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Medication Non-Adherence among Pediatric Patients with Chronic Illness

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ABSTRACT

Introduction: The pediatric populations face unique challenges in adhering to medication therapy because of their care dependency and varying developmental capacities. This review aims to provide a critical appraisal of recently published studies (1980-2013) on medication non-adherence among children. Specifically, it intends to summarize factors associated with pediatric medication non-adherence and to describe strengths and limitations of the interventions frequently used for improving medication adherence among the pediatric population.

Methods: A review of the literature was conducted for studies published in English on pediatric adherence to medication and therapeutic regimen between 1980 and 2013. Studies were included, if: (1) study populations were children and adolescents under 18 years of age; (2) study patients had chronic illnesses such as diabetes, asthma, HIV and mental health disorders; and (3) study outcomes and interventions concerned medication non-adherence.

Results: The number of studies reviewed was 76. Risk factors associated with pediatric medication non-adherence included age, peer pressure, disease, type of medication, health providers, and socio-demographic factors. Intervention strategies were education, cognitive/behavioral therapies, technologies, and multi-front approaches. However, few interventions were customized for the pediatric population with varying developmental capacities.

Conclusion: Improving medication adherence among pediatric patients requires individually tailored and patient-centered approaches that reflect varying developmental capacities of children.

Keywords: Children and adolescents, Literature review, Medication non-adherence, Pediatrics.

INTRODUCTION

A failure to control chronic illnesses in children and adolescents may lead to increased morbidity and mortality. A major reason for failure to prevent exacerbation of a chronic disease and its progression is a lack of adherence to drug therapy. In addition to health consequences, the cost of non-adherence to the healthcare system and to society is significant.

About 18% of the pediatric population suffers from ongoing medical conditions that require chronic medication therapies for control [1]. Empirical evidence suggests that average rates of medication non-adherence are ≥ 50% in young, chronically ill individuals who have diseases such as asthma, juvenile diabetes or mental health conditions (Table 1) [2-4]. These rates are similar to the medication non-adherence rates reported in older adults [5].

Clearly, the pediatric population faces unique challenges in adhering to medication therapy because of their care dependency and varying developmental capacities [6]. Unless

parents recognize the importance of medication adherence and live with their children; the children will be left alone to handle the challenging task of taking medications on their own. It is not fully known how parental care-giving evolves as children develop their own beliefs and attitudes. It is highly probable that medication adherence takes a back seat faced with pressing developmental issues such as peer pressures, school bullies, and vehicle driving.

Table 1: Rate of adherence for different chronic illness in the pediatric population.

Chronic Illness	**Adherence Rate**
Asthma	30%-70%
Epilepsy	45%-85%
HIV	<50%
Juvenile Diabetes	33%-86%
Mental Health Disorders	30%-60%
Transplant Related	30%-50%

What makes medication adherence more challenging for the pediatric population is that interventions to improve medication adherence are rarely developed specifically for children/adolescents. Intervention strategies developed for adults are not likely applicable or effective for children. This review aims to provide a review of recently published studies (1980-2013) on medication non-adherence among children. Specifically, it intends to summarize factors associated with pediatric medication non-adherence, to describe strengths and limitations of the interventions frequently used for improving medication adherence among the pediatric population, and to identify those interventions that are most successful in improving pediatric medication adherence.

METHODS

Search methods for the literature review

The literature published for the years ranging from 1980-2013 in English on pediatric adherence to medication and therapeutic regimen was searched. Electronic databases such as MEDLINE® (OVID), Pubmed, Google Scholar, PsycINFO® (OVID), and CINAHL (OVID) were used. The reference lists were also searched for potentially relevant articles.

A total of 76 potentially useful articles were identified and placed in Mendeley® Desktop database (version 1.8.3, Mendeley Inc., New York City, New York). Particular attention was given to the studies addressing adherence concepts like prevalence rates, barriers to adherence, and interventions to improve adherence. The majority of the literature on pediatric medication adherence was focused on patients with asthma and psychiatric disorders. The search terms used for the review were: "Medication Adherence in Children,'' "Medication Adherence in Children with Chronic Illness," "Adherence in Children," "Pediatric Adherence," "Pediatric Medication Adherence,'' "Pediatric Medication Compliance," "Risks of non-adherence in Children,'' or "Interventions to improve Medication Adherence in Children"

Inclusion criteria

Criteria for inclusion in the review were: (1) studies focusing on the pediatric population (children and adolescents under 18 years of age); (2) studies looking at issues with adherence in chronic illnesses; (3) studies which emphasized the prevalence rates, risks of non-adherence as well as describe the interventions specifically targeted to the pediatric population (Figure 1).

