27.1%) reported effect size based on pre-post differences and another 9 (12.9%) reported both. The mean weighted (by sample size) effect size across all adherence measures was in the small to medium range ($d = 0.34$, 95% CI = 0.34–0.73). Outcomes differed by type of intervention, as follows: behavioral ($d = 0.54$, CI = 0.34–0.73), multicomponent ($d = 0.52$, CI = 0.45–0.57), psychosocial ($d = 0.44$, CI = 0.23–0.65), educational ($d = 0.16$, CI = 0.10–0.22) and technology-based ($d = 0.08$, CI = −0.09–0.25). Mean weighted effect sizes were different depending on the regimen component that was targeted, with self-management, self-care behaviors, dietary change, and exercise-environmental changes yielding small to medium effect sizes (*d*'s ranging from 0.47 to 0.52), while medications yielded small effect sizes ($d = 0.20$). Mean weighted effect sizes were also different depending on disease type, with medium to large for cystic fibrosis ($d = 0.74$), medium for miscellaneous disorders ($d = 0.54$), small to medium for diabetes ($d = 0.38$), and small for asthma ($d = 0.23$). Studies that combined pre-post and experimental versus control group designs produced medium to large effect sizes ($d = 0.65$), pre-post only designs produced small to medium effect sizes ($d = 0.42$), and experimental versus control group designs produced a small effect size ($d = 0.23$). Effect sizes were also found to diminish over time as follows: 0–6 months follow-up $d = 0.63$ (CI = 0.46–0.80); 7–12 months $d = 0.24$ (CI = 0.06–0.42), and >12 months $d = -0.50$ (CI = −1.15–0.15). The authors' conclusion was that behavioral and multicomponent interventions are "relatively potent" in enhancing adherence to regimens for chronic pediatric diseases (Kahana et al., 2008).

The second meta-analysis on adherence interventions across chronic pediatric diseases includes 71 studies (Graves et al., 2010). A unique aspect of the Graves et al. meta-analysis is that it included single-subject design studies. Of the 71 studies, 34 (48.6%) used a comparison group design (e.g., experimental versus control group), 17 (24.3%) used a within-subject group design (1 group pre-post design), and 19 (27.1%) used a single-subject design. Of the group design studies ($n = 51$), 16 studies involved asthma (31.4%); 15 with type 1 diabetes (29.4%); 5 with CF (9.8%); 3 each with HIV/AIDS or post-transplant (5.9% each); 2 each with hyperlipidemia, JRA, and sickle cell disease (3.9% each); and 1 each with epilepsy, hemophilia, and phenylketonuria (2% each). Of the single-subject design studies ($n = 19$), seven studies involved type 1 diabetes (36.8%), three each with JRA and CF (15.8% each), two with asthma (10.5%), and one each with epilepsy, lung disease, various rheumatic diseases, and sickle cell disease (5.3% each). Of the 71 studies, 38 (54%) included a direct (A1C, body mass index, or pulmonary function tests) or an indirect health outcome measure (disease activity estimates, healthcare

utilization, or HRQOL). The weighted (by sample size) mean effect size across all of the adherence outcomes in the group design studies was in the medium range ($d = 0.58$, 95% CI = 0.51–0.65). The weighted mean effect across all of the single subject adherence data was in the large range ($d = 1.53$, 95% CI = 1.07–1.98). In contrast with more recent meta-analyses in individual disease groups, Graves et al. (2010) found that using a single intervention method had higher mean effect sizes (educational only $d = 0.56$, behavioral only $d = 0.51$, organizational only $d = 0.50$) than the studies with combined educational and behavioral interventions ($d = 0.36$). However, the follow-up analysis of between-group differences was not significant. Mean effect sizes were highest for group design studies involving patients with asthma ($d = 0.58$), followed by other illnesses combined ($d = 0.57$) and diabetes (0.42). Finally, the weighted mean effect size across all of the follow-up adherence data in the group design studies was in the medium range ($d = 0.48$, 95% CI = 0.28–0.69). The weighted mean effect size of the single subject follow-up adherence data was in the large range ($d = 1.44$, 95% CI = 0.99–1.89).

Related to health outcomes, Graves et al. (2010) found that the weighted mean effect size across all of the health outcomes in the group design studies was in the medium range ($d = 0.40$, 95% CI = 0.31–0.50) and for the single subject design studies in the large range ($d = 0.74$, 95% CI = 0.19–1.29). Health outcome measurements from studies using a pre-post design had a stronger mean effect size ($d = 1.27$, 95% CI = 1.05–1.50) than the studies using a comparison group design ($d = 0.22$, 95% CI = 0.12–0.32). Additionally, positive health outcomes were stronger in studies focused on children with asthma ($d = 0.86$, 95% CI = 0.67–1.05) compared to those targeting children with diabetes ($d = 0.29$, 95% CI = 0.13–0.45) or those targeting other diagnoses ($d = 0.24$, 95% CI = 0.10–0.39). Finally, in contrast to the adherence outcomes, effect sizes for the health outcomes were higher for studies using a combination of educational and behavioral interventions ($d = 0.74$, 95% CI = 0.55–0.94), while single intervention-type studies had the smallest effect size ($d = 0.16$, 95% CI = 0.02–0.30). Similar to most other meta-analyses, Graves et al. (2010) concluded that adherence interventions effectively increase medical regimen adherence with a small to medium effect size and have a positive impact on health outcomes. In contrast with other meta-analyses, Graves et al. (2010) found that adherence gains are maintained over time.

Wu and Pai (2014) examined healthcare provider-delivered adherence promotion interventions in pediatric asthma ($n = 23$ articles) and other pediatric chronic disease ($n = 14$ articles; diabetes, obesity, eczema, juvenile rheumatoid arthritis, HIV, and sickle cell disease). Interventions included behavioral interventions (e.g., increasing parental supervision of medication), educational interventions (e.g., providing basic information to families about the patient's illness and importance of adherence), healthcare provider-initiated actions (e.g., simplifying the treatment regimen or increasing contact with families), organizational interventions (e.g., pillboxes or calendars for self-monitoring), and other interventions (e.g., discussion with caregivers about their child's illness). Greater improvements in adherence were observed immediately after healthcare provider-delivered interventions ($d = 0.49$; 95% CI = 0.32–0.66) compared to longer-term follow-up ($d = 0.32$; 95%

CI = 0.10–0.54). Treatment effect sizes differed across the adherence domains measured, with the largest effect sizes observed for medical regimen completion (d = 0.57), medication refills (d = 0.51), and composite adherence measures (d = 0.61). Thus, a wide variety of behavioral interventions appear to be effective in increasing medication adherence in pediatric asthma and other pediatric chronic medical conditions. However, effect sizes vary by type of outcome measurement, and effectiveness may decrease over time.

Two additional recent meta-analyses that examined randomized controlled trials only for promoting adherence in mixed pediatric disease groups also demonstrated generally small but positive effect sizes (McGrady et al., 2015; Pai & McGrady, 2014). Pai and McGrady (2014) identified 23 articles of randomized controlled psychological interventions with 3898 participants. The most common chronic condition represented was asthma (n = 10, 43%) followed by diabetes (type 1 or type 2, n = 6, 26%) and other chronic conditions (n = 7, 30%; cancer, human immunodeficiency virus, inflammatory bowel disease, and juvenile rheumatoid arthritis). The majority of adherence-promoting interventions (n = 14, 61%) included both youth and their families. Authors evaluated technology-based interventions versus in-person interventions. Authors also evaluated adherence outcomes assessed via electronic monitors or bioassays versus adherence outcomes assessed via self-report or parent report. Mean effect sizes were small at post-treatment (d = 0.20, 95% CI = 0.08–0.31, n = 23) and follow-up (d = 0.29, 95% CI = 0.15–0.43, n = 9). Intervention type (technology versus in-person) and outcome measurement (electronic monitoring/bioassays versus self-/parent report) did not account for variation in treatment effects ($p > 0.05$).

McGrady et al. (2015) conducted an additional meta-analysis examining pediatric adherence intervention outcomes at the patient level, family level, or healthcare system level. Twenty randomized controlled studies that demonstrated positive effects on adherence, representing 19 unique samples, were included. An additional eight articles representing trials that did not significantly improve adherence were included in post hoc analyses. Pediatric adherence promotion interventions reduced healthcare utilization compared with control interventions ([a]SMD = −0.19, 95% CI = −0.35 to −0.03), with fewer ED visits, fewer hospitalizations, and fewer outpatient visits. Compared with control interventions, pediatric adherence promotion interventions also improved patient quality of life, caregiver quality of life, and family functioning, demonstrating small to large effect sizes ([a]SMD range = 0.35–0.95).

Conclusions from the Meta-Analyses

Overall, meta-analyses of pediatric chronic diseases show that adherence interventions produce small to medium effect sizes for improving medication adherence. Adherence interventions may also reduce healthcare utilization and improve patient

[a] aSMD = standardized mean difference

and caregiver health-related quality of life and family functioning outcomes. There is significant heterogeneity across interventions and measured outcomes. Adherence interventions that target emotional, social, and family processes appear to be more effective in pediatric type 1 diabetes, compared to interventions that target behaviors or monitoring only. However, other meta-analyses produce mixed results, and, thus, there does not appear to be a clear advantage of behavioral, educational, technology-based, or multicomponent interventions over the others at this time. Similarly, there are mixed findings regarding the stability of these small improvements in adherence over time. Systematic reviews and meta-analyses suggest that interventions in pediatric psychology for improving adherence can be effective; however, there are significant limitations to the literature that are discussed below.

Conclusions and Literature Limitations

The pediatric adherence intervention literature is still highly mixed. Behavioral interventions and family therapy-based interventions tend to demonstrate a positive impact on adherence, at least in the short run. Behavioral interventions also demonstrate a positive impact on health outcomes, such as disease activity, healthcare utilization, and HRQOL. Many technology-based (mobile and electronic health) studies demonstrate a positive impact on adherence in single studies and systematic reviews; however, results are inconsistent between studies, and a substantial portion of technology-based intervention studies do not demonstrate a meaningful impact on adherence. Significant limitations of the current pediatric adherence intervention literature are that intervention design and implementation vary widely from study to study, intervention studies are most often not replicated, and meta-analyses clearly demonstrate only small effect sizes that tend to decrease over time. Additionally, more research is needed regarding the impact of improved medical adherence on health-related outcomes, as many studies only measure adherence and not its impact on patient disease or quality of life. Thus, no pediatric adherence intervention is considered well-established at this time.

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Chapter 8
Strategies for Improving Adherence to Pediatric Medical Regimens

Educational Strategies for Improving Adherence

The "Why?" or Goals of Education

Clinicians need to be clear about why they educate. The overall goal of education is to increase patient and family knowledge about diseases, treatments, and the importance of consistent adherence. In short, clinicians want patients and their families to "know" stuff. The British philosopher, Gilbert Ryle, made an important distinction between two types of "knowing": *knowing that* and *knowing how* (Ryle, 1949). *Knowing that* means patients and their families can convey in verbal and/or written form that they understand information presented to them. Providers often ask patients and families or give them questionnaires to determine if they know about diseases, treatments that have been prescribed, and the rationale for such treatments. For example, providers would want a patient with type 1 diabetes to describe how diabetes involves failure of their pancreas to produce insulin, how they should check their blood glucose and perform insulin injections, and the importance of adjusting insulin doses based on diet, blood glucose levels, exercise, and stress. The patient may demonstrate that they "know" this information by responding correctly to verbal or written questions and prompts. However, an additional type of "knowing" is essential. *Knowing how* means patients and families can do something according to some specific standards. Referring to the patient with diabetes, providers would want some behavioral evidence that the patient can correctly test their blood glucose and properly prepare, time, and inject insulin based on their specific dietary, blood glucose, exercise, and stress levels. Providers need to make sure that patients and their families have a specific knowledge base relative to their health condition and treatment as well as the necessary behavioral repertoire to carry out their prescribed regimen.

M. A. Rapoff et al., *Adherence to Pediatric Medical Regimens*, Issues in Clinical Child Psychology, https://doi.org/10.1007/978-3-031-27484-8_8

The "What?" or Specific Objectives and Content of Education

Educational content and objectives are determined by the type of disease and recommended treatments. For chronic conditions, patients often must adhere to multiple regimen tasks, such as taking medications, following special diets, doing general and/or specific exercises, and monitoring symptoms. The provider who prescribes a particular regimen is responsible for determining the specific treatment plan based on evidence-based medicine and resulting consensus practice guidelines. Once a specific treatment plan has been developed, patients and families generally need to receive the core information described in the sections below. To illustrate, juvenile idiopathic arthritis (JIA) is used as an example.

What Is the Diagnosis and Related Information?

Information needs to be given about the disease, including its diagnostic label (e.g., JIA) and possible causes (e.g., unknown, but autoimmunity implicated along with some viral or other types of trigger). Providers also need to share details with families regarding the anticipated course (e.g., the subtype of JIA determines the extent and severity of joint involvement and associated symptoms) and general prognosis (e.g., with most children, JIA is controlled but not cured, and the prognosis for a normal and functional lifespan is generally good).

What Needs to Be Done to Control the Disease?

Patients and families need to know what they are to do for their treatment regimen (e.g., take anti-inflammatory medications, do special exercises, and wear protective splints on involved joints at night) and why such treatment is important (e.g., to reduce joint inflammation, control pain, increase joint range of motion, and avoid joint deformities).

What Are the Potential Negative Side Effects of Treatment?

A list of possible side effects should be given and how likely they are to be experienced (e.g., gastrointestinal irritation with medications for treating JIA are common). Also, specific ways to reduce side effects should be suggested (e.g., take medications with food to reduce irritation or warm affected joints before exercising by doing exercises in a hot tub). Understanding the rationale for treatments and identifying ways to minimize their adverse effects will likely contribute to better adherence.

What Are the Benefits of and Strategies for Enhancing Adherence?

Patients and their families need to be informed about how consistent adherence could be beneficial (e.g., following JIA treatment recommendations consistently can reduce inflammation and pain, increase functional activities, and reduce the need for additional diagnostic and treatment procedures). Providers can problem-solve with patients and families to identify evidence-based strategies that may help overcome personal barriers to enhance adherence. The strategies discussed in this chapter (e.g., how to monitor, prompt, and reinforce children's adherence to treatment recommendations) can be described verbally and provided in written form to patients and families to ensure understanding and to reference at home.

The "How?" of Educational Strategies

How patients and families are educated is critical. Sadly, provider education often is inadequate or infrequent, likely a function of time pressures in clinic settings. Nonetheless, several general principles and strategies are recommended to enhance the effectiveness of education. These are described below.

Education as an Ongoing Process

Particularly with chronic diseases, patient and family education is not fully accomplished in a single session at the time of a new diagnosis. Patients and their families are often distressed when a chronic condition is first diagnosed, and this distress may interfere with retention of information about the condition and its treatment. Also, chronic conditions are complex and have a variable course, which necessitates modifications in treatment plans and the need to re-educate. Moreover, drift can occur across time, and "bad habits" (e.g., incorrect steps for using an inhaler) can develop that negatively impact adherence. Similarly, as children age, they become more responsible for their regimen and may need targeted, direct education to ensure they fully comprehend their prescribed care (see Chap. 4 for more discussion). Thus, education continues over time and involves repetition and rewording of information as needed.

Effective Verbal Communication

Verbal instructions to patients and families must be clear, concise, and relevant to educational objectives. In addition, to facilitate patient or parent understanding and recall of information presented, clinicians should:

- Be friendly rather than businesslike
- Provide instructions early in the clinical encounter
- Stress the importance of the instructions
- Use short words and sentences and avoid jargon
- Use explicit categorization (e.g., "I am going to tell you what is wrong, what tests need to be done, and how to treat your child's illness.")
- Repeat information as needed, particularly when children are first diagnosed as patients and parents may experience emotional distress which interferes with recall
- Check for understanding of the information and openly encourage questions, including any barriers to adherence anticipated by the patient or family
- Determine if patient and family expectations and/or concerns have been addressed and secure a verbal commitment to attempt to follow the prescribed regimen

Written Communication and Other Media

Clinicians should use written materials (pamphlets, brochures, or instruction sheets) and other media (videos, computer programs, texting reminders or messages, and websites) to reinforce and enhance verbal instructions. However, most clinicians are not well trained in how to develop these educational materials. This situation often results in health education material that exceeds the reading level of parents and children (Singh, 1995). For example, one study found that reading grade level of written asthma plans ranged from 4.9 to 9.2, although the recommended level is fifth grade or lower (Forbis & Aligne, 2002). This situation is more complex for pediatric patients. Written and other educational materials must be designed to address normal variations in cognitive development for children at various ages. Duncan and colleagues developed pictorial asthma action plans accompanied by short phrases and words (Duncan et al., 2018). They conducted focus groups with stakeholders (patients, parents, and physicians) to obtain their unique perspectives on what topics should be covered. All stakeholders reacted positively to the pictorial action plans and viewed them as potentially effective compared to standard written action plans (Duncan et al., 2018).

