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# Medication Adherence in Children and Adolescents: A Review of the Recent Literature

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Medication adherence, the degree to which the patient takes his or her medication according to the treatment plan, is dependent on a variety of factors, including the patient's health beliefs, understanding of the rationale for the medication and goals of treatment, as well as the ability to accurately interpret administration instructions. In children, medication adherence is often complicated by the involvement of multiple family members and care providers; while in adolescents, the transition to self-care can be a significant challenge to maintaining consistent treatment.[1] This issue highlights the growing body of literature addressing these challenges, including recent papers describing tools for improving medication adherence.

## Adherence in Patients with Asthma

The role of health beliefs and the value of medication education in children with asthma has been well studied, but the results have been mixed. Klock and colleagues performed a one-year observational study of adherence to inhaled corticosteroids in 135 children 1 to 12 years of age and its relationship to parental health beliefs.[2] Parental perception of the necessity of inhaled corticosteroids for their children was high in this study, with a median score on the Beliefs about Medications Questionnaire of 17 out of a potential 25. The median adherence rate at final assessment was 84% (interquartile range 70-92%), the highest rate of long-term adherence reported in the pediatric asthma population to date. Of the 55 children with poor adherence (a rate < 80%), 25 (45%) had poor asthma control. In contrast, only 9 (11%) of the 80 children with good adherence had poor asthma control. Interestingly, the authors found no differences in parental illness perceptions and medication beliefs between the adherent and non-adherent groups. The authors concluded that nonadherence can occur even when there is concordance between parents and the medical team on the need for medications and the treatment goals.

The effect of treatment perceptions and medication knowledge on adherence to inhaled corticosteroids in adolescents was the focus of a study recently published in the *Journal of Asthma*.[3] The authors analyzed data from 182 adolescents (12-18 years of age). The mean score on the Medication Adherence Report Scale (MARS) was 20.3 $\pm$ 4.2 (range 7-25). Only 40% of patients were classified as highly adherent (a score of 23 or greater). Unlike the Klock study, belief in the necessity of treatment and sufficient medication knowledge were correlated with better adherence ($p < 0.05$). Adherence was also correlated with asthma control (OR 2.1, 95% CI 1.1-4.1). The most common reasons cited for non-adherence in patients with low MARS scores were forgetting to use the medication (56.1%), using it only when symptomatic (41.1%), and the desire to test "whether I can live without medication" (29.9%). Ten percent of patients were highly concerned about potential adverse effects. This paper highlights some important aspects of medication adherence in adolescents, such as concerns over adverse effects and the desire for a trial off therapy, which could be incorporated into counseling prior to the transition to self-care.

## Fathers and Asthma Care

An intriguing study by Friedman and colleagues at Massachusetts General Hospital evaluated the effect of fathers as caregivers for children with asthma on medication adherence.[4] Parents of 63 children between 5 and 9 years of age were asked to participate in a series of interviews. Adherence was assessed by electronic monitoring devices for inhalers or bottle caps. Mothers had higher scores than fathers on measures of involvement and belief in the need for medications, as well as four subscales of the Family Asthma Management System Scale (FAMSS): asthma knowledge, relationship with providers, symptom assessment, and response to symptoms. Scores were no different in the FAMSS subscales of

environmental controls/exposures, adherence (availability and appropriate use of medications), and balanced integration of asthma into family life. Estimates of the amount of involvement and the helpfulness of that involvement were both higher in mothers, with significant correlation between the estimates provided by the parent and his/her partner for both genders. There was no significant correlation between maternal or paternal scores for involvement and medication adherence. The authors concluded that while involvement of fathers was seen as helpful in family coping, fathers may not be as knowledgeable or skilled in assessing symptoms or providing care as mothers. Improving medication education for fathers and supporting an increased role for them in their child's asthma management may have positive long-term benefits for the family.

Adherence after Transplant

Solid organ transplantation requires life-long adherence to often complex medication regimens. Transplantation during childhood or adolescence presents an array of challenges for families, including the transition from parental control to self-care in the adolescent. To identify risk factors for nonadherence in this population, Connelly and colleagues reviewed the charts of 183 pediatric kidney transplant recipients.[5] Medication non-adherence was documented by healthcare providers in the medical records of 20% of patients. Time to first episode of non-adherence was shorter in patients 10 years of age and older compared to younger children (2.7 $\pm$ 1.7 versus 4.1 $\pm$ 1.9 years, respectively, $p = 0.032$). There were higher rates of non-adherence in African American patients (66% versus 34% for non-African American patients, $p = 0.004$) and males (77% versus 23% in females, $p = 0.014$). Patients in the non-adherent group were also older at the time of transplant (14 $\pm$ 4 versus 12 $\pm$ 6 years, $p = 0.014$). Non-adherence rates were higher in patients living farther from a transplant center ($p = 0.013$) and in families with legal issues ($p = 0.029$). As anticipated, non-adherence was associated with a higher rate of primary disease recurrence ($p = 0.024$), higher mean creatinine ($p = 0.019$), biopsy-proven rejection ($p < 0.001$), hospital readmission ($p < 0.001$), and graft loss ($p = 0.048$). The authors used their results to create a model to predict the impact of a patient's risk factors for nonadherence on graft outcome. Once validated, it may serve as a means of identifying at–risk patients who may benefit from additional services.