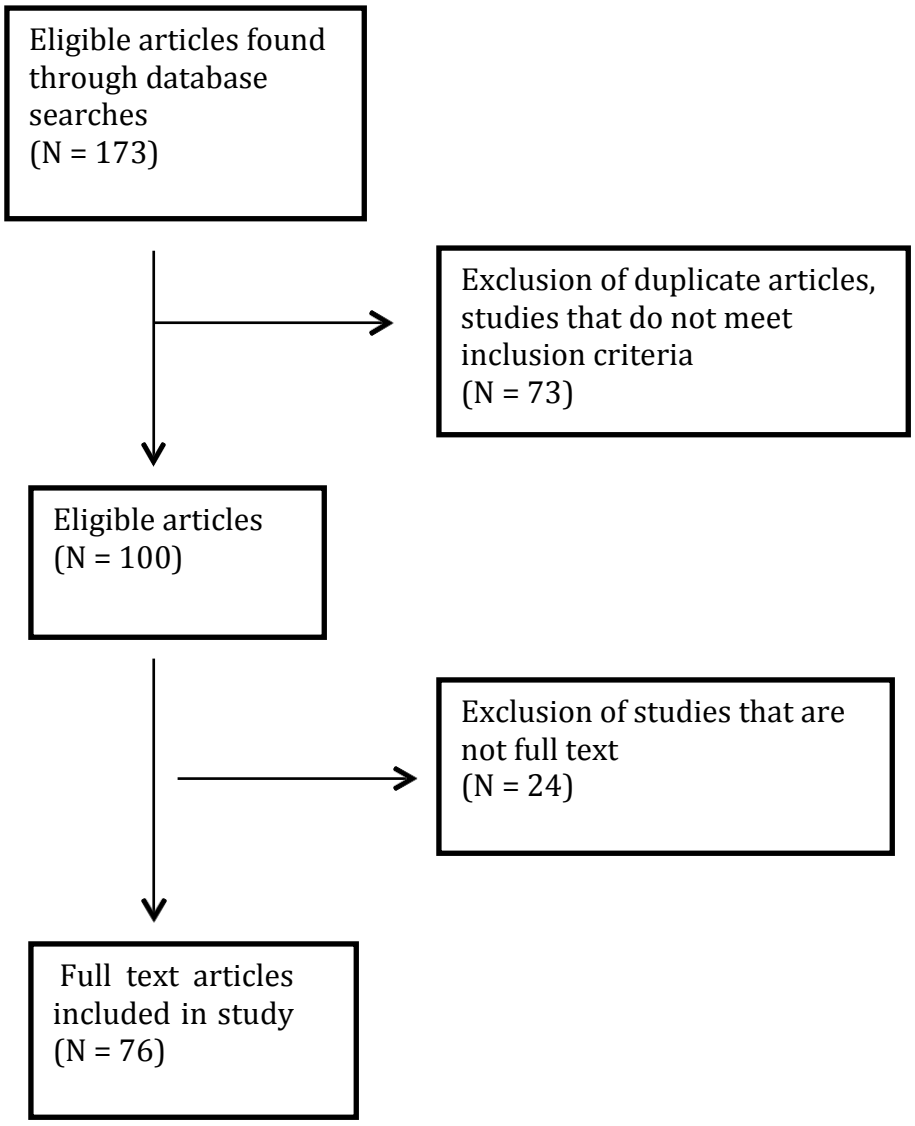

Figure 1: Flow chart of the review process.

RESULTS

This paper reviewed 76 studies including review articles published since 1980 on pediatric medication adherence issues. Pediatric chronic illnesses for which issues of medication non- adherence were frequently studied were juvenile diabetes, asthma and psychological illnesses such as depression and mood disorders. The result section has two parts: (1) barriers to medication adherence and (2) interventions to improve medication adherence.

Barriers to medication adherence in children

The literature reports numerous barriers facing children in adhering to medication treatment. This manuscript identified those barriers and classified them into those related to child development, parenting, patient care, and socio-demographics (Table 2). The classification recognizes the complex interplay among the child, the parent, the nature of the illness, and the medication treatment which all affect children's medication adherence behavior.

Table 2: Barriers to pediatric medication adherence.

Category	Barriers
Patient Development (Psychological)	Age (i.e., child or adolescence)
	Peer Pressure
Parents/Caregivers	Marital Conflict/Lone Parent Status
	Parental Medication Beliefs and Attitudes
	Health
	Parenting Style
Disease/Medication/Provider related factors	Disease-Specific Factors
	Medication-Specific Factors (e.g., dosage forms, palatability)
	Provider Characteristics
	Provider- Patient Communication
Socio-demographics	Age of Children
	Socio Economic Status of Parents
	Parenteral Education Level (Health Literacy) Racial/Ethnic predictors
	Financial Constraints

Child development factors

Adolescence: Children go through many developmental transitions as they become adults. As they mature, they should assume increased responsibility in taking medications as prescribed. However, studies of pediatric medication adherence have documented that poor medication adherence was highly correlated with increases in age of children [7-10]. Children as they become adolescent face tough challenges in making a fine balance between two contradicting needs of independence and parental Support [11]. Any shift in the balance would contribute to the vulnerability of children to medication non-adherence.