There are several formulas for calculating readability, including Dale-Chall, Fry, Flesch, and SMOG (Meade & Smith, 1991). These formulas consider the average number of syllables per word, average number of words per sentence, and/or word length in characters to calculate a standard reading score or approximate reading grade level from samples of a text. There are specific computer programs (Meade & Smith, 1991) and options within word processing programs that will rapidly calculate different readability formulas. However, there are variables other than readability level that should be considered in developing educational materials. These characteristics are summarized in Table 8.1.

Clinicians may not need to develop educational materials from scratch. There are well-developed educational materials available for patients with a variety of chronic health problems and their families, with many readily available on the Internet.

Table 8.1 Factors to consider when developing written health education materials

Factor	Recommendations
Organization	Use abstracts, headings, subheadings, and questions at the beginning, end, and/or interspersed throughout the text. Make sure paragraphs/sections address a single purpose or idea
Writing style	Use active rather than passive voice (e.g., "take this medicine right after breakfast" rather than "this medicine should be taken after breakfast")
Illustrations	Use pictures, drawings, diagrams, tables, graphs, or charts to illustrate concepts and summarize material. Make sure these are relevant to the content of the text and appropriate for the target audience
Typography	Use legibly and attractive type fonts, sizes, formats, and colors
Tailoring	Tailor material to target audience. Consider age, gender, cultural and experiential factors, and attention level. Use "focus groups" or small groups of persons from the intended audience to preview material and make changes prior to final version
Health literacy	Patients and families need to listen, read, understand, and use health information appropriately. Readability level generally should be at the fifth grade and lower for adults and matched to the reading level of children

Note: Adapted from recommendations by and Aligne (2002), Meade and Smith (1991), and Singh (1995)

Also, national organizations provide pamphlets and information on their websites for patients and their families (e.g., see Oermann et al., 2003, for their recommendations for the top 10 best websites for asthma education). Clinicians need to carefully review generic educational materials to determine appropriateness for their specific population of patients and families. Also, families need to be cautioned that not all information available on websites is correct. They should access websites sanctioned by governmental agencies (e.g., Maternal and Child Health, NIH) or national foundations with professional oversight (e.g., Arthritis Foundation; Cystic Fibrosis Foundation). They can also read articles that have reviewed and evaluated the content of websites (Croft & Peterson, 2002; Oermann et al., 2003).

There is good evidence that educational approaches combined with behavioral strategies are effective in improving adherence to regimens for pediatric diseases (Rapoff, 2010; Wu & Roberts, 2008). When patients are diagnosed with a chronic illness, such as type 1 diabetes, certified diabetes educators can provide information beyond just that about the disease. Rather, these educators can also share guidance regarding ways to promote adherence to regimen components, such as how and when to administer insulin, suggestions for dietary intake, and strategies for remembering to monitor blood glucose levels.

Modeling and Behavioral Rehearsal

Clinicians need to be certain that patients and their families know how to carry out regimen tasks. It is often not sufficient to provide verbal and written instructions, particularly for complex regimens. The clinician needs to model how to execute

more complex regimen tasks, give the patient and parent opportunities to practice the tasks under observation, and provide corrective feedback as needed. For example, children with asthma often have difficulty with proper administration of inhaled medications using a metered-dose inhaler (MDI) (e.g., Can et al., 2020). Inhaler use skills are critical because improper use of an MDI will result in medication being deposited into the mouth or throat and not into the lungs. Patients and their parents can be provided with specific written instructions with illustrations (see Fig. 8.1).

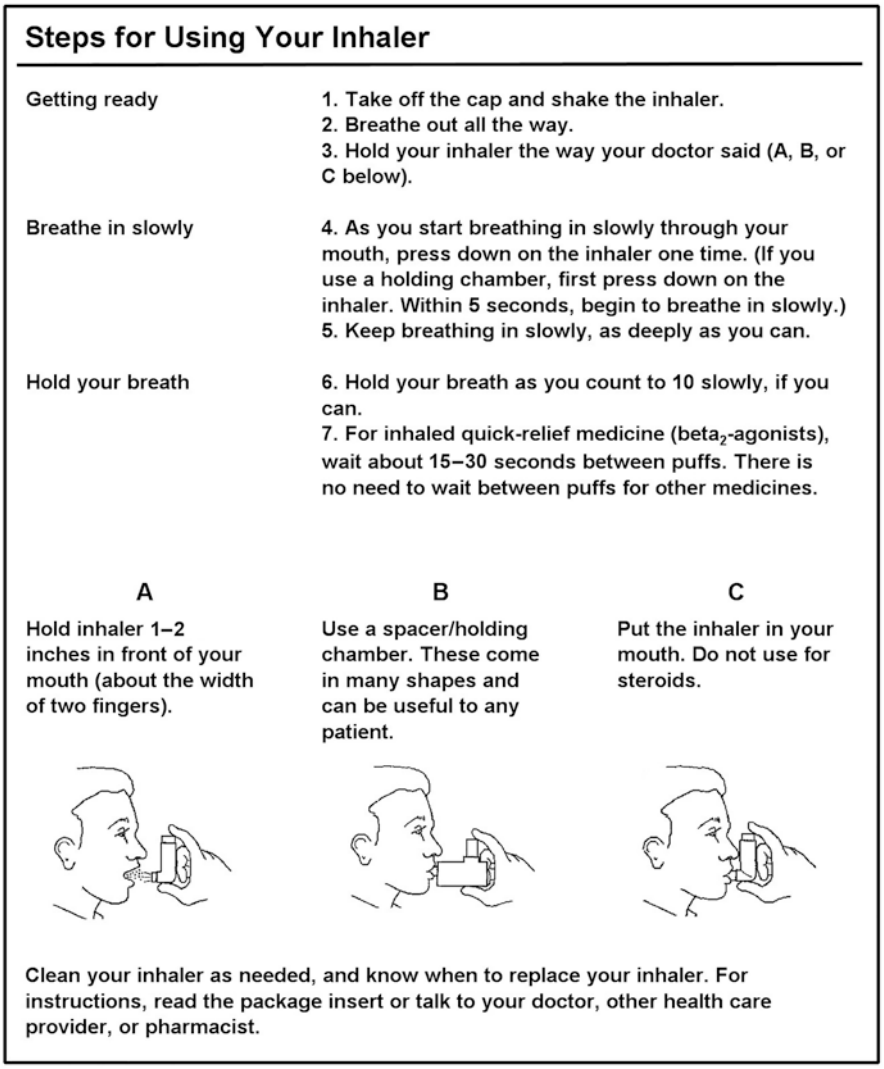


Fig. 8.1 Instructions for using a metered-dose inhaler. (Adapted from: National Asthma Education and Prevention Program (1997), in the public domain)

However, in most cases, proper MDI technique will need to be modeled by the clinician, and patients or parents will need opportunities to practice at clinic appointments to receive corrective feedback from the clinician (McCrossan et al., 2022).

Summary of Educational Strategies

Clinicians need to take seriously their role as educators. Patients and their families deserve to receive high-quality education that fosters knowledge about diseases and their treatments and the necessary behavioral skills to carry out regimens. There is some evidence that patients and their parents do not receive basic education about diseases and how to manage them. For example, one study found that 34.7% of patients with asthma reported receiving some education (e.g., how to use a metered-dose inhaler) from their providers (Orrell-Valente et al., 2011). Clinicians should remember that the desired outcome of educational efforts is to affect behavior change and not just improve scores on tests of knowledge. There is good evidence that educational strategies are *necessary but not sufficient* to sustain adherence, particularly to complex chronic disease regimens (Rapoff, 2010). Other strategies will often be needed.

Organizational Strategies for Improving Adherence

Increasing Accessibility to Healthcare

Some patients do not regularly contact the healthcare system. Accessibility to healthcare can be limited because of financial reasons, transportation problems, and inconveniences inherent to healthcare settings. Accessibility can be increased by putting patients and their families in contact with social service agencies that can assist them in finding transportation and medical coverage. Also, healthcare can be brought to the patient, through outreach clinics in schools, churches, or even in the patient's home. These types of outreach clinics may be cost-effective, if they reduce morbidity, mortality, and overuse of expensive medical services, such as emergency room visits. More recently, telehealth or video-based clinic appointments have become an option to help improve accessibility (e.g., Lin et al., 2020).

Consumer-Friendly Clinical Settings

Consider the following scenario. A mother brings her sick child to an outpatient acute care clinic, where she is confronted with harried and terse personnel who take 30 minutes to check her child in to see a doctor. She takes her child to the waiting

room, which is full of other parents with sick and crying children. The waiting area is sparse, devoid of proper play materials for children. After waiting another 15–30 minutes (by which time her child is quite irritable and crying), she is then ushered into a clinic room, which is sparse and lacking any books or play materials for her child. Her child is finally seen by a staff doctor or resident, after seeing a nurse and medical student. Her child never has been seen by this doctor before, and so the mother must catch the doctor up on her child's relevant medical history. She is briefly told what is wrong with her child and given a prescription, with little time to ask questions or receive assurance that her child is not gravely ill. Sound familiar? This scenario may be embellished but something like this can be observed in teaching hospital clinics around the country. This hypothetical mother may likely leave this clinic in no mood to cooperate or return to the clinic any time soon, unless her child continues to be acutely ill, in which case she may elect to take her child to the emergency department. The message here is that clinical settings need to be consumer friendly.

A consumer-friendly setting would yield a very different scenario. Pleasant and helpful personnel would greet the mother and child, and the child would be checked into the clinic in a timely fashion. The waiting area would be full of a variety of interesting and developmentally appropriate play materials. There may even be volunteers who would play with and read to children. The child would only stay in the waiting area for 10–15 minutes and then be escorted to a clinic room that again has engaging play and reading materials. A doctor, very familiar to the mother and child, would then enter the room, sometimes accompanied by a medical student. After the child is examined, the mother would be given a thorough explanation of what is wrong with her child and what treatment recommendations the doctor prescribes for her child's illness. The mother would also be given ample opportunity to have her questions and concerns addressed. She would then leave the clinic with specific and understandable instructions on how to treat her child and what to do if her child has worsening symptoms. In this consumer-friendly scenario, the mother is likely to leave the clinic more satisfied and more favorably inclined to carry out the doctor's treatment recommendations.

Perhaps providers would do well to consider healthcare as a competitive business (in the good sense of this) where they must outdo their competitors in delivering the best and most satisfying service to their customers. Taking this position would most likely result in having more attractive and responsive clinical settings. There would also be continuity of care, where the same physician sees a child at each clinic visit. Patient and family satisfaction with care is significantly associated with better adherence (e.g., Taylor et al., 2016). Continuity of care would also reduce the likelihood of conflicting and incongruent advice stemming from having different providers involved in the child's healthcare.

Increasing Provider Supervision

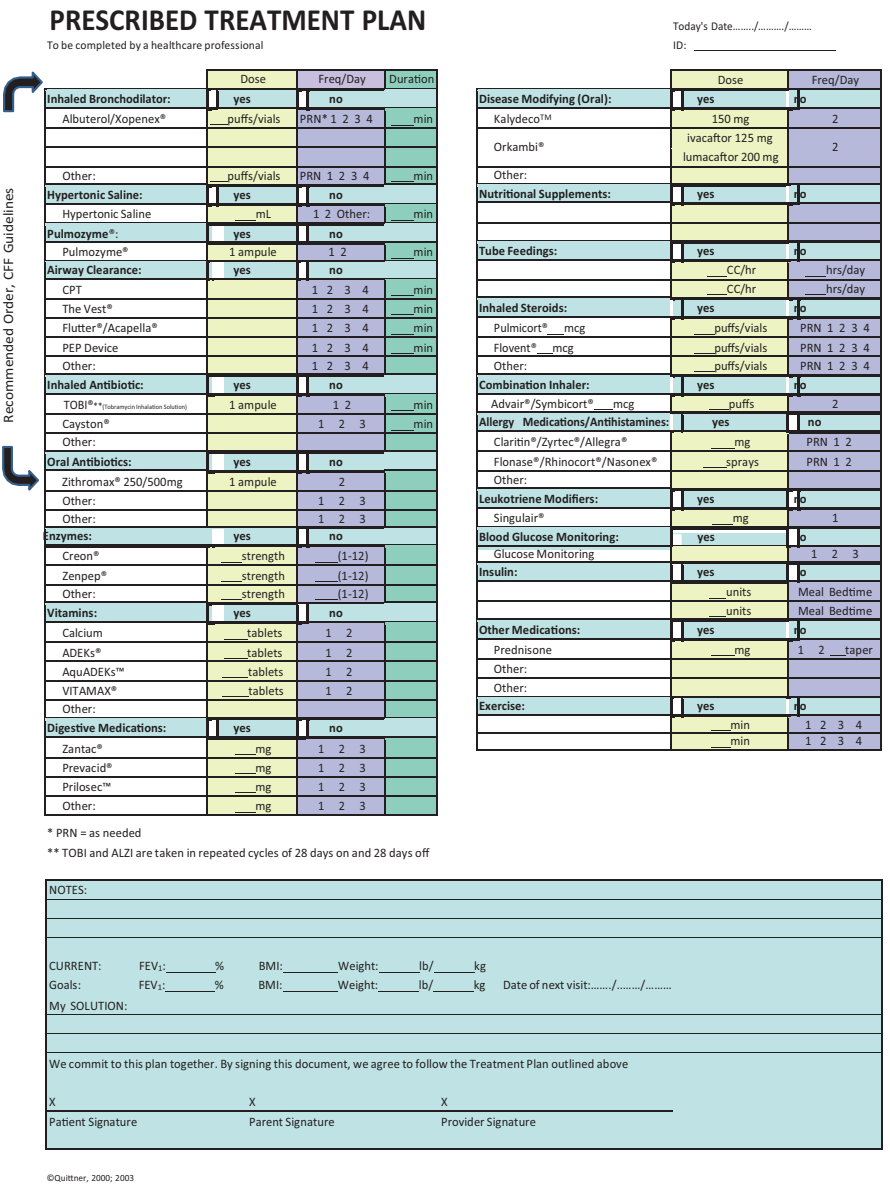
Provider supervision can take many forms. The most basic form is asking about adherence-related issues during clinic visits. This needs to be done in a nonjudgmental and specific way, which is more likely to foster open communication and effective problem-solving (see Chap. 5 for more guidance). If the patient and family have agreed to follow a particular regimen and still have trouble with being consistent, the provider can ask something like this: "Taking medication across time is hard for lots of people. What gets in the way or keeps you from being consistent in taking your medicine?" This type of questioning can lead to reduced social desirability in responding and effective problem-solving about how to reduce identified barriers. Rohan et al. (2013) demonstrated that healthcare providers can be trained to query appropriately and problem-solve with families in improving medication adherence in pediatric asthma.

Providers can increase supervision of regimens in other ways. Patients with adherence concerns can be brought back to clinic for more frequent follow-up visits. This allows for more opportunities to monitor progress and address any concerns. With adult patients, follow-up visits were significantly related to better medication adherence (Axelsson et al., 2015; Brookhart et al., 2007). Also, when having questions or concerns, patients and families can phone a "report line" or phone number staffed during the day and recorded after hours. Emails and texts can also be used to share information, including messages sent through electronic health records (e.g., EPIC). Staff can then respond in a timely manner to parental or patient concerns and address barriers to adherence (Rapoff & Barnard, 1991). Clinic personnel could also call patients and families at critical times (e.g., asthma exacerbations) when adherence is likely to be a problem.

To properly monitor regimen adherence, providers need to remember what they prescribed. Sometimes there is confusion between patients and providers about what has been prescribed, especially when changes are made in response to exacerbations, for example. This most often occurs with chronic disease regimens having multiple regimen components. To minimize confusion, providers, patients, or parents can keep track of regimen requirements and changes made over time using a standard form (see Fig. 8.2 for a sample form for patients with cystic fibrosis).

Simplifying and Minimizing Negative Side Effects of Regimens

Patients and their families have a finite amount of time, energy, and resources to devote to medical regimens, if they are to maintain some semblance of a normal family life (Patterson, 1985). Providers need to help them strike this balance by minimizing the complexity, costs, and negative side effects of regimens (Winnick et al., 2005). Reducing complexity might involve prescribing once daily versus multiple daily doses of medications. Indeed, prescribed daily doses were inversely



PRESCRIBED TREATMENT PLAN

To be completed by a healthcare professional

Today's Date...../...../.....