Loiselle and colleagues interviewed 66 transplant recipients (ages 11-20 years) and/or their caregivers about medication adherence and repeated the interview after a minimum of one year.[6] The majority of patients received a kidney transplant (59%), while 25% received a liver transplant, 15% a heart transplant, and one patient received a double lung transplant. The average time between transplantation and study participation was 5.1 years. Adherence was assessed by serum levels of the patient's tacrolimus, cyclosporine, or sirolimus. At baseline, 18% of patients reported non-adherence compared to 33% at follow-up. Caregiver reports of non-adherence were 27% at baseline and 30% at follow-up. Comparisons of baseline and follow-up values were not significantly different for either group. Serum medication assays below goal were more common than expected, occurring in 67% of patients at baseline and 56% of patients at follow-up, which may suggest greater non-adherence or changes associated with growth or the presence of drug interactions. While these results seem to show that medication adherence was maintained over time, many patients reported changes in medication-taking behaviors with some improving and others becoming less adherent. Additional research with more frequent assessments is needed in this population, but this preliminary study suggests that most transplant patients can maintain or improve adherence to their immunosuppressive regimens over time.

In a subsequent paper, these authors examined executive functioning in association with non-adherence in adolescents and young adults after transplant.[7] Thirty-nine patients and 41 caregivers participated in the study. Executive functioning was evaluated using Behavior Rating Inventory of Executive Function (BRIEF) scores. Compared with norm-referenced scores of healthy peers, transplant patients had significant dysfunction across multiple domains including inhibition, initiation, working memory, and organization. BRIEF global executive composite and metacognition index scores were significantly correlated with patient and caregiver-identified barriers to medication adherence, suggesting that evaluation of executive dysfunction post-transplant may be useful in guiding interventions to improve adherence.

Adherence in Adolescents with Diabetes

Data from the American Diabetes Association show that only 21% of adolescents with type 1 diabetes meet the guidelines for target hemoglobin A1c. Datye and colleagues recently reviewed the literature on adherence in this population.[8] Positive parental involvement, with collaborative monitoring continued even as the responsibility for treatment begins to transition to the adolescent, has been shown to be a strong predictor of better adherence. Recent studies have also identified a positive relationship between the involvement and helpfulness of fathers and improved treatment adherence. Reported barriers to adherence have included difficulty in communicating with healthcare providers (reported to be as high as 43% in one study),

treatment costs, and patients missing doses at meal times. Psychosocial barriers to adherence, such as depression, anxiety, and eating disorders, have been shown to occur at a higher incidence in adolescents with type 1 diabetes compared to the general adolescent population and may be another important area for future research.

Adherence after Emergency Medical Care

The first step in medication adherence is typically getting the prescription filled. Location and available transportation to a pharmacy, as well as the means to pay for the medication are potential barriers to adherence for all patients. To assess this initial step, Sammons and Yin performed a retrospective review of 152 patients and their families given 229 prescriptions in a pediatric emergency department.[9] Nearly a quarter of prescriptions (27.5%) went unfilled. In contrast to commonly held beliefs, there were no significant differences in the rate of prescriptions filled when patients were compared by age group (< 12 months, 1-3 years, 37 months-12 years, and 13-18 years), insurance status, or type of medication. The authors concluded that unique tools may be needed to promote medication adherence after discharge from emergency medical care.

Adherence in Sickle Cell Disease

A systematic review of 49 studies evaluating adherence in children and adolescents with sickle cell disease was published in the April 2016 issue of the *Journal of Pediatric Psychology*.[10] Sample sizes in these studies ranged from 8 to 763 patients (median 50), with a mean age of 8.4 years. Medication adherence was assessed by a variety of methods. Rates of adherence were higher for hydroxyurea (mean 73.7%) than iron chelators (56.1%) or prophylactic antibiotics (55.5%). Overall adherence to medications ranged from 29.6% to 86%, with a mean 70.8%. There was a significant association between older age and lower adherence rates. Poor adherence was associated with greater healthcare utilization, with higher rates of clinic visits and hospitalizations. The wide range of adherence rates was attributed to variation in the assessment tools used, causing the authors to recommend a more standardized approach to future research.