Adolescents have previously been called as "abusers of non-prescribed drugs on one hand, and as nonusers of prescribed drugs on the other" [12]. In contrast, younger children are more receptive of directions from their parents or caregivers for their medication needs although they are less capable of understanding the medication.

In a double blind randomized control trial, 122 children with asthma (ages ranging from 7-16 years) were treated with either an inhaled medication or a placebo for 27 months [13]. At the end of the trial, a statistically significant decrease ($p<0.05$) in medication adherence was found for children aged 9 years and above, for the first three months of treatment. The increased risk of medication non-adherence was also documented in a study involving 89 adolescents (mean age 16 years) with juvenile diabetes [14]. At least 28% of the adolescent patients were not adherent to their insulin regimen. In a study of pediatric cancer patients, 46 children (age range from 2.5 years to 23 years) and 40 parents were extensively interviewed at 2 weeks, 20 weeks and 50 weeks post diagnosis, regarding adherence issues to chemotherapeutic agents [15]. Medication adherence was measured from patient self-reports and corroborated with bioassays of serum medication concentrations. Significant correlations between children's age and adherence, not only to chemotherapeutic agents but also to non-chemotherapeutic medications, were found ($p<0.05$ and $p<0.01$, respectively), with adolescent patients being more likely to be non- adherent.

Peer pressure: Cognitive development plays a significant role in children's understanding of their chronic diseases, consequences of non-adherence, and medication management plans. When cognition is not fully developed, children would have difficulties accepting/acknowledging their disease, comprehending reasons for their medications, and understanding the consequence of non- adherence as well as the instructions on how to take their medications. It is no surprise that lack of understanding of chronic diseases and medication therapy regimen is reported to be the most common determinant of pediatric non-adherence [13,26]. Limited development in cognition also makes children vulnerable to peer-pressure. Children give more credit to what their friends think of them than to what they/their parents think of themselves. The possibility of stigmatization and embarrassment facing children who need to take medication in the company of friends are certainly significant risk factors for medication non-adherence. A layers onto this is the embarrassment of leaving class to obtain medications via a nurse or administrator during hours. In a cross-

sectional survey of parents with children suffering from ADHD (attention deficit hyperactivity disorder), embarrassment was implicated in 30% to 37% of those who had refused to take medication, especially in the adolescent patients [16].

Parental factors: Children naturally tend to emulate the beliefs and attitudes of their parents. If parents have non-favorable attitudes towards medication, children would follow their parents in developing those non-favorable attitudes. Observational studies have noted that marital conflict and lone parent status impede adherence for children [8,17]. Opposition of family members to the medication regimen has a negative influence on the children, especially if family members do not want to be involved in treatment or aftercare. The negative attitudes then would keep children from developing good behavior in medication adherence [18]. Children were also non- adherent to medication when parents lacked understanding of the diagnosis, were concerned about the effectiveness of drug therapy, and/or feared side effects from the medication [19]. In some cases, the parent simply forgot to give the medications to the child.

Studies reported that parents forgot one half of the information presented to them during a 15-minute meeting with a physician [20,21]. In an observational study involving 120 children/adolescents (mean age of 12.8 years) with prenatally acquired HIV, the most frequently reported barrier by either the caregiver or youth was "forgetfulness" [22]. This study also reported a discrepancy between children and their parents in identifying factors related to medication non-adherence. For more than half of the reported barriers, children differed from their parents. The discrepancy was especially noticeable with the following barriers: "forgot," "taste," "child was away from home," "child refused," and "child felt good." Children who knew their HIV status was more likely to report logistical barriers, such as scheduling issues. Children with a biological parent as their caregiver were more likely to report regimen or fear of disclosure as a barrier. The study suggested that getting the child and the parent involved in making treatment decisions would help eliminate the discrepancy.

Children medication taking behavior also depended on how parenting was done. Children who faced negative attitudes from parents had more problems in adhering to medication [8,17]. However, when parents were more supportive, more flexible, more nurturing, less critical and good at problem solving, their children had a good medication adherence [8].

Similarly, the extent to which parents found parenting stressful also affected pediatric medication adherence. In an observational study of 51 asthmatic children aged 18 months to 7 years, the relationship between the extent of parenting stress and medication adherence was examined using an electronic monitoring device (Smart-inhaler; Company, City State) [19]. The study reported a significant association between stress levels of parenting and medication non- adherence ($p=0.05$).

One study also reported that lack of parental supervision was associated with risk of medication non-adherence in the pediatric patient. The study was conducted in an academic teaching hospital and used a retrospective chart review of pediatric renal transplant recipients (n=112) [20-23]. About 32.5% of the recipients were determined to be non-adherent to drug therapy based on serum immunosuppressant concentrations. The primary reason for the medication non-adherence was the lack of parental supervision accompanied by conflict between the child and parents.