ID: _____

Recommended Order, CFF Guidelines

	Dose	Freq/Day	Duration
Inhaled Bronchodilator:	yes	no	
Albuterol/Xopenex®	___puffs/vials	PRN* 1 2 3 4	___min
Other:	___puffs/vials	PRN 1 2 3 4	___min
Hypertonic Saline:	yes	no	
Hypertonic Saline	___mL	1 2 Other:	___min
Pulmozyme®:	yes	no	
Pulmozyme®	1 ampule	1 2	___min
Airway Clearance:	yes	no	
CPT		1 2 3 4	___min
The Vest®		1 2 3 4	___min
Flutter®/Acapella®		1 2 3 4	___min
PEP Device		1 2 3 4	___min
Other:		1 2 3 4	
Inhaled Antibiotic:	yes	no	
TOBI®**(tobramycin inhalation solution)	1 ampule	1 2	___min
Cayston®		1 2 3	___min
Other:			
Oral Antibiotics:	yes	no	
Zithromax® 250/500mg	1 ampule	2	
Other:		1 2 3	
Other:		1 2 3	
Enzymes:	yes	no	
Creon®	___strength	___(1-12)	
Zenpep®	___strength	___(1-12)	
Other:	___strength	___(1-12)	
Vitamins:	yes	no	
Calcium	___tablets	1 2	
ADEKs®	___tablets	1 2	
AquADEKs™	___tablets	1 2	
VITAMAX®	___tablets	1 2	
Other:			
Digestive Medications:	yes	no	
Zantac®	___mg	1 2 3	
Prevacid®	___mg	1 2 3	
Prilosec™	___mg	1 2 3	
Other:	___mg	1 2 3	

	Dose	Freq/Day
Disease Modifying (Oral):	yes	no
Kalydeco™	150 mg	2
Orkambi®	ivacaftor 125 mg lumacaftor 200 mg	2
Other:		
Nutritional Supplements:	yes	no
Tube Feedings:	yes	no
	___CC/hr	___hrs/day
	___CC/hr	___hrs/day
Inhaled Steroids:	yes	no
Pulmicort®___mcg	___puffs/vials	PRN 1 2 3 4
Flovent®___mcg	___puffs/vials	PRN 1 2 3 4
Other:	___puffs/vials	PRN 1 2 3 4
Combination Inhaler:	yes	no
Advair®/Symbicort®___mcg	___puffs	2
Allergy Medications/Antihistamines:	yes	no
Claritin®/Zyrtec®/Allegra®	___mg	PRN 1 2
Flonase®/Rhinocort®/Nasonex®	___sprays	PRN 1 2
Other:		
Leukotriene Modifiers:	yes	no
Singulair®	___mg	1
Blood Glucose Monitoring:	yes	no
Glucose Monitoring		1 2 3
Insulin:	yes	no
	___units	Meal Bedtime
	___units	Meal Bedtime
Other Medications:	yes	no
Prednisone	___mg	1 2 ___taper
Other:		
Other:		
Exercise:	yes	no
	___min	1 2 3 4
	___min	1 2 3 4

* PRN = as needed

** TOBI and ALZI are taken in repeated cycles of 28 days on and 28 days off

NOTES:

CURRENT: FEV_1:_____% BMI:_____Weight:_____lb/_____kg

Goals: FEV_1:_____% BMI:_____Weight:_____lb/_____kg Date of next visit:...../...../.....

My SOLUTION:

We commit to this plan together. By signing this document, we agree to follow the Treatment Plan outlined above

X _____ X _____ X _____

Patient Signature Parent Signature Provider Signature

©Quittner, 2000; 2003

Fig. 8.2 A fillable prescribed treatment plan for cystic fibrosis. (Reprinted by permission from Dr. Alexandra Quittner)

related to adherence in a large systematic review of electronically monitored adherence data (Claxton et al., 2001). Also, multicomponent regimens can sometimes be introduced in a gradual and step-by-step fashion. The complexity is then increased when the patient masters prior steps in a sequence of components ordered in terms

of difficulty level. For example, exercise programs for chronically ill children could be limited to simple exercises and short periods and then gradually increased as the patient demonstrates mastery and increased stamina.

Tailoring regimens to patients' lifestyles and schedules can also reduce the demands of regimens. Clinicians can assess typical daily schedules of patients to determine how the prescribed regimen can be integrated into the patients' daily routines. It is usually easier to alter regimens than to alter established patient routines. To do this requires asking a patient and her family about a "typical day" where the clinician obtains information about what the child does from the time they wake up until they go to bed. The clinician then negotiates with the patient and family about how to integrate regimen requirements into the daily routine and to manage any anticipated problems (e.g., what to do when they must take medication while being away from home). We worked with one child with JIA who disliked doing specific exercises, but she enjoyed watching afternoon cartoons following school. We worked out a plan with the patient and her parents that allowed her do exercises while watching cartoons (an innovation added by her mother was to briefly turn off the TV if she stopped exercising).

With medications, parents may prefer oral liquid medications as they are easier to administer to younger children (Winnick et al., 2005). A surprising number of children and adolescents (and even adults) find it difficult to swallow pills, particularly larger ones. One retrospective chart review of 23 patients with HIV (4–21 years) who had received pill swallowing training found that they experienced a significant improvement in adherence and related improvements in viral load (Garvie et al., 2007). Thus, regardless of the patient's age, clinicians should always ask about the child's skills and comfort in swallowing pills or capsules. A pill swallowing protocol that has been in used for a variety of chronic diseases can be found in Table 8.2.

Patients sometimes stop regimens because they experience negative side effects. Providers need to help patients anticipate and minimize side effects as much as possible. Some medications, such as nonsteroidal anti-inflammatory drugs, cause gastrointestinal irritation and pain, which can be reduced by taking medications with food or taking antacids. Exercise can also be painful, particularly for children with rheumatic diseases. Gradually increasing the intensity of exercise or exercising in a hot tub can minimize discomfort. Doing range of motion exercises as part of rehabilitation from a burn injury can be painful, so the child not only could benefit from scar massage but also some distraction games and rewards for persisting through the discomfort.

Using Motivational Interviewing to Enhance Provider/Patient and Family Communication and Relationships

Motivational interviewing (MI) has been defined by its founders as "a collaborative, goal-oriented style of communication with particular attention to the language of change. It is designed to strengthen personal motivation and commitment to a specific goal by eliciting and exploring the person's own reasons for change within an

Table 8.2 Pill swallowing protocol used for children with cystic fibrosis encouraging pill swallowing in children

A behavioral intervention
Why is pill swallowing important?
Difficulty swallowing pills is a significant barrier to adherence in children. Learning to swallow pills is important for children who must regularly take oral medications. Swallowing pills without difficulty increases adherence, convenience for parents, and the efficacy of medications.
Behavioral intervention
• Uses successive approximations (steps) to establish the behavior (swallowing pills)
• Positive reinforcement (rewards) helps to get the behavior going and maintained
Preparation
• Create a pill swallowing kit, including candy (sprinkles, mini M&Ms, erds), small cups for water, empty gel capsules, stickers, and sticker charts.

• Ask parents to save gel capsules when they remove enzyme beads; these capsules can be used later. Or they can purchase gel capsules over the Internet.
Assessment
• Get approval from the child's physician, and check for allergies to the candies.
• Ask parents if eating candy is okay.
Instructions for successive approximations
Step 1: Ask the child to swallow a sip of water. Praise the child, "great job swallowing the water!" Let the child pick another sticker for this first success!
Step 2: Start with the smallest candy (sprinkles). Let the child feel the candy on their tongue and melting down their throat.
Step 3: Ask the child to "place the candy on the middle of your tongue. Tilt you head back a little, take a drink of water, and swallow the 'pill'."
Step 4: If the child is comfortable with steps 1–3, go on to the next larger candy.
Hierarchy
After several consecutive successes, the child may move on to the next size candy "pill." You can set the pace for moving through the hierarchy below:
• Sprinkles
• Mini M&Ms
• Nerds

(continued)

Table 8.2 (continued)

A behavioral intervention
• Empty pill gel capsule
• Finally, take the prescribed pill!
First session
• Praise the child for both effort and success.
• Most children find swallowing these sprinkles surprisingly easy.
• Sessions generally last 5–10 minutes and should be fun!
• Length of the session should be based on the child's attention and skill.
• If the child has difficulty with a larger piece of candy, end the session with a success by having the child swallow a smaller piece.
• {You can move backward on the hierarchy at any time!}
Homework
• Give the parent samples of each candy, blank sticker charts, and stickers to continue the program at home.
• Encourage the parent to practice each day and to reinforce progress with praise and stickers.
• Be specific about when they will practice (e.g., before dinner).
• After the child earns a certain number of stickers (determined by the parent), the child can earn a small prize, such as crayons, a coloring book, or extra time playing video games or with parents.
• Check progress and continue the pill swallowing program at the next clinic visit.
• This can also be done if child is in hospital.
Future sessions
• Begin the next session with the size candy the child swallowed at the end of the previous session.
• Once the child progresses through the three types of candy, he/she can swallow the empty pill gel capsule.
• Some children move through the hierarchy easily in one or two sessions. Other children may require two to six sessions.
• Be patient and make it fun!
• Continue to praise and reinforce pill swallowing until the behavior is well-established.
Other strategies at home
• Put the pill into a spoonful of ice cream, applesauce, or pudding, and let it slide down your child's throat.
• Swallow the pill with milk or juice instead of water to change the thickness and taste of the liquid.

Adapted with permission from a handout by Alexandra L. Quittner, Ph.D., Kristen K. Marciel, Ph.D., Avani C. Modi, Ph.D., & Ivette Cruz, M.S., *supported by NIH grant #RO1 HL69736*

atmosphere of acceptance and compassion" (Miller & Rollnick, 2013, p. 29). MI evolved from Carl Rogers' client-centered therapy, including Rogers' emphasis on the scientific study of the common process that promotes behavior change, such as empathy (Miller & Moyers, 2017). MI is particularly suited for patients/families who are initially ambivalent or less motivated to change (i.e., improve adherence). Using MI, providers avoid giving advice and instead focus on the patient's or families' own reasons for behavior change (Miller & Moyers, 2017). MI is often combined with other cognitive and behavioral strategies (e.g., problem-solving). This

therapeutic approach also focuses on increasing motivation to change, the "whether" or "why" of change, while structured and skill-oriented strategies focus on the "how" of change (Naar & Suarez, 2021). There are four core processes of MI:

- "Engaging or developing the therapeutic alliance is used to communicate understanding and acceptance of the patient's experience.
- Focusing is a process where the provider collaborates with the patient to set an agenda and concentrate on a target behavior change goal selected by that patient.
- The provider evokes or elicits patient-identified arguments for change.
- The planning process is when the provider helps the patient negotiate a plan for change by setting goals, helping the patient consider various options for change, deciding on a plan, and eliciting commitment to follow through with behavior changes" (Powell et al., 2014, p. 3–4).

To date, there is one published meta-analysis of MI interventions for changing health behaviors for children and adolescents (Gayes & Steele, 2014). The meta-analysis included 37 empirical studies that targeted 9 health conditions: obesity, asthma, HIV/AIDS, type 1 diabetes, infant health, dental health, accident prevention, sleep, and calcium intake. Overall effect size (Hodges's g) of MI compared to active or no treatment was $g = 0.282$, which was statistically significant and slightly higher than a small effect size. The effect sizes varied by health condition, with the largest effect sizes for type 1 diabetes, asthma, and calcium intake. The authors concluded that "MI is an effective and appropriate intervention for targeting child health behavior change" (Gayes & Steele, 2014, p. 521).

Most healthcare providers have not been trained in MI. Strategies successfully used in MI education have included having professionals respond to video scenarios or to vignettes, complete online education, consider a standardized client, employ self-assessment, and practice MI skills with feedback and coaching (Widder, 2017). Yet, many MI skills can easily be integrated into clinicians' routine interactions with patients and families. Resources for MI training, including introductory workshops, are readily available (www.motivationalinterviewing.org, accessed 2/9/22). There is a comprehensive resource for pediatric providers in the second edition of the book *Motivational Interviewing with Adolescents and Young Adults* (Naar & Suarez, 2021).

Summary of Organizational Strategies

Clinicians should avoid the tendency to assign "blame" to patients and their families for adherence problems. Healthcare providers might instead look "inward" first to determine what they do or fail to do that makes it more difficult for patients to follow prescribed medical regimens. Patients and families are burdened enough with the normal daily challenges of life plus additional problems created by disease and treatments. This burden can be lessened by reducing the complexity, costs, and aversive aspects of regimens. Also, the MI emphasis on empathy and patient-centered approaches for behavior change is an important addition to fostering effective communication with patients and their families.

Behavioral Strategies for Improving Adherence

Parental Monitoring and Supervision

The lack of parental monitoring and supervision of medical treatments is a significant contributor to nonadherence, particularly to chronic disease regimens (e.g., Zhang et al., 2016). This becomes critical as patients move into adolescence, where parental monitoring is episodic or nonexistent. Parents of teenagers can appreciate the conflict of trying to be sensitive to their teenager's need for autonomy while recognizing the necessity of providing continued monitoring and guidance. Clinicians need to emphasize with parents not to discontinue monitoring and support of their child's treatment regimen abruptly or completely, even during adolescence.

In cooperation with their children, parents can monitor adherence to treatments using standard forms, such as the one shown in Fig. 8.3. These forms can be placed on the refrigerator, and parents and children can "check off" when a particular regimen task has been completed. This type of monitoring may be used daily until adherence is consistently high, then faded out, and reinstated if adherence drops. Parents can also check medication supplies (e.g., pill containers or inhalers) and devices (e.g., blood glucose meters) for indirect evidence that their children are adherent or nonadherent.

Supervision of regimens needs to be done in a way that is sensitive to the developmental capabilities of children. With younger children, parents will likely have primary responsibility for administering treatments and monitoring disease symptoms. Supervision can then be reduced (but never completely discontinued) as children demonstrate that they can administer their treatments and monitor their disease symptoms consistently.

To avoid unnecessary conflict, parents should be cautioned to monitor and supervise regimens in a supportive and constructive way. They can sympathize (e.g., "I understand that it's hard to remember to take your medicine") but also communicate to their children the importance of adherence, noting that they are available to help their children consistently take care of themselves (e.g., "It's very important that you remember to take your medicine. Let's think of how we can help you to remember").

Prompting Adherence

The first author had a conversation with an 11-year-old boy with JRA who had been referred to for nonadherence to medications. The child was asked what prevented him from being consistent in taking his medications. He said, "It doesn't remind me." Sometimes patients forget, or their symptoms are apparently not noticeable enough to prompt adherence. In these situations, salient and reliable prompts are

Name _____ Dates _____

Regimen requirement	Sun	Mon	Tues	Wed	Thurs	Fri	Sat
Medications							
Exercises							
Diet							
Other							

Fig. 8.3 Treatment Regimen Monitoring Chart

needed to promote adherence. This can be done in several ways. Monitoring adherence and pairing regimen tasks with regularly occurring events (e.g., taking medications with meals) may help to prompt adherence (Park & Kidder, 1996). Also, relatively inexpensive watches or pill containers are available which can be programmed to beep at multiple times during the day to encourage adherence. Cell phones can also be programmed to give audible and text reminders for taking medications or completing other regimen requirements (e.g., see the On-Time Rx® program at www.ontimerx.com, accessed on 2/10/22).

Adherence Incentives

Ideally, patients are prescribed effective treatments that rapidly and pervasively resolve or control their health problems. Thus, the incentive to adhere is that patients get better, feel better, and do better. However, this ideal situation is not consistent with the experience of most patients, families, and providers. For example, nonsteroidal anti-inflammatory medications in the treatment of JIA may not effectively control symptoms for at least 8 weeks from the initiation of therapy (Lovell et al., 1984). Similarly, children with asthma can use their inhaled corticosteroid inhaler yet experience an asthma attack on the same day. More immediate incentives or positive consequences need to be programmed to bridge the temporal gap between initial adherence and the more long-range benefits of adherence. If adherence is then sustained, maximal therapeutic effects may be obtained and provide "natural" consequences (in the form of improved health and function) to further maintain adherence.

The first author and colleagues have taken this approach in utilizing token reinforcement and other programmed positive consequences to improve and sustain adherence to regimens for JIA (Pieper et al., 1989; Rapoff et al., 1985, 1988a, b) and asthma (da Costa et al., 1997). The basic format has been similar. We worked with families to identify target adherence behaviors to operationalize, measure, and alter. The reinforcement program involved giving tokens (points or chips) for adherence, taking away tokens for nonadherence, and requiring the patient to purchase basic and special privileges with the tokens. One such program, the Exchange Program, is reproduced in Fig. 8.4. These types of programs have been particularly effective in improving adherence to chronic disease regimens.

