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Review Paper

Treatment Adherence in Children with Cancer: A Mixed-Method Narrative Review

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ABSTRACT

Aims Non-adherence to treatment is a significant barrier to the management of childhood diseases, including cancer. Cancer survivors experience a high mortality rate due to secondary complications. This study aimed to explore the level of adherence to treatment in children with cancer.

Materials & Methods In a mixed-method narrative review, three databases — PubMed, Scopus, and the Cochrane Library — were searched in 2021-22. A total of 227 articles were retrieved. After initial examination, 43 articles were retained, of which 28 were excluded (5 due to duplication and 23 for reasons, such as participants' age, type of disease, and unavailability of full text, and 6 for poor quality). Finally, nine articles were included in the study. The inclusion criteria included English language, no time limit, type of cancer, research and review articles, qualitative studies, and the target age of childhood.

Finding Among the remaining nine articles, six were descriptive in type, two were clinical trials, and one was a review. Given a wide range of article designs, a mixed-methods approach was employed, along with a theme analysis (for studies with similar designs). The extracted themes were summarized under four main topics: prevalence of treatment adherence in children, factors related to adherence, adherence measurement instruments, and interventions to promote treatment adherence.

Conclusion Treatment adherence in children does not reach the ideal level of 95%, but interventions can improve treatment adherence. Treatment adherence is a multifactorial construct that is significantly influenced by children's families. This review has implications for health policy makers regarding pediatric cancer.

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Introduction

Malignant neoplasms are the leading cause of death in children under 14 years of age, with an annual incidence of approximately 100 per million [1, 2]. Childhood cancer outcomes have improved dramatically in recent decades [3]. More than 80% of children with cancer are cured with therapies, such as chemotherapy, radiotherapy, and surgery. Cancer survivors experience a high mortality rate due to secondary complications [4, 5]. Maintenance therapy is essential for survival and long-term outcomes in children with acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) [6].

The prevention of relapse is the primary goal of maintenance therapy, which requires patients to adhere to a long and complex course of treatment that is difficult for many patients and their families [7]. Non-adherence to prescribed treatment regimens during this phase is high (10%-94%). Research has shown that nonadherence during the maintenance phase aggravates prognosis, disease relapse, adverse effects, and mortality in pediatric patients with ALL and LBL [6]. Non-adherent patients were 3.9 times more likely to relapse [8]. Childhood cancer survivors are at risk of late treatment complications, such as cardiotoxicity and secondary cancers [9]. Adherence to post-treatment screening recommendations remains suboptimal even among high-risk survivors [10, 11].

Nonadherence is a key barrier in managing chronic childhood diseases, including cancer [12]. Medication adherence is crucial for patient outcomes, healthcare effectiveness, and costs [13]. Studies have shown that about 20% to 50% of treatment failures in childhood cancer are due to non-adherence to treatment [14, 15]. The World Health Organization defines adherence as the extent to which one's behavior is consistent with the agreed-upon advice of a healthcare provider. Nonadherence to treatment can significantly affect pediatric patients' health [16, 17].

Treatment adherence can be viewed as a continuum ranging from fully adherent to fully nonadherent, with most patients falling somewhere in between. It depends on many factors, and there is no simple explanation for nonadherence [18]. Long-term adherence depends on one's perception of an intervention's risks, benefits, and costs [19, 20]. Adherence is influenced by demographic factors, treatment regimen type and complexity, side effects, treatment regimen duration, and characteristics of the current or potential disease. Outcome expectations may also influence one's adherence. Adverse effects are usually immediate, whereas beneficial effects are observed only in the long term [19].

The patient's age group is another major factor influencing adherence [21]. Lansky et al. found that girls and boys younger than 15 years of age were equally adherent when given oral prednisone for acute lymphoblastic leukemia. Anxiety was positively associated with adherence behaviors in girls, whereas parental hostility and parental anxiety were positively associated with adherence behaviors in boys. However, it is unclear whether this is also true for cancer medications [22, 23]. While the role of disease biology and chemotherapy resistance in treatment failure has been extensively investigated, the role of patient and caregiver nonadherence to oral therapy has mainly been under-researched [3, 24].