Patient care related factors

Disease/illness specific characteristics: Pediatric patients develop different behaviors of medication adherence depending on the condition of their disease. In a number of chronic conditions, non-adherence has been found to increase with the length of time since diagnosis [8]. A study also reported that the existence of comorbid conditions increased medication non-adherence among children [24]. Adherence problems in children were reported to be greater where there is more functional impairment or additional physical handicap. For example, a pediatric patient felt more stigmatized when their conditions were visible and irrecoverable [8]. In a qualitative study, parents of 17 children/adolescents (age range from 7-14 years) with ADHD were asked to describe their experience of both parenting a child with ADHD and dealing with the child's medication. The prominent reason for parents to discontinue their child's medication was concerns about possible stigmatization of the child due to the illness [25]. Severity of

disease symptoms was also reported to increase the risk of medication non-adherence in children, as they might question the efficacy of their medication when the severity of symptoms persists [26].

Medication specific factors: Perceptions of pill size, pill taste, and complexity of the medication regimen facing pediatric patients and their caregivers were found to impact medication adherence [11]. Difficult-to- swallow preparations [27] were also reported to affect the pediatric medication non-adherence. Although the role of medication palatability and the magnitude of its effects on adherence have not been well studied, health care professionals and caregivers have observed that children refuse to take certain medications that taste or smell bad [27]. In a survey of 18 parents of children receiving highly active antiretroviral therapy for HIV infection, taste was cited as the reason for the difficulty associated with administering medications [28].

Timing of medication doses was also important to medication adherence. In a double blind randomized controlled trial of 122 pediatric patients (age range from 7-16 years) with chronic mild asthma, medications scheduled during the evening time had much better adherence (mean adherence rate 46.9%) as compared to that during the morning times (mean adherence rate 40.6%) [13]. This difference in adherence rate continued to be statistically significant ($p<0.05$) after 9 months. In a self-report study, only 7 of 75 mothers were adherent to dosing instructions for their children's antibiotics when timing of doses was considered [29].

The need to administer medications at school or daycare could compromise medication adherence among children. In a blinded observational study, 100 children (age range from 1 to 12 years) with otitis media who were prescribed antibiotic medication 4 times a day, 36% of the caregivers skipped the last dose of the medication, as the dose was scheduled way past the child's bedtime hours [30]. This study emphasized the need for physicians to pay particular attention to the child's routine such as awaking and sleeping habits before scheduling their treatment regimen. In a similar study of 29 preschool children (aged 15 months to5 years) with chronic asthma, doses scheduled during pre-school hours of the child were most likely to be missed (77% of the times) [31]. The study measured medication adherence based on an electronic inhaler timer device as well as a patient diary. For pediatric patients receiving highly active antiretroviral therapy for HIV, 77% of parents reporting the difficulty of drug administration reported the morning schedule as the most challenging [28].

Health provider influence: Relatively little research has been conducted on the influence of healthcare providers on pediatric medication non-adherence. One study recognized the patient-provider relationship as an important factor for medication adherence [11]. The behavior and attitude of the healthcare professional can have a positive or a negative effect on adherence. Children and their families who feel that their healthcare providers are not empathetic to their needs are less likely to adhere to the prescribed medication regimen [32]. Poor communication along with a lack of empathy towards children or their families by physicians and other healthcare providers contributes to an inadequate understanding of the therapeutic regimen [8]. In an observational study involving 50 adults with moderate to severe asthma, it was found that poor patient-clinician communication was a significant predictor ($p<0.001$) of lack of medication adherence (inhaled steroid regimen) in patients [33]. The quality of communication between the patient and the clinician, especially when physicians have greater empathy for patient needs and address their issues and concerns effectively, has been found to have a very strong association with medication adherence [33].

Socioeconomic/demographic variables

Age: As children grow, they go through many developmental transitions (Please refer to the section of child development factors for the linkage between age and development capacity). As they mature, they assume increased responsibility of taking medications as prescribed. Studies of pediatric medication adherence have documented that medication adherence is highly correlated to age of children [7-10], with adherence declining with increase in age. Also in a pediatric teaching hospital involving 89 adolescents (mean age 16 years) with juvenile diabetes, increased risk of medication non-adherence was observed among older children [14]. The authors found that at least 28% of the adolescent patients were not adherent to their

insulin regimen.

Race: In an observational interview study [34] consisting of parents of 259 students (Caucasian/African American) in an elementary school setting, parents of Caucasian boys, as compared to those of African-American boys and girls, were more likely to understand the symptoms of ADHD in their children, and to have a positive perception to the treatment for the illness. The study used inductive as well as deductive reasoning analyses of the coded interview data. The study suggested that parents might perceive symptoms differently based on the child's race. Similarly, in a cross-sectional survey of 254 parents on their child's ADHD medications across 6 pediatric primary clinics, attitudes towards the medications were reportedly more positive among Caucasian parents as compared to non-Caucasian parents [16].