Another frequently used strategy, particularly with adolescents, is contracting. Patients and their parents are taught basic communication and negotiation skills. They are then taught how to develop and implement written contracts which specify what the patient agrees to do, what the parents will provide in the way of consequences for adherence (or sometimes nonadherence), and how to monitor and evaluate patient and parent participation. A generic handout that describes this process is shown in Fig. 8.5.

Discipline Strategies

In lecturing to medical students on the topic of medical adherence, we ask them if they have seen "bratty" behaviors on the pediatric inpatient ward among chronically ill children. Invariably they describe incidents where children with cancer or other chronic diseases are exhibiting negative behaviors and their parents respond ineffectively. We tell the medical students that we need to appreciate how difficult it is for parents of chronically (and maybe terminally) ill children to discipline their children who already have many negatives in their lives. Studies show that these

The Exchange Program is a way for you to encourage your child to take his/her medications more consistently. It is based on the well-established principle that people tend to engage in behaviors that bring rewards and/or allows them to avoid unpleasant events. To earn basic privileges, your child will be required to take all his/her medications in front of you each day. Your child can also earn special privileges (usually engaged in on the weekend) by earning basics on a certain number of days per week. "Basic" and "special" privileges are described below with specific examples.

In addition to awarding privileges, it is very important to praise your child immediately after he/she takes his/her medications. In the long run, the positive attention you show to your child for taking his/her medications will be more important in encouraging further cooperation and responsibility for his/her treatment. If your child consistently takes his/her medications, he/she is more likely to feel better and be more active which should be rewarding for you and your child.

There are two types of privileges your child can earn: basic and special. Basic privileges include the use of the telephone, watching TV, and playing outdoors (but not off the property). Basic privileges are earned as a package, on a daily basis, and a day ahead of time. For example, if your child takes his/her medications on Monday, he/she earns basic privileges for Tuesday.

Your child can also earn special privileges depending on the number of days he/she has earned basics during the week (and you give permission). For the first week on the program, your child must earn basics on 4 of 7 days to earn a special privilege; for the second week, 5 of 7 days; for the third week, 6 of 7 days; and for the fourth week, 7 of 7 days. You and your child will come up with a list of special privileges which may include things like renting a movie, renting a video game, or going out for pizza.

To keep track of how often your child earns basics, use the attached form. This form will also help you determine if your child has earned basics on the number of days required per week to earn a special privilege. Posting this form on the refrigerator will help you and your child to remember to fill it out. Also, it will remind you to praise your child and to award privileges for taking his/her medications.

Fig. 8.4 The Exchange Program for Improving Medication Adherence. (Source: Michael Rapoff, Ph.D., 1988, Professor Emeritus, University of Kansas Medical Center, Department of Pediatrics, mrapoff@kumc.edu)

What if your child does not earn basics? This means that he/she cannot engage in basic privileges for the next day and is restricted to doing homework, school-related reading, and regular jobs and chores that you may assign. If your child does not earn basic privileges, you can be sympathetic and encourage your child to take his/her medications the next day in order to earn basics for the following day. However, it is vital that your child not be allowed to engage in basic privileges he/she has not earned. Children sometimes get upset about this, but do not give in, and let your child engage in privileges he/she has not earned. Also, avoid nagging or lecturing your child. This makes things worse.

Weekly Privilege Summary

Instructions: For each day, record the date, whether basic privileges have been earned for the next day, and your initials. At the end of the week, add up the total number of days basics were earned and whether your child met his/her weekly goal for earning a special privilege.

Day and date	Basics earned? (circle one): Y= yes; N= no	Parent Initials
Monday / /	Y N	
Tuesday / /	Y N	
Wednesday / /	Y N	
Thursday / /	Y N	
Friday / /	Y N	
Saturday / /	Y N	
Sunday / /		

Total number of days basics earned this week =

My child met his/her weekly goal? (Circle one): Yes No

This handout is for parents and children/adolescents who want to learn how to negotiate and contract for changes in behaviors that have a negative impact on the family. To negotiate means to "meet and discuss with another in order to reach an agreement." A contract is a written agreement of what has been worked out in negotiations. By adhering to the following guidelines, most families find that they can work out disagreements in a constructive way. Some families may need the assistance of a professional counselor, at least initially, to implement these guidelines.

How to Negotiate (The Family Meeting):

Chose a *convenient time* to meet as a family. After dinner is usually a good time since most families are together and it does not compete with other activities. Silence phones to avoid interruptions and set a specific time limit for discussions. Most families meet at least one a week for about 30–60 minutes.

Avoid family meetings after there has been a big "blow-up." Wait until anger has subsided and then set a time for discussion. Choose some to *lead the family meeting*. (This is most often a parent.) The leader is responsible for making sure the family meeting is orderly and positive with everyone having a chance to be heard.

Several *rules for effective negotiation* should be followed during family meetings:

Leader Encourages Everyone to Speak

The leader should ask if anyone has anything to discuss. Start with one person and then go to the next. This will help to avoid confusion and give everyone a chance to be heard. Discuss one or two issues per family meeting. Don't try to solve all problems in one meeting. The leader should make sure everyone stays on task and does not shift to other issues or problems not under discussion for a particular meeting.

Use "I" Messages

Family members should specify problem/complaints in a constructive and non-attacking way. For example, a parent is upset because one of the children has not been completing homework assignments. Instead of saying, "You have been irresponsible

Fig. 8.5 Negotiating and Contracting for Behavior Change Guidelines for Families. (Source: Michael Rapoff, Ph.D., 1988, Professor Emeritus, University of Kansas Medical Center, Department of Pediatrics, mrapoff@kumc.edu)

and lazy about doing your homework?" the parent might say, "I am concerned that because your homework assignments have not been getting done, your grades will suffer. I would like to see you be consistent in completing daily homework assignments." These "I" messages (the second example) are much more likely to lead to effective problem-solving as compared to "YOU" messages which often lead to name-calling and defensiveness on the other person's part.

Communicate Constructively

Children (and parents sometimes) may need to be reminded about how to state problems/complaints in a constructive way. If a family member begins to state a complaint in an attacking or non-constructive way, the leader should politely interrupt the person and remind them to state the problem in a constructive way. Occasionally, (particularly when families first begin having meetings), a child or teenager may interrupt others and continue to speak in a negative way during discussions. This person can be asked to leave the meeting (for a short time) until they cool off. Most children and teenagers will correct this negative pattern if they receive constructive feedback and realize that decisions that affect them will be made without their input if they choose to be disruptive during family meetings.

Offer Solutions

Once the specific problem has been identified in a constructive way, the person who identified the problem should suggest a possible solution. Others are then encouraged to offer their opinions.

Plan for Monitoring and Evaluating Solutions

A plan to solve the problem should then be voted on. The plan should include a specific way to monitor how it is working and a time limit for determining if the plan has been effective.

Develop Written Contracts

To formalize solutions to problems, families may find it helpful to draw up a written contract which specifies the conditions of agreements reached during family meetings.

Fig. 8.5 (continued)

The next section provides details of how to develop contracts.

Parents may find it necessary to overrule a decision made in a family meeting.

This should only be done under unusual circumstances and after the reasons have been thoroughly discussed with the children.

Contracting for Behavior Change

To be effective, contracts should be positive, mutually negotiated, and fair to all parties. Contracts should focus on specific behaviors (responsibilities) to be performed instead of vague references and descriptions. (For example, “Pick up dirty clothes in bedroom and put them in a hamper each night” is a better description than “Be more responsible about cleaning the bedroom.”) Contracts should specify rewards/privileges which will be given after behaviors are performed. Specific ways to monitor the terms of the contract should be spelled out clearly. The time period that the contract is in effect should be specified. At the end of the contract period, there should be a review of the contract with modifications made as necessary. Contracts can also include a bonus for performance that exceeds some specified level and a penalty for failure to perform to some minimum level. (This is optional.)

Fig. 8.5 (continued)

Sample Contract

Effective date: April 11, 2009

Family contract for: John Jones and Mr. And Mrs. Jones

Responsibilities	*Privileges*
John will complete the following regimen components each day: take pancreatic enzymes with each meal and snack; administer inhaled antibiotic and bronchodilator medications in the morning, in the afternoon, and in the evening; do chest physiotherapy 3 times; and take inhaled steroid medication twice per day.	If John completes his all regimen requirements each day, he can have phone and TV privileges in the evening. If John completes all his daily regimen requirements on 6 of 7 consecutive days, he can go out with his friends on Friday or Saturday night. If John completes all his daily regimen requirements on 7 of 7 consecutive days, he can go out with his friends on Friday and Saturday night.

Monitoring: Mr. or Mrs. Jones will directly observe whether John completes his daily regimen requirements at least during the first 2 weeks this contract is in effect. For each 2 consecutive week periods John completes all daily regimen requirements, Mr. or Mrs. Jones will observe on 1 less day until John is observed on 3 of 7 days. They will then observe periodically and at unannounced times.

Fig. 8.5 (continued)

Bonus: If John completes all regimen requirements each day without reminders by parents, he can use the family car on one of his weekend nights with his friends.

Penalty: None

_____

John

_____

Mr. Jones

_____

Mrs. Jones

parents, relative to parents of healthy children, are more likely to excuse their children's misbehavior and fail to set and enforce consistent limits (Ivers et al., 1994; Walker et al., 1995). We try to explain to parents of chronically ill children that setting and enforcing reasonable limits is vital to fostering self-discipline in their children. We emphasize to the parents that their children will need more self-discipline than healthy children because their children must cope with the regular demands of life, as well as the consequences (such as adhering to complex regimens) of living with a chronic health problem. Clinicians need to provide parents with concrete recommendations for effective discipline.

So, what is "effective discipline"? There is general agreement that skilled or effective discipline involves the following: (1) a positive environment that promotes appropriate behavior; (2) regular monitoring of children's behavior; (3) ignoring trivial or minor problems; (4) structuring the environment and redirecting children to more appropriate choices; (5) consistent consequences for negative behaviors (such as time-out or other sanctions); and (6) following up on parental instructions. In contrast, undesirable discipline involves inconsistency, noncontingent consequences, harsh punishment, and negative parental demeanor (Cipani, 2004; Socolar et al., 1997). Clinicians need to underscore to parents that effective discipline is not just punishment for negative behaviors. Nonetheless, despite parents' best efforts to provide positive consequences for appropriate behavior, all children (even those with chronic diseases) must contact negative consequences for misbehavior at times (which may include refusing to adhere to their medical regimens).

We often recommend using time-out for younger children (less than 10 years of age) for outright refusals to complete regimen tasks (and oppositional and aggressive behavior in general). Our protocol for time-out, specifically for medical nonadherence, can be found in Fig. 8.6. For older children, we recommend response cost

Time-out is a discipline strategy to reduce negative behaviors. It involves placing your child in a dull place for a short time immediately following an unacceptable behavior. Time-out is generally used with children from 18 months to 10 years. It is effective in reducing problem behaviors such as tantrums, hitting, not minding, and many others. Time-out works best when combined with positive attention and other consequences for appropriate behaviors.

This handout describes the use of time-out when children refuse to take medications, do special exercises, or follow other treatments that have been prescribed by a physician or therapist (so called, "medical nonadherence"). If children do not follow their medical treatments consistently, they may not get the full benefits of therapy. They may even become more seriously ill or disabled by their illness.

Please note that time-out for medical nonadherence should only be used when other techniques have been tried, such as making the regimens easier to follow, reducing negative side effects of regimens, and educating children about their illness and treatment.

A. Preparing to Use Time-out

1. Purchase a small portable kitchen timer.
2. Select a place for time-out, such as a chair in the kitchen. It needs to be a dull but *not* scary or dangerous place. Make sure it is a place where your child can't see the TV or play with toys.
3. There needs to be agreement between all caregivers in the home about how to use time-out and when to use it.

B. Practicing Time-out

1. Before using time-out, discuss it with your child during a time he or she is not in trouble.

Fig. 8.6 Using Time-out for Medical Nonadherence: Guidelines for Parents. (Source: Michael Rapoff, Ph.D., 1988, Professor Emeritus, University of Kansas Medical Center, Department of Pediatrics, e-mail: mrapoff@kumc.edu)

2. Tell your child there are two rules when in time-out:

Rule 1: The time will start only when your child is quiet. If your child yells, cries, talks, or says bad words, the timer is reset as soon as he or she is quiet.

Rule 2: If your child leaves time-out before you let him or her, you will lead him or her back to time-out without saying anything, and restart the time when he or she is quiet.

3. After explaining the rules and having your child repeat them, do a practice time-out to make sure he or she understands the rules.

C. Steps for Doing Time-out

Step 1: If your child refuses to take his or her medicine (e.g.), say to your child, "You are not taking your medicine like I asked you to, you have to go to time-out." Say this calmly and only once. Don't threaten or warn your child. If your child does not go to time-out right away, physically guide him or her to time-out. This may mean walking with your child, taking your child by the hand and leading him or her, or (for little ones) carrying him or her to time-out.

Step 2: When your child is sitting in time-out quietly, set the time for a specific number of minutes. A good rule of thumb is a maximum of 1 minute of *quiet* for each year of life. A 2-year-old would have 2 minutes; a 3-year-old, 3 minutes; and a 5-year-old, 5 minutes.

For children over 5 years, the maximum quiet time is still 5 minutes. If your child makes noises, talks, screams, or cries, reset the time without saying a single word to your child. Do this each time he or she makes any sounds. If your child leaves time-out before the quiet time is up, lead him or her back to time-out and restart the time.

Step 3: After your child has finished time-out, go to him or her and say, "You have been quiet, would you like to get out now?" Your child has to say yes or nod his or her head. If he or she refuses, then restart the time. Don't say this from across the room.

Fig. 8.6 (continued)

procedures, such as token fines and brief "grounding" periods which can be reduced by completing extra chores. However, these negative consequences should only be considered when other strategies previously described (e.g., reducing negative side effects, employing positive incentives) have been attempted and found to be inadequate to improve adherence.

Self-Management Strategies

A variety of strategies can be described under the rubric of self-management, including goal setting, monitoring, and self-administered consequences. Two general strategies will be highlighted here: problem-solving and cognitive restructuring. Children with chronic diseases are faced with many challenges that require effective problem-solving skills, which generally involve the following steps: (1) recognizing and defining the problem; (2) generating possible solutions; (3) developing and implementing a plan; (4) evaluating the outcome of the plan; and (5) revising or selecting another plan if unsuccessful. These skills are especially important as children move into adolescence and are faced with peer influences and social situations that may be lead them to compromise their health. Problem-solving can be rehearsed with patients using standard or patient-generated vignettes. For example, the following vignette relates to glucose testing for patients with diabetes (from Thomas et al., 1997, p. 559): "Now, imagine that your friends ask you to a video game arcade, and it's almost time for you to test your glucose. You don't have your test materials with you, and your friends are impatient to leave. If you stop and test, they will leave without you." Patients can also be asked to keep a diary to identify situations where they are tempted to make compromises related to their regimens that can have deleterious effects on their health. They can then cycle through the problem-solving steps to come up with a plan for managing these challenges. Problem-solving skills trained improved adherence to oral medication in youth (ages 11–18) with inflammatory bowel disease.

Cognitive behavioral theories (Hayes, 1989; Kendall, 1993) emphasize the influence of thoughts or self-generated rules on behavior. Cognitive processes can contribute to adherence problems in two general ways: (1) patients and/or families can fail to generate rules or thoughts about diseases and regimens when it would be helpful to do so (such as "I need to take my medications consistently to give them a chance to work"); or (2) patients and/or families may generate counterproductive rules or thoughts (such as "I'll take my medicine depending on how I feel"). When patients fail to generate helpful thoughts, clinicians can assist them by suggesting helpful thoughts or rules that support better adherence to medical regimens. When they generate unhelpful thoughts, clinicians can help patients challenge or test the validity of these thoughts and substitute more helpful ways to think about their diseases and medical treatments. Clinicians need to recognize the importance of context when teaching patients and their families cognitive restructuring techniques.

Step 4: After time-out is over, ask your child if he or she is ready to take the medicine (or do other things the doctor or therapist prescribed). If he or she still refuses, place him or her back in time-out, and repeat steps 1, 2, and 3. If your child takes his or her medicine, praise him or her, and give other rewards you may have agreed to provide.

D. Special Problems

- *What if your child takes medicine but then spits it out or throws it up?* Check with your doctor about giving another dose (especially if your child swallows some of the medicine). In most cases, you can just give a replacement dose after time-out.
- *What if a brother or sister teases or gives attention to the child in time-out?* Make them take the child's place in time-out. That usually stops them from teasing or giving attention to the child in time-out.
- *What if your child gets so upset in time-out that it makes his or her illness worse?* Check with your child's doctor. In most cases, children should be required to finish time-out as outlined above. In rare cases, medical treatment (such as inhaler medications for children with asthma) may be necessary before resuming the time-out.