Parents are responsible for their child's adherence and can offer insights into nonadherence causes [16, 25]. Many children also need medical care at home. Home care tasks included administering oral medications, providing daily oral care to prevent mouth ulcers, caring for the child's central catheter line, keeping the child hydrated during chemotherapy, and closely monitoring the child's response to treatment. Many families have difficulty performing the complex medical tasks that they expect to perform. Other forms of nonadherence to treatment include inappropriate use of antibiotics or oral steroids and failure to perform oral care, which can cause infections that require hospitalization. These problems, in turn, increase the cost and inconvenience of treatment. Overall, adherence issues can lead to serious problems during treatment and increase the treatment burden for all involved [26].

The primary measure of medication adherence in the existing literature on chronic childhood diseases, including childhood cancer, has been based on the percentage of doses taken as prescribed. This measure does not reflect clinically crucial patterns, such as medication timing, and its use alone can yield unreliable results [27]. In a recent study, the Pediatric Oncology Group monitored children, adolescents, and young adults with ALL using electronic monitoring devices that recorded the date and time each pill bottle was opened [3]. Self-report measures are low-cost and allow patients to assess their medication adherence [27]. Adherence reports from doctors, parents, or patients often overestimate adherence and poorly identify nonadherence patterns. [28]. Studies on interventions that improve medication adherence are generally lacking in pediatric populations [3]. Kahana et al. analyzed 70 interventions to enhance adherence in youth with chronic diseases, categorizing them as educational, behavioral, multicomponent, psychosocial, or technology-based [29].

Considering the limited body of research on treatment adherence in children with cancer, more focus on adolescents, the existing gap in information about the level of treatment adherence and its nature in children, the increased number of children with cancer and the importance of treatment adherence in their survival, the present review was conducted with the following question: What is the state of treatment adherence in children with cancer?