Socioeconomic status: Children from families of low socioeconomic groups have more difficulties with keeping appointments, reporting children's reactions to treatment, and adhering to dietary and medication regimens [8]. Families with low socioeconomic status may not have access to medications because of high costs. As a result, they can develop a negative attitude towards the medication, and thus be at increased risks of medication non-adherence [35].

Interventions to improve pediatric adherence

Several different types of interventions have been used in an attempt to improve adherence in the pediatric patient. These include education, cognitive/behavioral therapy (CBT), and the use of technology. Further, multi-front approach that combines several types of interventions has been tested for the pediatric patient.

Educational interventions

Educating the patient (child and family) regarding their chronic illness was a critical factor for improving long-term adherence to the medication regimen. In fact, the National Council on Patient Information and Education states that the prescribing healthcare professional play important role in educating patients [36]. Educational interventions ranged from written materials like brochures or picture books to verbal forms of education that may include such things as telephone counseling, structured home visits, or videotapes (Table 3). Education mainly concerned the nature of the illness, treatment rationale, and benefits of adhering to the medication treatment plan.

Table 3: Brief overview of educational interventions in pediatric adherence.

Authors	Illness	Age (year)	Study Design	Sample Size (n)	Study Period (month)	Adherence Measure	Adherence Outcomes
Farber et al. [75]	Asthma	Feb-18	RCT	56	6	Broad behavior health scale	Adherence was slightly higher in intervention group than control. (p=0.01)
Clark et al. [38]	Asthma	07-Oct	RCT	835	24	Telephone Interviews	Intervention group showed better adherence as compared to control. (p<0.0001)
Hughes et al. [40]	Asthma	Jun-16	RCT	95	24	Medication Diary	No significant group differences for adherence. (p>0.005)

Holzheimer et al. [42]	Asthma	02-May	RCT	80	3	Medication Diary	No significant group differences for adherence. (p>0.05)
Baum et al. [43-67]	Asthma	Jun-16	RCT	20	3	Medication Diary, Blood	No significant group Differences for adherence
Butz et al. [39]	Asthma	02-Sep	RCT	221	12	Electronic Nebulizer monitor	No Differences for adherence. (p=0.79) significant group
Berrien et al. [41]	HIV	1.5-20	RCT	37	3	Self-Report, Dispensing frequency	Intervention group showed better adherence than control for both self- report and dispensing frequency; but not statistically significant (p=0.07) not statistically significant (p=0.07)

Randomized Control Trials

A randomized controlled trial (RCT) investigated the impact of 3-month of intensive educational intervention that was provided by a family coordinator to children with chronic asthma from the urban Latino and African-American community [37]. At the end of the study period, the treatment group demonstrated improved knowledge, self-efficacy and adherence. Another RCT implemented a comprehensive educational intervention school-based asthma program in 14 elementary schools in low income neighborhoods [38]. Education was provided to 835 children from these schools from grades 2 to 5 and their parents for 24 month. The educational intervention resulted in significant benefits in terms of improved knowledge, lesser symptoms, lesser absenteeism, and improved adherence in particularly for children with persistent asthma.

However, not all studies reported a statistically significant effect of educational interventions on medication adherence.

An RCT involving 221 children (aged 2 to 9 years old) with chronic asthma showed that an at-home educational intervention had no significant beneficial impact [39]. The study participants had previous medical diagnosis of persistent asthma. Parents of children in the educational intervention group received 6 home visits of 1-hour sessions. A 2 year RCT also reported that educational home visits for asthma management did not significantly improve adherence among 95 asthmatic children [40]. Interventions included 3- month clinic visits, education, and home visits by a specially trained research nurse. Control subjects received regular care from a family physician or pediatrician.

No beneficial effect of education was also reported for patients with HIV. In an RCT conducted for 37 pediatric patients with HIV, eight structured home visits done by a nurse did not significantly improve medication adherence (p=0.07) [41]. Interestingly, one study examined whether educational mediums (i.e., picture book, video tapes, both) would improve adherence for children [42]. Although the overall adherence rates were not significantly improved, the study shed light on the possibility of different educational mediums to provide effective knowledge

for the patients and their families. The authors reported that children exposed to both picture books and video tapes had significantly greater gains in asthma related knowledge than those in the control group. This was especially so in the young children (aged 2 to 5 years) who did not respond favorably to generic educational materials. The study recommended that clinicians use evidence-based educational techniques to keep children focused when providing them with education. Along with pediatric patients, their families/caregivers should also be counseled about the medication therapy and their concerns in order to ensure their buy-in and to instill a positive attitude toward medication adherence for their children. Language barriers can prove to be an obstacle to medication adherence. Interpreters and bilingual staff can assist to translate educational materials. They can also reinforce instructions provided by healthcare practitioners including assistance with medication technique training (e.g. how to effectively use inhaler, injection, or dropper use).