Table 8.3 provides examples of adherence-relevant thoughts and the contexts under which these thoughts can lead to positive or negative outcomes for patients.

Acceptance and Commitment Therapy (ACT)

ACT is one of the "third wave" behavior therapies but differs in its focus on a functional contextual approach to behaviors. ACT assumes that behaviors can have different functions for a person in different domains, that different behaviors can belong to similar functional classes, and behavioral change is best accomplished by manipulating contextual factors (Coyne et al., 2011). The goals of ACT for health behavior change interventions are not replacing previous unhealthy psychological events with new healthy ones, but rather concurrently cultivating acceptance of unhealthy events, defusion from strict adherence to those events (i.e., observing the

Table 8.3 Adherence-related thoughts about treatments and diseases that can have positive or negative consequences

Thought	Possible positive consequences	Possible negative consequences
"I take my medicine depending on how I feel; sometimes more, sometimes less."	Useful guide for PRN (as needed) medications if the person can appropriately match with symptoms	Failure to achieve therapeutic drug level for continuous regimens
"This medicine is causing harm or making me feel worse."	Could avoid potentially serious side effects	Premature discontinuation of effective treatment (especially when side effects are not serious and temporary and can be minimized)
"This medicine (treatment) is not helping."	Discuss with provider, and treatment is modified, or other treatments are added	Premature discontinuation of effective treatment (especially if insufficient time has elapsed to judge efficacy)
"I don't really have this disease."	If true, then avoids unnecessary treatments with possible negative side effects	If false, heightens the potential for decreased quantity and quality of life
"My disease is not that bad."	If true, then unnecessary treatments are avoided	If false, heightens the potential for decreased quantity and quality of life

events for what they are as just thoughts in our brain, rather than being entangled and fused with them), and commitment to behaviors that support living in ways that serve healthy goals that are valued by the person (Zhang et al., 2018).

The major components of ACT are (a) *cognitive defusion*, which is deliteralization of thoughts and seeing them as verbal events rather than actual events (e.g., one way to do this is have patients repeat words over and over until the words lose their meaning); (b) *acceptance* (as opposed to experiential avoidance), which involves awareness and compassionate acceptance of unpleasant things (e.g., thoughts, feelings, images, bodily sensations) without any attempt to alter or avoid them; (c) *being present*, defined as ongoing, nonevaluative awareness of psychological and environmental events as they unfold; (d) *self as context*, where self is seen as a constant, unchanging perspective from which the person can observe thoughts, emotions, and external experiences as they come and go (e.g., therapist might ask a child to imagine himself in a safe place, noticing strong emotions as they pass like storm clouds); (e) *values* or domains of importance to people, with the goal of having youth to identify behaviors that will move them in valued directions versus away from them; and (f) *committed action* which refers to committing to actions that service one's valued goals even when psychological discomfort is present (Coyne et al., 2011). Measures of key ACT constructs, such as *The Avoidance and Fusion Questionnaire for Youths*, have been developed and validated for children, adolescents, and parents (Coyne et al., 2011).

ACT-based interventions have been effective in randomized controlled trials with adults for increasing physical activity, smoking cessation, and weight management (Zhang et al., 2018). ACT has also been recommended to enhance traditional

behavioral interventions for individuals with type 2 diabetes (Cardel et al., 2020). In a randomized controlled trial, ACT was tested as an intervention for parents of children with asthma (Chong et al., 2019). At total of 168 parents and their children (3–12 years) completed the study. Parents in the ACT group received a four-session, group-based ACT plus asthma education intervention which was compared to a control group who received an asthma education talk plus three telephone follow-ups. Children whose parents were in the ACT group had significantly fewer emergency room visits due to asthma exacerbations at 6 months postintervention. Parents in the ACT group also reported a significant decrease in psychological inflexibility, anxiety, and stress. Although promising, the researcher recommended that future studies should include a measure of adherence to asthma medications. Other researchers have cautioned that "given the developing state of this literature, any inferences regarding the efficacy of ACT with children and teens are premature" (Coyne et al., 2011, p. 390).

ACT can be a very challenging intervention to master. Like our patients, it has been conditioned in us to view disturbing thoughts, feelings, images, and bodily sensations as detrimental to our mental and physical health and worthy targets to be eliminated by our interventions. Ideas, such as acceptance of negative events and committing to a course of action despite these negative events being present, are not easy concepts or natural ways of learning. Because of the complexity of ACT, practitioners are urged to receive formal training. Helen Brown, Ph.D., has recommended the "17 best ACT programs and courses" (see Acceptance & Commitment Therapy Training: Top 17 Courses (positivepsychology.com), accessed 2/16/22). The 15 best books on ACT-based therapy have been recommended online by Melissa Boudin, PsyD: see 15 Best Acceptance and Commitment Therapy Books – Choosing Therapy, accessed 2/16/22). We would add one other book, a comprehensive training manual for therapists wanting to learn ACT (Luoma et al., 2017). Greco and Hayes (2008) also published a book that discusses age-appropriate adaptations of acceptance and mindfulness strategies for youth.

Psychotherapeutic Interventions

In some cases, medical nonadherence can be embedded in, or exist concurrently with, more serious patient or family psychosocial difficulties (Rapoff & Barnard, 1991). For some patients, nonadherence may be part of a broader pattern of externalizing (e.g., oppositional behavior) or internalizing (e.g., depression) problems. There may also be significant parental or family problems (e.g., parental depression, marital conflict, or domestic violence). Children with chronic health problems and their parents are at risk for psychologic morbidity, and most do not receive necessary mental health services (Bauman et al., 1997). Psychosocial problems may need to be addressed before or concurrent with efforts to manage medical nonadherence by mental health professionals who have extensive experience with children and

families in medical settings. However, underlying patient or family dysfunction is rarely the primary contributor to medical nonadherence, and providers would do well to look elsewhere unless their evaluation reveals the presence of significant patient or family dysfunction.

In rare cases, nonadherence to medications for life-threatening diseases affecting young children has been considered medical neglect on the part of the parent(s). A study conducted at Arkansas Children's Hospital identified six patients with HIV who had high viral loads despite having documented sensitivity to antiretroviral medications and caregiver report of regular adherence (Roberts et al., 2004). These six families were exposed to a three-step intervention: (1) a home healthcare nurse made home visits to provide support at least two times per week for at least 2 weeks; (2) the child was hospitalized for 4 days to directly administer medications and further educate and support caregivers; and (3) failing the other two steps, a physician-initiated medical neglect report was made to the Arkansas Department of Human Services. Caregivers of four of the six children responded to the intervention after step 2, and the remaining two were placed in foster care with subsequent improvements in viral load (Roberts et al., 2004). These are extreme cases but do set a precedent for considering life-threatening nonadherence by caretakers of young children as medical neglect.

Summary of Behavioral Strategies

There are several cognitive behavioral change strategies available to assist patients and their families to improve and sustain adherence to medical regimens. They have been found to be the most effective adherence-improvement strategies, particularly for chronic disease regimens (Rapoff, 2010). However, clinicians must be careful to individualize these interventions to address the unique environmental and cognitive contexts of specific patients and their families.

Individualizing Interventions: Barriers to Adherence and Functional Analysis

Whether a particular strategy or set of strategies is effective in each clinical context depends on how well variables relevant for an individual patient and family have been identified and can be modified to improve adherence. Indeed, "one size does not fit all." Clinicians need to individualize interventions to address the unique environmental and person-related factors that impact adherence. Two such strategies will be discussed here: (1) addressing unique "barriers" or obstacles to adherence and (2) functional analysis or identifying functional relationships that are applicable to behaviors for patients and their families.

Barriers to Adherence

The purpose of this approach is to obtain patient and family perspectives on potential events or situations which may interfere with adequate adherence. This can be assessed via structured interviews, questionnaires, or having patients keep written diaries. Modi and Quittner (2006) developed the *Barriers to Adherence Interview* for children (over 10 years old) with asthma or cystic fibrosis and their parents. Parents and children are first asked to identify barriers to regimen components (e.g., airway clearance, nebulized medications, inhaler use) and to rate how often a barrier occurs and how difficult it is, on a 5-point scale, with 1 = "not at all" and 5 = "a lot." They are then presented a list of 25 barriers and asked to identify any additional barriers from the list and rate frequency and difficulty for each barrier endorsed. Barriers were endorsed quite similarly across illnesses and informants, with the most common barriers being forgetting, oppositional behaviors, and difficulties with time management. Although not statistically significant, moderate negative correlations were found between scores on the barriers measure and parent and child self-report, pharmacy refill, phone diary, and electronic monitoring measures of adherence (Modi & Quittner, 2006).

Tsai and colleagues developed and tested the psychometric properties of two barriers questionnaires, one for parents and one for patients with JIA (Tsai, 2013; Tsai et al., 2014). They found that test-retest reliability (over 19 or fewer days) was adequate (r's ranged from 0.62 to 0.67, all p's ≤ 0.004) for the patient barriers questionnaire and adequate for the parents' version (r's ranged from 0.74 to 0.78, all p's < 0.001). Concurrent validity was demonstrated by significant correlations between patient and parent reports of adherence and the barriers questionnaire. Convergent validity was demonstrated by significant correlations with established measures of related constructs, such as the *Child Adherence Report Questionnaire* for patients with JIA and the *Parent Adherence Report Questionnaire* for parents. The most common barriers reported by both patients and their parents were "patient forgets," "parent was not there to remind patient," "hard to take medication when not at home," and "medication tastes bad." The clinician could use this information to design interventions to address endorsed barriers (such as a reminder strategy to help patients who forget medications). The *Barriers Questionnaire* for patients with JIA is shown in Fig. 8.7.

If standard barrier measures are not available for a particular illness, clinicians can conduct clinical interviews with patients and their families. For example, we routinely interview patients and their parents separately and ask: "What gets in the way of you taking your medicines (or doing exercises, following your diet, etc.)?" One young man with JIA mentioned several barriers related to taking his anti-inflammatory medication when interviewed by the first author: (1) it was harder to remember to take his medications when he was not hurting; (2) when he was under time pressures in the morning to get ready for school and catch the school bus, he sometimes forgot; (3) when he got back home late in the evening from after-school activities, he was tired and ate supper, and after he went to bed, he did not want to

get out of bed even if he remembered he had not taken his evening dose; and (4) he admitted that when he was angry with his parents, he would not take his medicine to "get back at my parents."

Once information has been obtained about barriers to adherence unique to a particular patient and family, evidence-based strategies (e.g., problem-solving, motivational interviewing) can be used to address these specific barriers. For example, clinicians can engage patients in problem-solving to identify potential ways to reduce barriers. With the above-mentioned patient with JIA, we strategized about several options to overcome barriers, such as prompting himself to take medications by setting his watch alarm and ways to manage his anger toward his parents without compromising his health (e.g., conflict resolution and cognitive restructuring of anger-inducing thoughts).

Barriers Questionnaire – Patients with JIA

Patients with arthritis or joint pain find it hard at times to be consistent in taking medications prescribed by their doctor. Below are some things (barriers) that make it hard for patients to be consistent in taking prescribed medications. Please look at the list of barriers, and for each, tell us (1) if you have **ever** experienced this barrier (please circle "yes" or "no"), and, if so, (2) how often you experienced this in the **past 7 days** (please circle one of the possible choices). Also, please write down any other barriers you have experienced that are not on the list.

Thank you very much for filling out this form.

		Have you **ever** experienced this?	How often did you experience this in the **past 7 days**?
1.	I just forget when to take my medications	Yes / No	Never / sometimes / often
2.	It is too hard to take my medications when I am not at home	Yes / No	Never / sometimes / often
3.	I get confused about how many pills of each kind of medication to take	Yes / No	Never / sometimes / often
4.	I feel physically worse when I take the medications	Yes / No	Never / sometimes / often
5.	The pills are too hard for me to swallow	Yes / No	Never / sometimes / often
6.	My parent(s) is/are not always there to remind me to take my medications	Yes / No	Never / sometimes / often
7.	The medications taste bad	Yes / No	Never / sometimes / often

Fig. 8.7 Identifying barriers to adherence for patients with JIA

8.	I am not sure that I need the medications	Yes / No	Never / sometimes / often
9.	I started to feel better and did not need the medications anymore	Yes / No	Never / sometimes / often
10.	Several adults take care of me, and I am often in different places (daycare, school)	Yes / No	Never / sometimes / often
11.	I ran out of the medications	Yes / No	Never / sometimes / often
12.	The drug store ran out of the medications	Yes / No	Never / sometimes / often
13.	I try to avoid medications that involve injections	Yes / No	Never / sometimes / often
14.	Sometimes I just simply won't take the medications	Yes / No	Never / sometimes / often
15.	We did not refill my medications because we did not have enough money	Yes / No	Never / sometimes / often
16.	It is hard to fit taking medications into what I do every day	Yes / No	Never / sometimes / often
17.	I do not like the medications' side effects	Yes / No	Never / sometimes / often
18.	I do not understand why I need to take my medications when I am feeling well	Yes / No	Never / sometimes / often

Are there any other things that get in the way of taking medications that were not on this list? If yes, please write them down here.

Fig. 8.7 (continued)

Functional Analysis

Functional analysis involves identifying relevant, modifiable, and (potentially) causal variables that are applicable to a specified set of target behaviors for patients and their families (Friman, 2009; Haynes & O'Brien, 1990). Although this approach has been historically aligned with applied behavior analysis (see special issue, *Journal of Applied Behavior Analysis*, 1994, volume 27, number 2), its applicability has been extended to clinical psychology in general (Sturmey, 1996; Yoman, 2008). The following steps for conducting a functional analysis can be gleaned from the literature:

- Target behaviors are operationally defined.
- Antecedent events that predict the occurrence or nonoccurrence of target behaviors are identified. Hypotheses are developed concerning the consequences that maintain behaviors (or could maintain behaviors, in the case of low-rate appropriate behaviors), which are of two major types: to obtain something desirable or to avoid/escape something undesirable.
- Direct observational data are collected, when possible, to provide at least correlational confirmation of hypotheses about antecedent and consequent events (Horner, 1994; O'Neill et al., 1990).

Contrary to misconceptions about applied behavior analysis, private events (such as thoughts, feelings, and physiological events) can be entered into a functional analysis as target behaviors (e.g., pain intensity), antecedent events (e.g., dysfunctional thoughts), or consequent events (e.g., pain reduction as consequence of taking medications). However, private events are not afforded any special status compared to other variables.

Information obtained for a functional analysis can be obtained by structured interviews, questionnaires, or (preferably) direct observation over extended periods of time (see O'Neill et al., 1990, for examples of each). Results of the functional analysis are then clinically or experimentally tested by modifying antecedent and consequent conditions and assessing the effects on target behaviors (Allen & Warzak, 2000). For example, the first author and colleagues worked with a 7-year-old girl with severe JIA who was nonadherent to medications, wearing wrist or knee splints at night, and doing a prone lying exercise to prevent hip contractures (Rapoff et al., 1985). Extensive interviews with this patient and her parents and direct observations in the home were conducted to identify relevant variables which contributed to her nonadherence. Antecedent conditions identified included proximal or more specific events (e.g., mother having to excessively prompt and "nag" the child to adhere) and more molar events (e.g., large family with limited financial resources and a mother who felt "overwhelmed" with general child-rearing tasks and stressors of having to care for a child with a severely limiting disease). Consequent conditions identified included the lack of positive consequences for adherence (e.g., child was ignored when she was adherent because she was doing "what was expected" of her) and the almost exclusive reliance on verbal reprimands as a consequence for nonadherence. A token reinforcement and time-out program were implemented to address these antecedent and consequent conditions, and we assisted the family in finding financial support for medical and psychosocial services. Also, we worked with the mother on establishing effective child-rearing skills with all her children. This intervention was effective in improving adherence to each regimen component, and there was some evidence for improvement in joint function.

Technology-Based Interventions

Most children, adolescents, and their parents are very savvy when it comes to understanding and using technology, such as the Internet and phone apps. A survey by the Pew Foundation in December 2010 found that 66% of American adults (18 years and older) had broadband Internet access in their homes, with 81% of 18–33 years having access (Pew Internet & American Life Project, 2010). Adolescents in the United States and beyond are comfortable using the Internet as a source of health information (e.g., Borzekowski et al., 2006; Gray et al., 2005). In designing interventions to improve adherence, we need to take advantage of emerging technologies to reach more patients and their families and to engage them in finding ways to enhance adherence and health outcomes.

eHealth interventions have been defined as "…applications of technology that seek to either improve a client's understanding of health information or us technology as a surrogate for the clinician in treatment delivery" (Cushing & Steele, 2010, p. 937). They offer several advantages: (1) they can be highly structured, thus enhancing treatment fidelity; (2) they can also be tailored to the specific barriers patients and families are facing; (3) more patients and families can have access to adherence interventions from their homes, making them cost-effective; (4) engaging elements such as audio, animation, and interactivity can be built into these programs to make them more attractive and encourage adherence to the adherence interventions; (5) with Internet-based programs, outcome assessments can be online, and use of the programs can be monitored in real time (Drotar et al., 2006; Ritterband et al., 2003).