Behavioral Predictors of Adherence in Epilepsy

Preliminary data from an on-going longitudinal study examining factors associated with adherence in children and adolescents with newly diagnosed epilepsy has been recently published.[11] Ninety-one patients between 2 and 12 years of age and their parents have participated in the study to date. Six assessment tools are being used to evaluate potential factors that might affect adherence, including the barriers subscale of the Pediatric Epilepsy Medication Self-Management Questionnaire. Early predictors (factors identified within the first month after diagnosis) of adherence at 2 years included socioeconomic status, epilepsy knowledge, family problem-solving, and family communication. Based on these preliminary findings, the authors recommend that education and psychosocial interventions be offered to families at diagnosis to minimize or eliminate barriers to treatment.

Health Literacy and Medication Adherence

In the February 2016 issue of *The Journal of Pediatric*s, Dharmapuri and colleagues described their assessment of the relationship between health literacy levels and medication adherence in adolescents.[1] The authors surveyed 138 patients between 12 and 21 years of age at an urban adolescent health center using the Rapid Estimate of Adult Literacy in Medicine scale for teens (REALM-TEEN) and the Adherence to Refills and Medications Safety scale (ARMS). The REALM-TEEN literacy tool evaluates the ability of the subject to read aloud a list of 66 medical terms. The ARMS tool consists of 14 questions answered using a 4-point Likert scale, with lower scores indicating better adherence.

Results from 118 respondents (81%) taking one or more medications were analyzed. The median REALM-TEEN score was 57 (range 0-66), corresponding to a $6^{th}$-$7^{th}$ grade health literacy level. The median ARMS score was 21 (range 14-56), indicating poor medication adherence. Chronic illness was correlated with a lower ARMS score ($p = 0.003$), as was having a learning disability ($p = 0.041$). Neither gender nor self-health rating was related to ARMS scores. There was no significant correlation between REALM-TEEN and ARMS scores ($p = 0.069$). The authors suggest that the low ARMS scores in these patients may have resulted from a lack of understanding of the survey tool and may not necessarily indicate medication nonadherence. They call attention to the need for further exploration of the role of learning disabilities in medication nonadherence and the development of interventions suited to both the patient's developmental stage and cognitive level.

Methods for Improving Adherence

A recent systematic review adds a new degree of depth to previous assessments of the impact of behavioral interventions to promote adherence.[12] The effectiveness of these interventions, including training in self-care skills, family communication, and problem-solving, have been evaluated from the patient and family perspective, but not on a macro (societal) level. Using data from 20 studies, the authors found that compared to controls, interventions to promote adherence improved patient quality of life with a standardized mean difference (SMD) of 0.41; 95% CI 0.13, 0.67, $p = 0.005$. Overall, caregivers reported both better quality of life and improved family functioning, SMD 0.77; 95% CI 0.11,

1.42. p = 0.02. At the macro-level, adherence promotion interventions reduced all forms of healthcare utilization, including clinic and emergency department visits as well as hospitalizations, with a SMD of -0.19; 95% CI -0.35, -0.03, p = 0.02.

While behavioral interventions can improve adherence, many patients do not have access to healthcare providers for these services. A study of telehealth as a tool to enhance medication adherence in children with inflammatory bowel disease is currently under development by a collaborative of 15 children's hospitals throughout the United States.[13] The 12-month study will enroll 194 patients 11 to 18 years of age who will be randomized to education plus telehealth behavioral interventions versus education alone. Skype sessions with a psychologist or psychology trainee will be used to conduct a functional analysis of the family's specific barriers to adherence and deliver targeted training such as development of organizational skills or the use of reminder systems. Additional sessions will include transitioning responsibility for care from the parent to the patient, maintenance of adherence gains, and problem-solving for future barriers. If the project results in improved adherence, more providers may turn to this tool to expand services to their patients.

With an estimated 75% of children having access to a mobile device, there is tremendous potential to use these tools to improve medication adherence. Many new applications have been developed that provide both education and dose reminders. AsthmaCare, an app developed by clinicians from Nationwide Children's Hospital (https://www.nationwidechildrens.org/asthmacare), provides daily reminders for medication use and personalized trigger avoidance measures.[14] It rewards the user with points for controller medication use and frequency of interaction with the app. In a 30-day trial of 24 patients 9 to 16 years of age, all used the device at least once per day, with 80% using it multiple times per day. The majority (81%) accumulated enough points to unlock the highest reward tier, with the remaining patient achieving the second-highest reward level. The average score on a test of knowledge on avoiding asthma triggers improved from 36.9% at baseline to 53% after 30 days of using the app. All patients preferred the app to a written asthma treatment plan and would recommend it to friends and family members with asthma.

Summary

Improving medication adherence in children and adolescents requires optimization of a wide range of factors, including the family's health literacy, commitment to health maintenance, and understanding of both dose administration and monitoring for adverse effects. The past several years have seen a significant increase in research in this area, with the development and assessment of a number of new tools that may be of benefit when working with pediatric and adolescent patients and their families.

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