Cognitive/behavioral therapies (CBT)

Cognitive/Behavioral Therapies (CBTs) focus on the theoretical framework of behavior change, the Unified Theory of Behavior Change [43], which offers an integrative model for understanding and intervening to alter behavior. CBTs use goal setting, reinforcing with rewards, contingency contracting, problem solving, motivational interviewing, and linking medication regimen with established routines. These methods have been used to improve medication adherence in pediatric patients such as those of asthma, diabetes, sickle cell disease, and renal transplants (Table 4).

Table 4: A summary of cognitive/behavioral interventions in pediatric adherence.

Authors	Illness	Age (year)	Study Design	Sample Size (n)	Study Period (month)	Adherence Measure	Adherence Outcomes
Galatzer et al. [48]	Diabetes	7-24	Exp	223	6	Ratings by judges (clinical psychologist & social worker)	Intervention group showed better adherence as compared to control (*p<0.001)*
Brazil et al. [44]	Asthma	10.8	Exp	50	3	Questionnaire	Intervention group had fewer asthma attacks and better knowledge/self-management behavior that control.
Boardway et al. [45-53]	Diabetes	12-18	RCT	19	9	Self-report Questionnaire	No significant Group differences for adherence
Smith et al. [50]	Asthma	1-16	RCT	217	9	Self-report Questionnaire	Intervention group Showed better Adherence as Compared to control.
Bonner et al. [37]	Asthma	4-19	RCT	119	3	Cognitive Perception Questionnaire	Intervention group showed Better adherence as compared to control

Berkovitch et al. [54]	Sickle Cell	9-84	RCT	45	6	MEMS	No significant group differences for adherence
Fennell et al. [47]	Renal Transplant	5-18	Quasi	29	3	Blood testing, pill counts	Intervention superior to control for prednisone and azathioprine
Anderson et al. [46]	Diabetes	10-15	Exp	85	24	Blood glucose monitoring, questionnaire	Adherence improved in the experimental group (*p<0.03)*
Channon et al. [45]	Diabetes	14-18	Exp	22	6	Motivational Interviewing	Improved glycemic Control in experimental group compared to control experimental group compared to control
Knight et al. [49]	Diabetes	14-18	Exp	34	6	Motivational Interviewing	Experimental group showed improved perception of diabetes control and adherence.

Exp: experimental, Quasi: quasi-experimental, MEMS: medication event monitoring system, RCT: randomized control trials

Majority of the reviewed studies [37,44-50] demonstrated that CBTs had a positive impact on medication adherence and patient perceptions about medication compliance and illness control. However, interestingly, all the studies included routine educational counseling. In one RCT of a large number of pediatric patients (n=217), cognitive interventions coupled with regular educational counseling led to a significant improvement in adherence rate; the treatment group had the medication adherence of 78% as compared to the 54% of the control group ($p<0.001$) [50]. In another RCT, adherence also increased more in the treatment group receiving the cognitive intervention than in the control group [37].

Motivational interviewing is defined as a "client-centered, directive method for enhancing intrinsic motivation to change attitudes and behaviors by exploring and resolving ambivalence" [51]. Motivational interviewing has been used successfully in treating addictions such as smoking or substance abuse in adults and also been applied to assess adult patients' level of motivation to adopt medication-adherent behaviors [52]. Two studies reported that motivational interviewing provided a positive reinforcement for adolescents with chronic diabetes to deal with their adherence issues. One study [45]. utilized motivational interviewing techniques during the six month intervention on 22 diabetic adolescents (age 14-18 years). At the end of the six month period, the authors found that motivational interviewing was significantly associated with improved glycemic control. The other study [49] randomly assigned 20 Type-1 diabetic adolescents to groups of treatment (motivational interviewing) and control (standard therapy). Interventions were provided for one hour every week for six weeks. The authors observed a positive shift in the perception of the illness, as well as more feelings of control and acceptance by subjects who received motivational interviewing.

Contrarily, some other studies [47-54], reported that CBT did not improve medication adherence. In a RCT of children receiving prophylaxis for sickle cell disease [54] adherence measured based on the Medication Event Monitoring System was not significant different regardless of behavioral intervention. It is important to note however that adherence increased from 66% to 79% in those receiving behavioral intervention while it decreased from 69.3% to 66% in control subjects. Another CBT study utilized an incentive mechanism of reinforcements/rewards for good adherence behavior for children with renal transplants [47]. However, its effects on adherence

were inconclusive. Adherence was improved for some medications like prednisone and azathioprine ($p \leq 0.05$), but not for cyclosporine.