There are, however, a number of barriers that need to be addressed when using technology-based interventions (Rapoff, 2013): (1) we need to make sure patients and families are proficient in using programs; (2) confidentiality is a significant issue, and information conveyed over the Internet must be protected and HIPPA compliant; (3) technology-based interventions are expensive to develop and require a multidisciplinary team consisting of pediatric psychologists, physicians, nurses, other allied healthcare professionals, developers/programmers (computer, Internet, app), graphic artists, health informatics evaluators, and statisticians for database development; (4) the use of technology must be monitored for quality control purposes; (5) the programs need to be easy to use, and avoid putting excess burdens on patients, their families, or healthcare providers (Drotar et al., 2006; Fisher & Fried, 2003; Ritterband et al., 2003); (6) the lack of professional monitoring is not usually possible for patient or family chat rooms, Twitter, Facebook, and email and text exchanges (so patients and families should discuss content with their clinician); and (7) the lack of personal contact with clinicians may have unexpected negative effects on the therapeutic relationship.

eHealth and mHealth interventions have been developed for patients with asthma (e.g., Kosse et al., 2019), chronic pain (e.g., Palermo et al., 2009), cystic fibrosis (e.g., Davis et al., 2004), encopresis (e.g., Ritterband et al., 2003), headaches (e.g., Connelly et al., 2006), HIV (e.g., Spratt et al., 2017), juvenile arthritis (e.g., Stinson

et al., 2010), sickle cell disease (e.g., Badawy et al., 2018), and type 1 diabetes (e.g., Brown et al., 1997; Deacon & Edirippulige, 2015). In general, these programs produce significant increases in knowledge of disease and its treatment, but not always significant effects on adherence and health outcomes. This should not be surprising given the content of some of these programs. For example, the Starlight Foundation asthma program, "Quest for the Code," is designed for children and teens 7–15 years and covers the following topics: early warning signs and symptoms, identifying and avoiding triggers, myths about asthma, how asthma affects the lungs, proper use of asthma medication devices, long-term control medicine and quick-relief medicine, measuring and monitoring peak flow, and how to answer questions from peers about asthma. The program is very engaging and includes voice-overs by famous actors. Nevertheless, this and other programs lack specific strategies for enhancing adherence. For example, patients and families might instead select from a list of barriers, and the program would use branching capabilities to provide them with specific and tailored strategies for overcoming the barriers they endorsed. In Table 8.4, we present the essential elements of cell phone app or Internet-based programs for enhancing adherence resulting from a brainstorming session.

Another potentially useful technology for enhancing adherence is telehealth, which has been used with patients with asthma and type 1 diabetes (Chan et al., 2007; Heidgerken et al., 2006; Gelfand et al., 2003). Although telehealth interventions have not been studied extensively, one program for children with asthma was a randomized controlled trial that showed significantly better inhaler technique and significantly higher adherence compared to office-based care (Chan et al., 2007). Even without these structured intervention programs, patients and families could be provided cameras and Internet access to discuss and strategize with clinicians various ways to enhance adherence and disease self-management.

Conclusions

Interventions for improving adherence to medical regimens are often suggested in the literature, but there is clearly a need to individualize these interventions based on an assessment of the unique personal, family, social, and environmental factors that are present for patients and families. Such a thorough assessment will better equip clinicians to identify educational approaches, changes in healthcare delivery, and behavior change strategies which may be helpful in improving adherence. We also need to take advantage of existing technologies, like the Internet, to convey educational information and specific strategies for enhancing adherence and health outcomes. One meta-analysis (Cushing & Steele, 2010) found promising results for pediatric eHealth interventions, particularly for those incorporating behavioral and not just educational strategies. Also, the efficacy of eHealth interventions was comparable to interventions delivered face-to-face.

Table 8.4 Essential elements of Internet or cell phone-based programs for enhancing adherence to pediatric medical regimens

1. It would individualize by type of disease and developmental level of patients.
2. It would include an educational component:
(a) Type of disease
(b) How doctors diagnose
(c) Causes/triggers
(d) Course of disease/prognosis (being careful about discussing long-term complications)
(e) Recommended treatments and what they are intended to accomplish
(f) Potential negative side effects and how they can be minimized
(g) Importance of consistent adherence
(h) Chalkboards online where children and parents can talk with each other
3. It would include a behavioral component:
(a) Have patient/family discuss with provider how to simplify regimen and reduce side effects if they appear
(b) Cueing/prompting (calendars, text messages, watch alarms) and assess if strategies were used
(c) Monitoring of adherence to regimen components (self and parents)
(d) Incentives for adherence (point system, contracts) and confirming they have adhered to the program
(e) Addressing barriers to adherence and problem-solving
(f) Disincentives for nonadherence (time-out for younger children, loss of points, brief loss of privileges)
(g) Addressing regimen-related thoughts that may be helpful or not in promoting adherence (e.g., “I feel ok, so I don’t need to take my medicine”)
(h) If electronic monitoring is available, download periodically, and give feedback to patients and families (e.g., bar graph showing % adherence for past 2 weeks)
(i) Monitor symptoms and link to adherence
(j) Booster sessions online and the timing of these need to be determined
(k) Families would have the ability to access strategies even after completing the program
(l) Include family and patient-only sessions within the program
(m) Include communication and problem-solving training
(n) Address how responsibility is allocated within the family for implementing regimen components
(o) Monitor changes in treatment plans for individual patients to make sure they are up to date and agree with their provider’s recommendations
4. It would need to be flashy, attractive to patients, have good graphics and music, not too wordy, and embed opportunities for patients to respond (answer questions, practice a skill like using a monitoring strategy).
(a) Would need creative people to write scripts and choose graphics and music
(b) Would need information technology people to program
(c) Mix up child and adult voice-overs for recording of the script
(d) Expert review of content and focus groups with families in developing the programs

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Chapter 9
Ways to Advance Pediatric Medical Adherence Research

Settle on a Standard Definition of Adherence

As discussed in Chap. 1, the definition of adherence by the World Health Organization retains important elements of the old standby definition by Haynes (1979) and adds language which implies that agreement to follow regimens has been secured from the patient and parents. The definition offered by the World Health Organization defines adherence as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (World Health Organization, 2003, pp. 3–4). If we all use this definition, it may become the standard here in the United States and internationally. This definition is also consistent with an approach to addressing adherence issues that involve patients and families in decision-making and foster collaboration.

Develop Standard Scores Derived from Adherence Measures and Determine Cutpoints for Classifying People into Adherent and Nonadherent Categories

Several scores were recommended by Kastrissios, Flowers, and Blaschke (1996) for medication adherence:

- *Fraction of Doses* (Fr), where Fr = the number of doses taken ÷ the number of doses prescribed. This is the metric derived from pill counts, and the product is multiplied by 100 to obtain a percentage.
- *Daily Count Index* (DCI), where DCI = the number of days on which the prescribed number of doses were taken ÷ the number of days of monitoring. Again, the product is multiplied by 100 to obtain a percentage. This can be derived from

M. A. Rapoff et al., *Adherence to Pediatric Medical Regimens*, Issues in Clinical Child Psychology, https://doi.org/10.1007/978-3-031-27484-8_9

electronic monitoring but not usually pill counts (unless they are done daily, which is unlikely).

- *Prescribed Intervals Method* (PI), where PI = the number of prescribed dosing intervals (± some "forgiveness" interval, such as 2 h) ÷ the total number of possible intervals. This can be derived from electronic monitoring, and the product is multiplied by 100 to obtain a percentage.
- *Exact Daily Adherence* (EDA), where EDA = the number of days when doses were taken as prescribed (including at the recommended dosing interval ± a forgiveness interval) ÷ the total number of days of monitoring. Again, this can be derived from electronic monitoring, and the product is multiplied by 100 to obtain a percentage. This index is derived from the DCI and PI methods and is the most stringent of all the indices.
- *Therapeutic Coverage* (TC), where TC = the number of hours of therapeutic coverage ÷ the total number of hours monitored.

Again, the product is multiplied by 100 to obtain a percentage. TC can only be approximated by electronic monitoring (with knowledge of a drug's half-life). Direct assessment of TC requires pharmacokinetic studies using assays.

For other regimen components, other dimensions will be important, such as duration and intensity of exercise. Cutpoints need to be based on data suggesting that a certain minimum level of adherence is necessary to see meaningful therapeutic changes. This is going to vary by disease and regimen types. The old standard of 80% for medication adherence is not sufficient for some regimens, such as the need for up to 95% adherence to antiretroviral medications in the treatment of HIV (Kobin & Sheth, 2011). An excellent example of determining adherence cutpoints is a study by Modi, Rausch, and Glauser (2011b). They electronically monitored adherence to antiepileptic medications among 124 children who were newly diagnosed with epilepsy. Adherence was determined based on the first 6 months of therapy using group-based trajectory modeling. They identified five trajectories: (1) "severe early nonadherence" group where adherence dropped to zero after the first month of therapy; (2) "severe delayed nonadherence" group where they initially had high adherence but gradually dropped to 20% over time; (3) "moderate nonadherence" group that had significant variability in adherence over time (mean = 70%); (4) "mild nonadherence" group (mean = 85%); and (5) "near perfect" group which maintained adherence around 100% over time. Their results suggest intervening early to boost adherence for many children who are newly diagnosed with a chronic condition.

Revise, Rework, and Make Adherence Theories Relevant to Pediatrics

Virtually all the theories which offer predictions about why patients adhere or fail to adhere to medical regimens have been based on studies with adults. The validity and utility of downward extensions of these models to children and adolescents need to

be verified. Theories are important in that they influence how studies are designed and how researchers react to and make sense of data obtained from their studies. Clinicians and researchers should be careful in adopting existing theories that fail to adequately address the developmental needs, challenges, and capacities of children of various ages and stages of development. For example, assessing self-efficacy perceptions would be relevant for children after they acquire the necessary language and cognitive facility to make these types of judgments about their capabilities to perform a given action. Before they acquire the prerequisite skills, the self-efficacy judgments of parents or caretakers would seem to be more relevant.

Develop Reliable, Valid, Sensitive, and Practical Self-report Measures of Adherence

The more objective measures, such as assays and electronic monitoring, can be invasive, expensive, and not available for all regimen components. Soliciting patient and caretaker reports about adherence remains the most direct and practical way to assess adherence in clinical practice. The way questions are posed can affect how willingly and accurately patients and caregivers report about adherence. Framing questions in a nonjudgmental and time-limited fashion will likely yield more honest and useful reports about adherence. Structured telephone interviews appear to be clinically feasible and would limit recall bias. Also, structured interviews allow clinicians to address ongoing concerns and barriers related to adherence that are revealed by patients and caretakers during periodic phone interviews. As reviewed in Chap. 5 (Table 5.2), there are several promising self- and caretaker report instruments. Some of these, however, are rather lengthy, and further work needs to be done to make them shorter without compromising reliability and validity. For example, the Pediatric AIDS Clinical Trials Group 377 developed a self-report measure for patients to assess adherence to medications for HIV. Patients are asked about the number of missed doses of medication during the preceding 3 days before a clinic visit. “Full adherence” was defined as missing no doses during the 3 days, and “non-full adherence” was defined as missing at least one dose. This measure predicted treatment outcomes with full adherence found in 92% of the children with significant drops in viral loads (Van Dyke et al., 2002).

Continue to Develop Electronic Monitor Measures of Adherence, and Extend Them to Regimen Components Other than Medications

As reviewed in Chap. 5, electronic methods of data collection have been extended to regimen components other than oral medications, such as topical medications (Tusa et al., 2006). There is also the capability for technology-based data collection

methods that can be entered by patients or parents and accessed by researchers and clinician in real time. Data collected by electronic methods can be downloaded and shared with patients and families to enhance adherence (Kamps et al., 2008).

Develop and Standardize Practical Measures of Disease Activity and Quality of Life

Pediatric psychologist will need to work with their medical subspecialty colleagues to determine measure of disease activity relevant to specific chronic diseases. As reviewed in Chap. 6, pediatric psychologists have been very active in developing and validating HRQOL measures with their medical colleagues (Palermo et al., 2008). We need to continue this work because the goal of adherence enhancement is that patients have less disease activity and a better quality of life.

As with adherence measures, clinically meaningful cutpoints need to be determined for classifying disease activity as improved, in remission, or worsened. For example, pediatric rheumatologists have determined cutoff scores for classifying patients with juvenile arthritis as having active or inactive disease using a combination of measures including physician ratings of disease activity, parent and child ratings of well-being and pain, physician determination of active joints by physical exam, and the Westergren erythrocyte sedimentation rate, a laboratory measure of inflammation (Consolaro et al., 2012). These measures had good construct and discriminant validity and are feasible for routine use in clinics.

Validate Primary and Secondary Interventions to Prevent or Minimize Anticipated Declines in Adherence over Time

Most interventions are designed for children who are suspected of being nonadherent to the extent that it compromises their health. *Primary* prevention would focus on patients not yet exhibiting "clinically significant nonadherence" (CSN) which has been defined as "inconsistencies in following a particular regimen that may result in compromised health and well-being" (Rapoff, 2000). Strategies for enhancing adherence at the primary level could involve educational, organizational (e.g., simplify the regimen), and simple behavioral ones (e.g., increased monitoring by providers). *Secondary* prevention would focus on patients for whom CSN has been identified early in the disease course, or their nonadherence has not yet compromised health and well-being. Strategies for enhancing adherence at the secondary level might include more frequent monitoring of adherence by caregivers, positive social reinforcement, and routine disciple strategies (e.g., time-out for younger children). The role of pediatric psychologists would be to train healthcare providers (particularly nurses) to implement primary and secondary interventions and experimentally evaluate the results of these interventions (e.g., Rapoff et al., 2002).

Make Better Use of Single-Subject Design Methodology for Intervention Studies

Although randomized, between-groups, controlled clinical trials (RCTs) are considered the "gold standard" for experimentally evaluating the efficacy of treatments, there is a long tradition in medicine and psychology of investigating the effects of interventions at the individual level using single-subject designs (Barlow et al., 2009). Single-subject designs offer a number of advantages over traditional group designs: (1) they provide flexibility in the choice of independent variables and allowance for changes in these over the course of a study (if something is not working, an intervention can be modified and introduced as a new condition); (2) they accommodate for small sample sizes (appropriate for studying rare conditions or smaller sample sizes available at any one site); (3) they are appropriate when there are ethical objections to withholding treatment; (4) they are better at exposing individual variability in outcome measures; (5) they produce results that are more easily understood by clinicians (who work at the level of individual patients); (6) they have greater potential for attracting busy clinicians to do clinical research; and (7) they are recognized as legitimate designs that can help to establish empirically validated treatments and evidence-based practices (Barlow et al., 2009; Rapoff & Stark, 2008). The most common designs are the reversal and multiple baseline designs that can be used when one patient or more (see Barlow et al., 2009, for the authoritative book on single-subject designs). There have been advances in developing statistical analytic methods for single-subject designs that go beyond just using visual analysis to analyze study outcomes (see Kratochwill & Levin, 2014).

Develop and Test Innovative Adherence Promotion Strategies and Innovative Ways to Deliver the Interventions

It would be better to spend our precious time, resources, and funding to develop and test interventions rather than continuing to feed the correlational machine that promises to discover factors that predict adherence but fails to take the next step of manipulating factors to affect adherence. As documented in Chaps. 7 and 8, we know a fair amount about which strategies can be effective in enhancing adherence. We are also making progress in designing and delivering interventions in attractive and cost-effective ways, such as technology-based programs. Having developed and tested interventions, we know how difficult and time-consuming the process can be, but we are setting a good example for those that we mentor by investing the efforts in enhancing adherence.

Conduct Multi-site, Randomized Controlled Adherence Intervention Trials

Our medical colleagues have been doing this for many years to develop new drugs and test other medical interventions. Those of us who serve on advisory panels or study sections should lobby for greater funding of multi-site studies. The National Institutes of Health allow multiple principal investigators which should help encourage multi-site studies. By joining together, we can problem-solve about adherence promotion strategies and ways to deliver them and increase our sample sizes needed to adequately power intervention studies.