Technology-based Interventions

Technology-based interventions aim to reduce the burden of environmental constraints in adhering to medication therapy.

For instance, automatic messages to refill prescriptions via home/cell phones and reminders to take medication via pill reminder boxes, beepers or other handheld devices have been used to remind parents/youths to take the medication [55]. These types of interventions are useful to adolescents, who are very technology-savvy, in helping them adhere to their therapeutic regimen. Technological advances such as smart phone applications or interactive games targeted especially towards children have been used to help educate the parents/youths about their medications and illness management (Table 5).

Table 5: Brief overview of technological interventions in pediatric adherence.

Authors	**Illness**	**Age (year)**	**Study Design**	**Sample Size (n)**	**Study Period (month)**	**Adherence Measure**	**Adherence Outcomes**
Guendelman et al. [56]	Asthma	8-16	RCT	34	3	Asthma diary, Interview	Intervention group showed better adherence behavior as compared to ($p<0.03$)
Horan et al. [57]	Diabetes	12-19	Exp	20	4	Blood glucose testing	Intervention showed control group better adherence behavior as compared to control (*$p<0.02$*)
Shames et al. [59]	Asthma	5-12	RCT	119	13	Survey Questionnaire	Asthma related quality of life and knowledge significantly improved in treatment group after 52 weeks. (*$p<0.05$*)
Homer et al. [60]	Asthma	3-12	RCT	106	8	Emergency and hospital visits, self-report, school absenteeism	No significant group Differences for adherence
Rubin et al. [58]	Asthma	7-12	RCT	54	12	Self-report called the Asthma Condition Scale	Intervention group showed Better adherence behavior as Compared to control (*$p<0.004$*)

Brown et al. [61]	Diabetes	8-16	RCT	59	6	Interview, Questionnaire	Intervention group had reduced hospital visits (*p ≤0.05)* and increased self-efficacy as compared to control (*p≤0.08)*

RCT: randomized control trials, Exp: Experimental

A RCT involving 134 children and adolescents (aged 8-16 years) with asthma demonstrated that an interactive device called Health Buddy (Health Hero Network, Mountain View, California) was more effective in asthma management than the asthma diary that is commonly kept for adherence management [56]. In another RCT, a micro-computer based system called Diabetes in Self Control was used to facilitate self-management of insulin therapy in 20 adolescents with diabetes [57]. At the end of the study, the treatment group exhibited a significant improvement in adherence behavior as compared to the control group who were given traditional counseling ($p<0.02$).

Computer-assisted video games have had a positive impact on medication adherence in the pediatric population. In a RCT involving 54 children with asthma, a computer-assisted video game called Asthma Command was introduced as the intervention for the treatment group, while the control group played normal video games [58]. At the end of the 1-year study period, the intervention group made a significant improvement in asthma-related knowledge, medication adherence, hospital visits, and school absenteeism. In another RCT involving 119 children with moderate to severe asthma from low income urban areas in California, an asthma education video game resulted in a significant improvement in quality of life and asthma self- management knowledge ($p<0.05$) [59]. Despite this, there was no significant difference in clinical outcomes measures, including medication adherence. Similarly, an interactive educational computer program, Asthma Control, which used a graphic display of a child going through simulated daily events, showed significant improvements in asthma self-management knowledge and satisfaction of care, although the impact on medication adherence was not significant [60]. Lastly, use of an educational video game for individuals with diabetes (Packy & Marlon) produced a significant improvement in medication adherence in 31 children with diabetes [61]. The game also positively influenced the child's self-efficacy and communication ability.

Multi-approach or combination interventions

No single intervention has proven effective in improving medication adherence across all scenarios. A combination of intervention techniques specifically targeted for the unique situation of the child/adolescent and the family is usually the best. In fact, multi-component approach, wherein educational interventions used in combination with other intervention techniques such as behavioral/cognitive and technological interventions have shown optimal effect on adherence (Table 6) [52].

Table 6: Brief overview of multi-approach interventions in pediatric adherence.

Authors	**Illness**	**Age (year)**	**Study design**	**sample size (n)**	**Study Period (month)**	**Adherence Measure**	**Adherence Outcomes**
Guendelman et al. [56]	Diabetes	13.1	Obs	42	1	Interview questionnaire	Intervention showed improved knowledge self-perception ($p<0.0001$), and self-efficacy ($p<0.01$) as compared to

							control.
Wysocki et al. [63]	Diabetes	Dec-17	RCT	119	3	RCT 119 3 Interview, questionnaire, biochemical data	Out of the 3 groups, the behavioral intervention group showed improved adherence behavior ($p<0.05$)
Ellis et al.	HIV	06-12	Obs	19	3	Retrospective chart review	No significant group differences for adherence
Baum & Creer [64]	Asthma	Mar-14	RCT	16	2	Pill count, serum theophylline level, self-monitoring	No significant group differences for adherence
Burkhart et al. [64]	Asthma	07-Nov	RCT	42	1	Peak Log, Asthma Diary	No significant group differences for adherence
Perez et al. [65]	Asthma	Jun-14	RCT	29	6 Session	Interview, self-report	Intervention group showed better adherence behavior as compared to control ($p<0.05$)
VanEs Nagelkar [66]	Asthma	13.6	RCT	112	12	Questionnaire	No significant group differences for adherence
Anderson et al. [67,68]	Diabetes	13-18	RCT	60	18	self-report	Adherence was found to be slightly better in intervention group (< 0.04)

Mendez & Belendez [69-76]	Diabetes	Dec-18	Quasi	37	12 sessions	Self-report, blood glucose testing	Intervention group showed better adherence behaviour as compared to control (p<0.00)

RCT: randomized control trials, Obs: observational, Quasi: quasi-experimental, MEMS: medication event monitoring system, RA: rheumatoid arthritis

A RCT employed an innovative 4 week peer-support intervention coupled with educational sessions [62]. The educational sessions were conducted by psychologists and involved 21 diabetic adolescents and 21 of their peers (n= 42). The RCT used multiple tools such as Diabetic Social Support Inventory (DSSI), Diabetes Education and Support Assessment (DESAT), Teen Adjustment to Diabetes Scale (TADS), Diabetes Responsibility and Conflict Scale (DRC) and Self-Care Inventory Scale (SCI) to measure improvement in adherence. Of the tools used for the intervention study, DESAT, DSSI and DRC showed significant results in effectively improving adherence. Significant improvements were also observed in adherence- related knowledge and self-management.

In another RCT, 119 diabetic adolescents and their families were assigned to Current Therapy, Behavioral Family Systems Therapy (BFST) or Education and Support provided by pediatric psychologists [63]. At the end of 3 months, patients in BFST group showed significant improvements in adherence-related behavior that was accompanied by a reduction in symptoms. Another RCT investigated the use of CBT with an electronic adherence-monitoring device (Peak Log) for 42 children with asthma [64]. At the end of 5-week period, there was no significant improvement. An RCT also examined the effects of self-management educational counseling and cognitive-behavioral strategies on medication adherence in 29 children and adolescents with asthma [65]. At the end of the study period, children in the intervention group exhibited better asthma knowledge ($p<0.001$), self-management skills ($p<0.000$) and medication adherence ($p<0.05$). Younger children benefitted more from the multi-approach intervention as compared to the adolescents ($p<0.09$).

While some studies reported statistically insignificant improvement in medication adherence, the experiment group typically exhibited positive adherence behavior in terms of disease knowledge, self-management skills and self-control over medication regimen [64-67]. In a RCT involving 112 adolescents with asthma, the combination of education and group therapy led to superior adherence at 24 months, but not at 12 months [66]. In a study of adolescents with insulin dependent diabetes, clinic-based peer-supported problem-solving strategies helped the adolescents to become more involved in their medication regimen and glucose control; hence, they exhibit better adherence than the control group which was given standard care [67,68].

DISCUSSION

This literature review summarized various risk factors of medication non-adherence among children who are at a vulnerable phase, both emotionally and developmentally. A plethora of studies have examined the issue of non-adherence in the pediatric population. Important risk factors are complex family environments, and varying levels of developmental and cognitive capacities facing children and adolescents.

Despite extensive research on the issue of non-adherence among children, few studies documented effects of intervention techniques specifically targeted for improving medication adherence among the population. It is unfortunate that approaches to improving adherence in children were often based on conjecture gained from adult interventions. There is lack of systematic theory-based research that has specifically focused on pediatric population. Adherence research in pediatric population thus seems fragmented, with research in each chronic illness (asthma, juvenile diabetes and mental health disorders) being disconnected.

Effective interventions appear to be those that involve a patient specific approach where both children and their family are equally involved in the treatment decisions. Studies that

documented positive adherence outcomes utilized multiple sessions of behavioral and educational interventions. Evidently, effective interventions need to provide information regularly throughout the treatment rather than just at the treatment initiation [69-73].

Technological interventions have demonstrated some promise in improving adherence in children. It is important to identify those technological interventions that work best for children apart from adults. It is also important to recognize that young children with known poor adherence face complicated family environments. Unless interventions are tailored to accommodate specific needs of vulnerable children, children would be continually at risk of medication non-adherence [74-76].

CONCLUSION

Medication non-adherence in the pediatric population poses unique challenges because children are vulnerable, both emotionally and developmentally. It is imperative to recognize complex family environments as well as developmental and cognitive issues in children that might lead to non-adherence. One of the challenges to improve medication adherence for the pediatric population is to tailor interventions typically developed for adults in research settings such that they fit special needs of children in real world settings.

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