Calculate Effect Sizes in Our Intervention Studies, and Document the Clinical Significance/Social Validity of Our Research

A statistically significant treatment effect gives us confidence that the obtained difference between treatment and control groups is not just chance findings. However, it does not give us confidence about the size, importance, or clinical significance of the effect.

The *Journal of Pediatric Psychology* requires authors to report effect sizes, as do many APA journals. Effect sizes provide information about the magnitude and direction of differences between groups or the relationship between two variables. The most common effect size is calculated by using the "standardized mean difference," which uses the differences between the post-test means in the numerator of the equation and the standard deviation units in the denominator (see Durlak, 2009, for methods for calculating and interpreting effect sizes). Using this formula, a positive effect size would indicate superior results for the treatment group, and an effect of zero would indicate no effect at all. Cohen (1988) recommends interpreting effect sizes as "small" (d = .20), "medium" (d = .50), and "large" (d = .80). As reviewed in Chap. 7, mean effect sizes for adherence intervention studies for chronic pediatric diseases were in the small (d = .20; Pai & McGrady, 2014; d = .34; Kahana et al., 2008) to medium range (d = .58; Graves et al., 2010).

Although effect sizes give us more information than traditional p values, they do not reliably determine if our results are clinically significant or meaningful. A good example is the famous physician's low-dose aspirin trial to reduce the risk of death by heart attack. The effect size was very small (r = .02), but there was a significant risk reduction (44%), and with a large sample size of 22,071, the results were highly significant (p = <.00001), and the trial was stopped early (Steering Committee of the Physician's Health Study Research Group, 1988). We need to go beyond effect sizes and assess the clinical significance of our research.

"The clinical significance of a treatment refers to its ability to meet standards of efficacy set by consumers, clinicians, and researchers" (Jacobson & Truax, 1991,

p. 12). The term "social validity" comes out of the applied behavior analysis tradition and is a broader and more inclusive term than clinical significance. Social validity is assessed at three levels (Kazdin, 1977; Wolf, 1978):

- Goals: Are the specific goals of treatment what society wants? Do they focus on goals relevant to interested parties such as children, parents, referral sources, and third-party payers?
- Procedures: Are the treatment procedures acceptable to consumers in terms of costs, ethics, and practicality?
- Effects: Are effects of an intervention satisfactory to consumers?

One way to assess the social validity of goals is to ask consumers to choose their goals and rate their progress toward these goals. Another way is to assess barriers to adherence and target those identified by patients and caregivers for intervention. To assess social validity of procedures, we can ask patients and caregivers to provide Likert-type ratings of the acceptability of interventions and whether they would recommend it to others. Kazdin (1980) was the first to develop and validate a generic instrument (the *Treatment Evaluation Inventory*, TEI) for assessing treatment acceptability. The TEI is a 15-item questionnaire with items rated on a 7-point Likert scale. It has been modified and shortened to nine items (Kelley et al., 1989). To assess social validity of effects, patients and parents can also be asked whether they improved, stayed the same, or became worse following treatments (Rapoff, 2010). We can also ask judges to rate observations for evidence of changes following intervention. For example, Finney, Rapoff, Hall, and Christophersen (1983) had teachers and graduate students randomly rate chosen videotapes at baseline and post-treatment for the presence of "distracting" behaviors of two adolescents treated for tic disorders. The ratings were much lower at post-treatment, which agreed with objective coding of tic behaviors by trained observers.

Some have argued for determining if the magnitude of change for individual patients treated is statistically reliable. The most popular index in the literature is the Reliable Change Index (RCI) proposed by Jacobson and Truax (1991). The formula for calculating the RCI is as follows:

$$\text{RCI} = \frac{X_{\text{post}} - X_{\text{pre}}}{S_{\text{dif}}}$$

X_{post} is the person's post-test score, X_{pre} is the person's pre-test score, and S_{dif} is the standard error of the difference between two scores. The change is considered reliable or unlikely due to measurement error if the RCI is greater than 1.96 (Ogles et al., 2001).

Health-related quality of life (HRQOL) measures have been collected on healthy and ill children (Varni et al., 2003, 2007). Normative comparisons can be made using these data sets. If, because of an intervention to improve adherence, children with chronic illness fall within the normative range of healthy children on HRQOL scales, that might be considered a clinically significant effect. We need to collect

more longitudinal data on adherence and to determine cut points for self-report and electronically monitored adherence. Modi and her colleagues have been collecting longitudinal data on adherence to antiepileptic drugs. In one study, they compared parents' ratings of adherence to electronically monitored adherence. Parents' ratings of adherence were over the period of 1 week prior to their child's clinic visit, and electronically monitored adherence over the 1 week prior to the clinic visit was used as the reference criterion. They tested the sensitivity and specificity of three cut points, 50%, 80%, and 90%, based on parent ratings and found that the 90% cut point demonstrated the most sensitivity and specificity to electronically monitored adherence, but specificity was still low at 28%. They came up with a "correction factor" for parent-reported adherence which was 0.83. So, if a parent reported 100% adherence, a clinician could interpret this rate at approximately 83% with the correction factor (Modi et al., 2011a).

Standards determined by expert consensus could be proposed to determine meaningful outcomes. In the chronic pain literature, the consensus by many different studies and investigators is that a 2-point change on a 0–10 pain rating scale is a meaningful change (Rapoff, 2010). Others have suggested a 50% reduction in pain scores from baseline to post-treatment for individual patients (Hicks et al., 2006). Intervention studies have used expert opinion to establish standards for meaningful clinical change such as an NIH consensus panel recommending optimal calcium intake levels of 1500 Ca per day for children (Stark et al., 2005).

Define, Document, and Minimize Attrition in Research Studies

Attrition or the loss of eligible participants is a significant threat to the internal, external, and statistically validity of intervention studies (Karlson & Rapoff, 2009). Attrition may compromise the internal validity by altering random composition of groups and their equivalence. External validity may be compromised due to the potential for attrition to limit the generalizability of results to only those who are retained in a study. For example, those participants retained in a study may be more adherent or have other characteristics that differ from those who drop-out. Attrition may also compromise the statistical validity by reducing sample size and power or by systemically altering the variability of samples.

As shown in Fig. 9.1, attrition can occur at any phase of a study and can have different impacts on a study. Enrollment refusal occurs when participants who are otherwise eligible either decline to participate or cannot complete requirements. Whereas post-randomization attrition occurs when participants do not receive the allocated intervention, prematurely discontinue the intervention, or do not complete follow-up measures after receiving the intervention. Determining reasons for or predictors of attrition is usually done by asking participants why they refused or dropped out and/or by using available demographic or disease-related information to compare those who complete a study to those who drop-out.

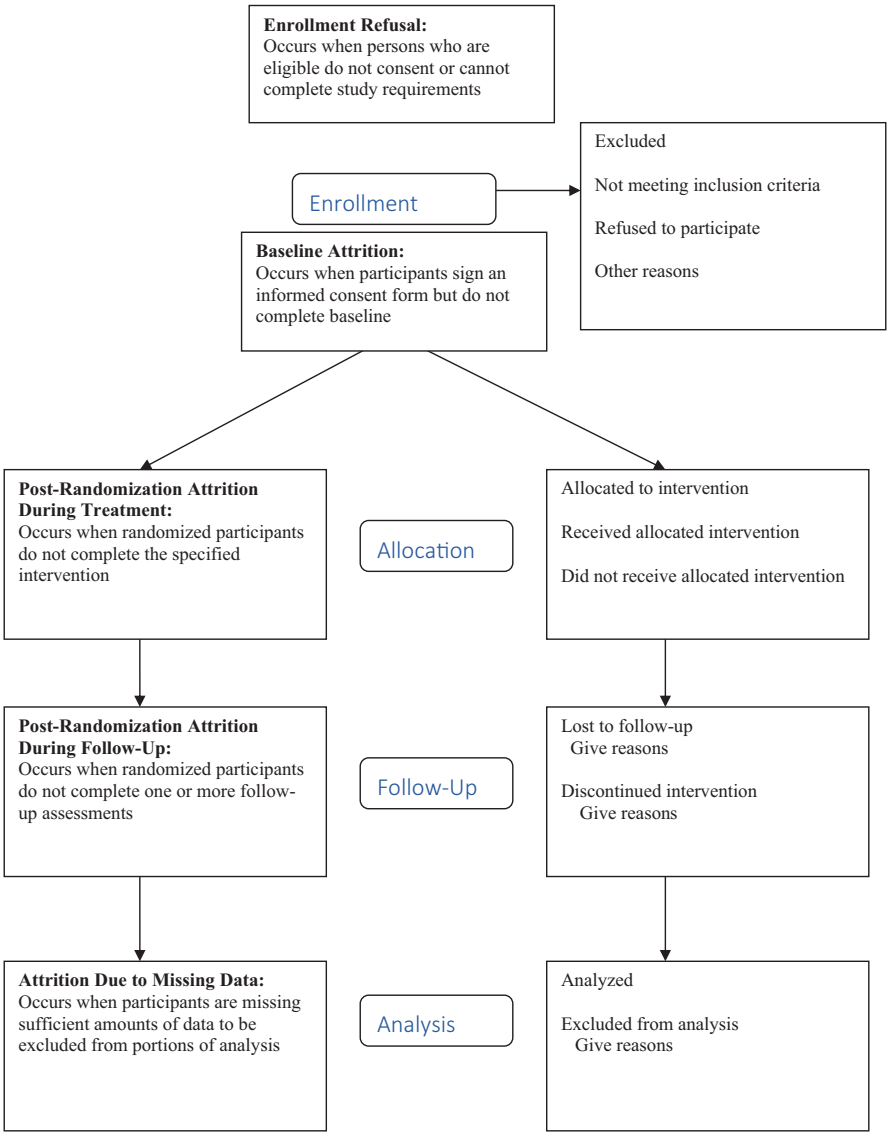

Fig. 9.1 Definitions of attrition. (Reprinted by permission from Karlson and Rapoff (2009))

Karlson and Rapoff (2009) reviewed attrition rates in 40 cognitive behavioral interventions involving children and adolescents with a chronic medical condition. Mean rate of enrollment refusal was 37%, and mean rate of initial follow-up attrition was 20%. Mean rate of extended follow-up attrition was 32%. Strategies that can be used to limit attrition include tailoring recruitment in the study population, providing personalized feedback, maintaining consistent study procedures, providing incentives for participation, and using intensive tracking measures (Karlson & Rapoff, 2009).

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Chapter 10
Cultural, Ethical, and Legal Issues Involved in Adherence Clinical and Research Activities

Cultural Issues

Definitions of Culture

There is no clear consensus in the literature on how to define culture. We found two that we thought were reasonable and comprehensive, yet succinct. Rosal and Bodenlos (2009) defined culture as "…what is learned, shared, transmitted intergenerationally, and reflected in a group's values, beliefs, norms, behaviors, communication, and social roles" (p. 39). Tan-McGrory, Madu, Kenst, and Betancourt (2020) defined culture as "…as a system of beliefs, values, rules, and customs that is shared by a group and used to interpret experiences and direct patterns of behavior" (p. 340). Both definitions emphasize shared beliefs and rules/norms and their impact on behavior. It would be easy to see how these elements of culture could impact patients and caregivers' understanding of medical regimens and whether they adopt them.

Why Is Culture Important?

As documented in Chap. 2, socioeconomic status (SES) and race have been consistent predictors of adherence to pediatric medical regimens, with lower SES and ethnic minority status predicting lower adherence. Ethnic status also affects choices patients and caregivers make about treatment of chronic diseases. One study found that parents of Latino children with juvenile arthritis or arthralgia were likely to use complementary and alternative medicine (CAM), with the most common modalities being prayer and massage therapy to treat pain (Zebracki et al., 2007). The researchers did not measure adherence to conventional treatments so there is no way to ascertain if use of CAM had any effect on adherence to mainstream treatments.

M. A. Rapoff et al., *Adherence to Pediatric Medical Regimens*, Issues in Clinical Child Psychology, https://doi.org/10.1007/978-3-031-27484-8_10

They also did not measure health outcomes, so there is no way to know if CAM benefited pain. They did find improved psychological functioning but only for the children with arthralgia. The researchers recommended that pediatric rheumatologist educate families about the potential benefits and limitations of CAM.

Health outcomes are also affected by cultural factors. One study compared Hispanic and non-Hispanic children in the United States with acute lymphoblastic and electronically monitored adherence to mercaptopurine. In addition to significantly lower rates of adherence in the Hispanic group, they also found significantly higher rates of relapse (Bhatia et al., 2012). Also, survival rates in sub-Saharan Africa for children with malignant solid tumors are much lower than those in other parts of Africa, such as Egypt and South Africa. In developed countries the survival rates approach 80%, but in Africa >80% of children do not survive. The researchers attribute these differences to resource deficiencies, inadequate healthcare budgets, the lack of trained providers, scarce lab facilities, and inconsistent drug supplies (Hadley et al., 2012). So not only can race and country of origin affect health outcomes, but they also affect access to adequate healthcare.

Outcomes for treatment of asthma in young people and adults are known to be poorer among minorities and those with lower SES status, including higher rates of emergency room visits due to acute exacerbations (Haselkorn et al., 2008). Contributing factors for this discrepancy in outcomes include lack of access to care, symptom perception, lower literacy levels, and lack of understanding of how to manage asthma effectively (Harrington et al., 2015; Poureslami et al., 2012; Stewart et al., 2013). Culturally specific education programs for children with asthma have shown positive results in decreasing hospitalizations for acute exacerbations and improving asthma control and quality of life (McCallum et al., 2017).

The American Psychological Association adopted new guidelines to "provide psychologists with a framework for providing multiculturally competent services." The guidelines cover multicultural competence in clinical service, research, education, and consultations (https://www.apa.org/monitor/2018/01multicultural-guidelines).

Cultural Factors in Clinical Activities

Providers need to consider cultural influences in clinical encounters with diverse patient and family populations. Tan-McGrory et al. (2020) discussed the following guidelines:

1. Ask patients and families about what is important to them, and share how you intend to address their concerns.
2. Involve them in the decision-making process, including children as young as 7 years old if they are cognitive capable. Inquire if they want certain family members involved in making decisions. In certain cultures, the patriarch of the family is heavily involved in making decisions.

3. Ask about customs that may impact healthcare decisions, such as dietary preferences. Religious beliefs can also be impactful in what type of tests or treatments is acceptable. For example, those in the Jehovah's Witnesses faith prohibit blood transfusions.
4. Assess language proficiency. About 20% of the US population speak other languages. Lack of English proficiency can lead to misunderstanding of treatment instructions and adversely affect adherence and treatment outcomes. Use American Translation Association-certified translators when needed, and do not rely on family members who speak English to translate unless there is an emergency.
5. Immigration status may be important, particularly for undocumented immigrants who may not have health insurance, may lack access to healthcare, and may not disclose information from fear of being deported.
6. Be aware of styles of communication, differences in personal space, eye contact, and body language. Be aware that lack of resistance to recommendations or deference to the provider may not mean the family agrees with treatment recommendations.

Cultural competency has been addressed extensively in the nursing literature. Sharifi, Adib-Hajbaghery, and Najafi (2019) proposed a competency conceptual model that is reprinted in Fig. 10.1. They detailed the antecedents to competency,

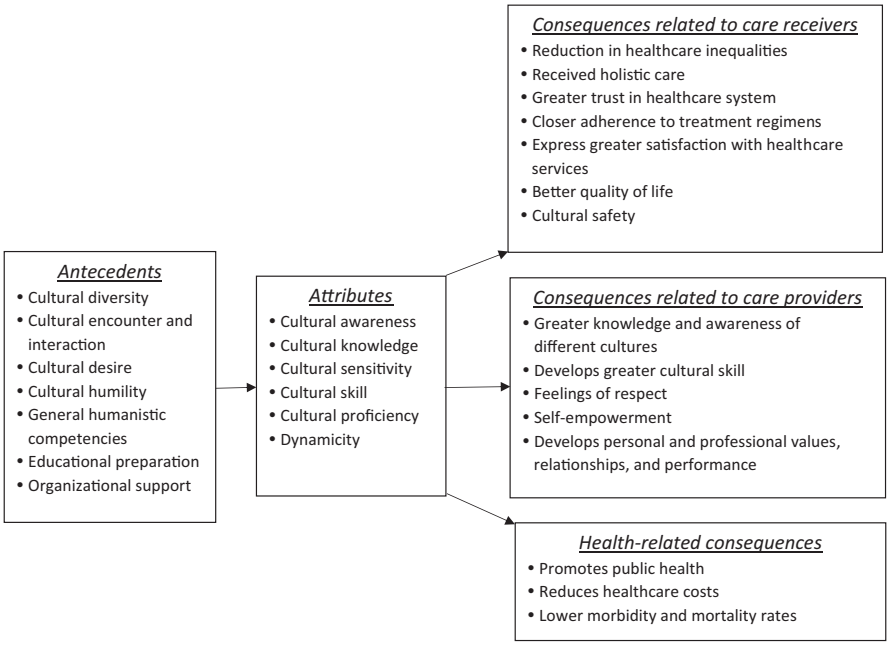

Fig. 10.1 Proposed conceptual model of cultural competence. (Reprinted from Sharifi et al. (2019), Copyright (2019), with permission from Elsevier)

such as education preparation; attributes of competency, such as dynamicity (being dynamic or energetic); and consequences of competency for those receiving care, for providers, and health-related ones. This model provides a useful guide on how to develop cultural competency at the provider and organizational level.

Cultural Issues in Research Activities

Race, ethnicity, and SES are the most widely researched culture-related variables in healthcare studies (Clay, 2017). However, there is no uniform way these types of data are collected. For example, SES has been measured by household income, education, occupation, and perceived social status (Cheng & Goodman, 2015).

The following are suggestions for improving research to examine the impact of culture-specific variables in adherence and health-related studies in pediatrics.

1. We need to standardize culture-related measures such as race, ethnicity, and SES and include them in research on adherence and health outcome disparities (Cheng & Goodman, 2015).
2. We need to examine family-related cultural factors (such as how decisions are made in diverse families) and their impact on acceptability of recommended treatments, adherence, and health/QOL outcomes (Clay, 2017).
3. We should focus on cultural variables that may serve as strengths or protective factors (such as religious practices) that enhance the effectiveness of interventions (Clay, 2017).
4. In the discussion section of reports on interventions with minorities, it may be appropriate to include cultural assumptions and biases that may have influenced the results or interpretation of the results (Clay, 2017).
5. We need to develop culture-specific interventions. There have been some developed for children with asthma that have resulted in reduced hospitalizations due to exacerbations and improved QOL (McCallum et al., 2017).
6. We need to increase the cultural diversity of our research by recruiting students and research staff from ethnic and minority groups. These diverse students and staff might also be more effective at recruiting minority research participants. Lescano and her colleagues adapted an HIV prevention intervention for Latino youth by translating intervention components into Spanish and using bicultural and bilingual facilitators to lead workshops (Lescano et al., 2020).

Conclusion

We need to include cultural competency training in our graduate school programs, medical school and residency programs, and professional conferences so that providers will be more competent to provide clinical services and research to promote adherence to medical regimens with ethnic and minority groups. We also need to

make a concerted effort to recruit diverse populations for our research studies and report on culture-related variables in our publications. Finally, another priority is to recruit ethnic and minority students who will be in a position to provide culturally competent clinical services, research, and training for students when they are faculty members.

Ethical Issues

King (2009) placed ethical issues in adherence in the context of different "relationships": clinician-patient; researcher-study participant; government-citizenry; and payer-client. We will use these contexts to discuss ethical issues related to clinical and research activities in adherence.

Clinician-Patient Relationship

Two competing models of ethical responsibility are relevant to clinical activities: beneficence and autonomy. The principle of beneficence is defined in the American Psychological Associations ethical principles as "psychologists strive to benefit those with whom they work and take care to do no harm" (American Psychological Association, 2010). Potential benefits of clinical activities to improve adherence to effective medical treatments include the prevention of disease, relief from pain, reducing the impact of disabilities, and prolonging life. The principal harms are death, disability, pain, and reduced quality of life (King, 2009). There is some who believe that clinicians are "morally obligated" to enhance patient adherence to medically effective and indicated regimens (King, 2009). Healthcare providers should have adequate knowledge, skills, and be willing to education and motivate patients to adhere and provide close supervision (Jensen, 1979).

Autonomy places an emphasis on valuing the beliefs and opinions of patients and caregivers and giving them necessary information to make informed decisions about adherence (King, 2009). Providers should strive to arrive at a "negotiated contract" with patents and caregivers on what degree of adherence is needed to improve health and quality of life (Jensen, 1979). Part of this is securing informed consent from patients and caregivers which involves describing the services to be provided, any limits on confidentiality (especially in the case of minors), and if the intervention is experimental in nature or developing (Rae et al., 2017). Because pediatric psychologists are often part of an interdisciplinary team in medical settings, informed consent should also spell out the purpose of consultations between team members and the need for consultations (Rae et al., 2017). There is some debate about when and if consent should be obtained from children. There is consensus that age is not sufficient to determine a child's ability to give consent. There are other factors that are important to consider, such as cognitive and social abilities (McCabe, 1996; Rae et al., 2017).

Another issue is when confidentiality can be broken. All states in the United States mandate that confidentiality can be broken if (1) a child is suspected of being neglected or physically, emotionally, or sexually abused; (2) a court order is issued; and (3) imminent danger to a patient or others is likely (Rae et al., 2017). In working with teenagers in clinical settings, we describe to them that the information they divulge in therapy will not be shared with their parents unless that indicate they are planning to harm themselves or others (although we often wonder if suicidal ideation is underreported because of this information given to teenagers). In usual circumstances, pediatric psychologists have to weigh the right versus the need for parents to obtain confidential information about their child.

Another issue is whether patients and caregivers have a right to refuse preventive or treatment services. Some pediatric practices have refused to continue to treat children if their parents do not consent for them to be vaccinated, even though the American Academy of Pediatrics encourages pediatricians to continue to work with these families (Diekema, 2015). This is an especially poignant issue as we write this book in the midst of the worldwide COVID-19 pandemic, and promising vaccines have been developed. Another dilemma is whether children can refuse treatments or efforts to extend their lives if they are terminally ill. Some believe that these measures should not be forced on children if they are optional for adults in similar circumstances (Rae et al., 2017).

Researcher-Study Participant Relationship

The ethical principal of "nonmaleficence" applied to research involves the responsibility of investigators to minimize harm to participants. Research can be unethical if the design of the trial is not adequate to answer the research questions and the data cannot be meaningfully analyzed (King, 2009). Informed consent and assent are critical and should describe the purpose of the study, procedures or interventions, time commitments required of participants, the discussion of potentially sensitive information, limits of confidentiality, how participants will be assigned to different groups, the risks and benefits of participation (Rae et al., 2017), and if the intervention is effective, will it be offered to those assigned to the control group after the study is completed. Informed consent should also describe any incentives or compensation that will be provided to participants, without being coercive. One recommendation to minimize coercion is to offer small amounts of compensation at different data collection points rather than paying out in one large sum (Rae et al., 2017).

A debated ethical issue in the adherence assessment literature is about how much information should be given to research participants on how and when their adherence is being monitored. This particularly applies to electronic monitoring. When participants are fully informed about electronic monitoring, they have increased their adherence prior to clinic visits (so called "toothbrush" or "white coat" adherence effect) and even "dumped" doses prior to visits (Driscoll et al., 2016; Modi

Table 10.1 Advantages and disadvantages of different forms of adherence monitoring

Type of disclosure	Full disclosure	Authorized deception	Withholding	Stealth
Definition	Informed consent complete explanation of methods of adherence monitoring	Informed consent with no details about exact monitoring procedure Full disclosure at the end of participation	Acknowledgment of and consent for monitoring only at the conclusion of the study	Not aware of being in the study at all
Advantages	Minimizes the risk of psychological effects Preserves participant autonomy	Reduces the impact of monitoring on subject's adherence behavior	Adherence data are unaffected by Hawthorne effects	Closest representation of clinical experience Best data to analyze patient behaviors
Drawbacks	May interfere with normal adherence behavior and therefore may not reflect true clinical experiences	Requires a degree of deception and adherence data may be biased	If subjects are permitted to drop out, biased adherence data may be obtained	Highest risk of mistrust and loss of participant autonomy

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et al., 2012; Riekert & Rand, 2002). Patel, Moore, Craver, and Feldman (2016) have described different levels of deception in adherence monitoring and the advantages and drawbacks of these different forms of disclosure (see Table 10.1).

Researchers need to consider the advantages and drawbacks of these levels of disclosure. One possibility is to obtain full disclosure or authorized deception from parents and not child participants, but it might put parents in a difficult situation of deceiving their child, and for younger children, parents administer most treatments. The other possibility we mentioned in Chap. 5 is that the reactive effects of measurement may diminish over time, and a run-in period of 2–4 weeks could be done at the beginning of the study and the data collected during that time would not be used in the data analysis.

Pediatric psychologists have a unique role in serving on Institutional Review Boards. They often have to evaluate and explain to their medical colleagues the procedures or manipulations that are proposed in a psychological study. They also have to describe measures proposed and if they are psychometrically sound. Psychologists also can explain how a proposed study can potentially advance the field of study.

There are some unique ethical issues related to eHealth interventions, including recruitment, informed consent, debriefing, privacy and confidentiality, participants' safety, and the delivery of interventions online (Wu et al., 2014). In recruitment, some investigators recruit directly from the community, while others recruit through

gatekeepers, such as healthcare providers. Recruiting directly from the community presents challenges of verifying conditions and symptoms reported by children and caregivers. Threats to privacy and security can be addressed by using secure websites and using screen names rather than actual names in online communications. Also, to ensure health data are protected, users need to log on with secure passwords, programs can be designed to close automatically after a period of inactivity, encryption can be used, and firewalls can be used to protect communications and content (Wu et al., 2014).

Government-Citizenry Relationship

Most would agree that the government has an obligation and right to protect public health. Interventions directed at individuals by the government are considered appropriate, such as breast cancer screenings, safer sex practices, wearing seat belts, smoking cessation campaigns, and promotion of exercise (King, 2009). These interventions are not without controversy as there are competing models. "Paternalism" implies that the government knows what is best for its citizens, while "rugged" individualism implies that citizens know what is in their best interest and want less governmental interference in their lives (King, 2009). These views are being played out as we write this book during the COVID-19 pandemic where wearing of masks, social distancing, and avoiding large crowds are being recommended or even mandated by health and governmental agencies. There are those individualists who refuse to follow these preventive measures and protest against regulations that "limit their freedom." Health promotion and disease prevention may require institutional and society-wide changes, including regulations (King, 2009). Adherence to effective preventive and treatment regimens needs to be promoted by health and governmental agencies through funding of research to advance the field and find ways to integrate best practices for adherence promotion in our healthcare settings.

Payer-Client Relationship

According to King (2009), there are two main ethical issues in this relationship. One is whether payers will cover the costs of prevention and health maintenance services. Payers may be more likely to increase health insurance premiums for those at increased genetic or behavioral risk and decrease premiums for those engaging in healthy behavioral lifestyles, such as not smoking or being overweight and exercising regularly. The other ethical issue is whether people will be able to choose their own healthcare plans (King, 2009). Currently there are millions of Americans who lack access to basic health services, particularly among ethnic minorities and poor people.

Conclusion

There is a clear need to further the discussion of ethical principles as they affect our clinical and research activities on adherence and to further the public health of our citizens. Our students need to have more training in how ethical issues impact our research and practice. There are some unique challenges for the growing field of eHealth programs to promote adherence, which have been shown to be efficacious as face-to-face delivered interventions (Rapoff, 2013). These need to be addressed to protect the privacy of participants in these interventions.

Legal Issues

Two major legal issues have been discussed in the literature relevant to adherence: medical neglect and religious objections to medical care.

Medical Neglect

Medical neglect has been defined by the American Academy of Pediatrics (AAP) as "failure to heed obvious signs of serious illness or failure to follow physician's instructions once medical advice has been sought" (Jenny, 2007, p. 1385). The prevalence of medical neglect is about 2.8 per 100,000 in children younger than 1 year (Jenny & Metz, 2020). The AAP recommends that providers consider five factors in diagnosing medical neglect.

1. "A child is harmed or is at risk of harm because of lack of health care;
2. The recommended health care offers significant net benefit to the child;
3. The anticipated benefit of the treatment is significantly greater than its morbidity, so that reasonable caregivers would choose treatment over nontreatment;
4. It can be demonstrated that access to health care is available and not used; and
5. The caregiver understands the medical advice given" (Jenny, 2007, p. 1385).

It is vital that providers are prescribing an effective treatment that does no harm. Providers also need to attempt to educate parents about their child's treatment.

Medical neglect has been documented with highly active antiretroviral therapy (HAART) in the treatment of perinatally acquired HIV in young children. One study in Canada found that caregivers of 19.8% of 134 infected children had involvement with child protective services for medical neglect related to inadequate adherence of the caregivers in administering treatment (Azzopardi et al., 2014). A study conducted at Arkansas Children's Hospital documented nonadherence (by viral assays) to HAART regimens by caregivers of six young children with HIV. The providers took a stepwise approach to attempt to remedy the problem. First, a home

healthcare nurse was sent to the home to work with the family on adherence. If that did not work, then directly observed therapy was done with the child in the hospital and demonstrated that treatment was effective. If viral loads were still elevated after taking the first two steps, a medical neglect report was filed, and the children were removed from the home. Out of the six children, two were removed from the home, and their viral loads improved in foster care (Roberts et al., 2004).

The AAP recommends the following intervention options for addressing medical neglect, listed from least to most restrictive:

1. Use a translator if the family is not proficient in English.
2. Make sure the family's views of their child's condition and concerns are addressed.
3. Educate the family about the child's condition and the need for adherence to treatment.
4. Enlist the help of extended family members.
5. Involve the family in developing a treatment plan.
6. Develop a written contract for the treatment plan that is understood by the family and involves their input.
7. Provide community resources as needed such as visiting nurses, transportation, financial assistance, and respite care.
8. Arrange for directly observed therapy in the home by a nurse or other professional.
9. Consider a partial or day-hospital program to address adherence issues.
10. Make a referral to protective services for medical neglect. In some extreme cases, a child may need to be placed in foster care (Jenny, 2007, pp. 1387–1388).

Religious Objections to Medical Care

The other legal issue addressed in the pediatric literature is religious objections to medical care. There are some religious groups, such as the Jehovah's Witnesses, who refuse blood transfusions on religious grounds. A web-based national poll of US parents in 2014 found that 3.6% planned to refuse all non-influenza vaccines for their children under the age of 7 years (Frew et al., 2016). Some parents have cited religious objections to having their child vaccinated, such as the use of fetal tissue in the production of some vaccines (Phadke et al., 2016).

The AAP Committee on Bioethics' (1997) position on religious objections to medical care is that "constitutional guarantees of freedom of religion do not permit children to be harmed through religious practices, nor do they allow religion to be a valid legal defense when an individual harms of neglects a child" (p. 279). The Committee also recommends that "…physicians who believe that parental religious convictions interfere with appropriate medical care that is likely to prevent substantial harm or suffering or death should request court authorization to override parental authority…" (p. 280).

Conclusion

Nonadherence to effective treatments particularly for young children where parents are completely in charge of administering treatment can be medical neglect. The AAP has provided clear guidance on how to address adherence issues when children are not being given appropriate treatments, particularly life-saving ones such as HAART for HIV (Jenny, 2007). If disputes about treatment recommendations arise between providers and caregivers, the AAP also recommends bringing these disputes to the Institutional Ethics Committee in their practice setting (American Academy of Pediatrics, Institutional Ethics Committees, 2001).

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Conclusion: The Inflated Importance of Adherence

What a paradoxical way to end a book that has emphasized the importance of adherence in improving the health and well-being of children. There are, however, broader psychosocial and medical contexts to consider. *Patient nonadherence may be part of a mosaic of patient and family struggles*. Medical adherence problems may be symptomatic or exist concurrently with patient and/or family dysfunction. For example, a depressed adolescent who has a chronic disease may not have the energy and coping resources to adequately adhere to a complicated medical regimen. These psychological problems need to be addressed by competent mental health personnel who have extensive experience working with patients and families in pediatric settings.

Additionally, *the outcome of medical treatment does not solely depend on adherence*. There are other factors to consider. Subtherapeutic drug assays may reflect low adherence but can also be due to inadequate dosing, pharmacokinetic variations in drug metabolism, and interactions with other drugs. We also must address healthcare disparities for minority children and adolescents. For example, African American children with asthma living in urban areas have been undermedicated according to nationally recognized treatment guidelines (Eggleston et al., 1998; Halterman et al., 2002). However, the overall message of this book is still relevant. *When confronted with less than adequate outcomes in the treatment of chronic diseases, a reasonable beginning is to investigate the contribution of patient adherenc*e.

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M. A. Rapoff et al., *Adherence to Pediatric Medical Regimens*, Issues in Clinical Child Psychology, https://doi.org/10.1007/978-3-031-27484-8

Index

M. A. Rapoff et al., *Adherence to Pediatric Medical Regimens*, Issues in Clinical Child Psychology, https://doi.org/10.1007/978-3-031-27484-8