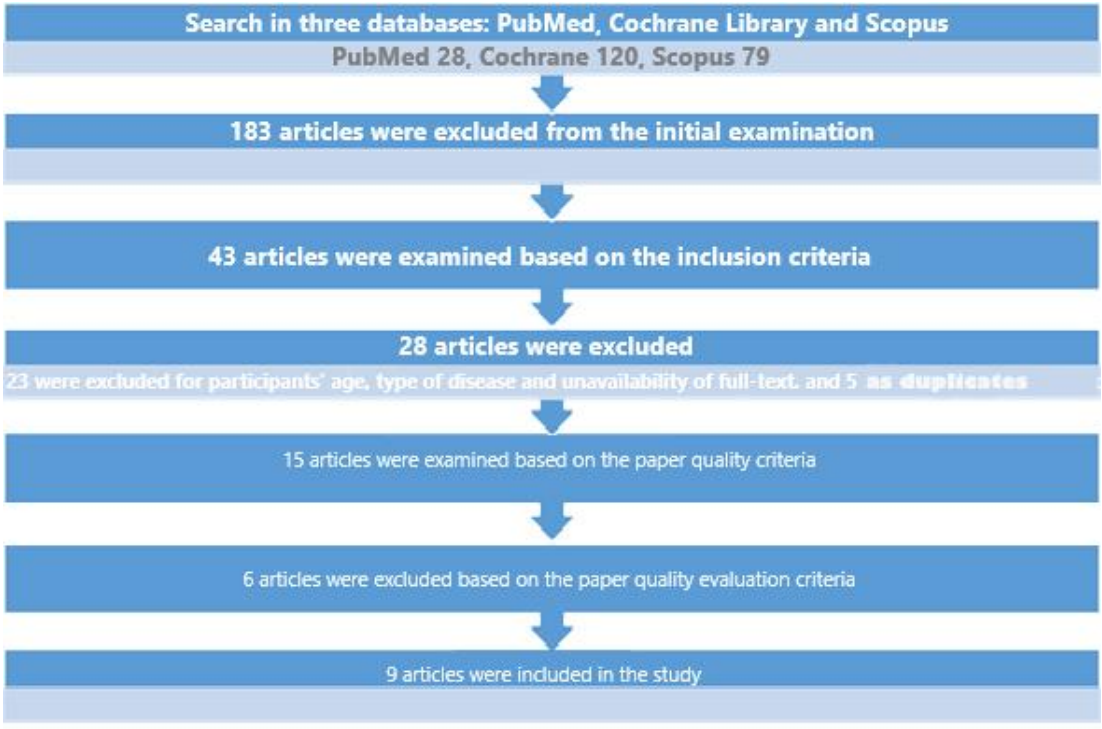
Materials and Methods

This narrative review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews. A mixed-method approach was employed based on the study's aim of comprehensively investigating medication adherence in children with cancer. This method allows the examination of both quantitative (e.g., adherence levels and related indicators) and qualitative aspects (e.g., barriers and experiences of families and patients). This approach provides a more comprehensive picture and a deeper understanding of the phenomenon of medication adherence in children with cancer.

An initial search was conducted in 2021, and then the search was complemented in 2022. This was because few studies specifically addressed adherence in the pediatric oncology population. The search keywords were "treatment adherence," "children," "cancer," and "malignancy." The search was conducted using the following three databases: PubMed, Scopus, and Cochrane. A total of 43 articles were retrieved, 28 of which were excluded after an initial evaluation (five due to duplication and 23 for not meeting the inclusion criteria for reasons, such as participants' age, type of chronic disease, and unavailability of full text). Fifteen articles were assessed for quality; six were considered poor and excluded from the study. Finally, nine articles were included in the study. (Figure 1 shows the search results.)

For the initial database search, the search was limited to adherence to treatment in children with cancer, English-language publications, and no time limit, because few studies were available on adherence to treating children with cancer. All types of cancer were considered in research, review articles, and qualitative papers on childhood. The exclusion criteria included adolescence and older age, other chronic childhood diseases, gray literature, books, and certain items, such as bone marrow transplantation, due to differences in care. The evaluation criteria for the reviews were based on AMSTAR, empirical articles using JADAD, and descriptive articles using the MMAT quantitative article evaluation guideline.

Figure 1. Results of Database Search



Results

Finally, nine articles were included, of which six were descriptive, two were clinical trials, and one was a review article. Given the breadth of study designs, a narrative synthesis approach was employed along with a thematic analysis (for studies of similar designs). The extracted themes were summarized under four main themes: prevalence of treatment adherence in children, factors related to adherence, adherence measurement instruments, and interventions to promote treatment adherence (Table 1). Table 2 summarizes the results.

Table 1. Extracted Themes

Theme	Theme-Related Results of Literature
Level of treatment adherence	(10)(Salaverria) 87% (16)(Rohan 86% (18)(Rifky) 55.8% (19)(Bhatia) 74% (5)At the end of month 1, and decreased to 91.85% at the end of month 5 (Bhatia) 95% (20)(Afungchwi) 59% (4)(Rohan) 59.2%
Factors associated with treatment adherence	Lack of funds, household needs, unexpected events, such as weather conditions (Salaverria) Low socioeconomic status and low education level of large families with five or more members (Rifky) Poverty (Afungchwi) Financial problems, patient personality factor, patient age group, perception of disease and treatment, adverse effect of treatment (Goh), Adherence rates among patients were significantly higher in single-parent/single-child families than in patients with nuclear families (and families where mothers were full-time caregivers compared to families with other caregivers), and adherence rates were significantly lower in patients from low-income families (Bhatia)(5)
Adherence measurement instrumentation	Non-adherence to missed appointments at the centers (Salaverria) and a week or more delay for chemotherapy or follow-ups (Afungchwi) MEMS electronic monitoring device (Rohan, Rifky) Questionnaire specific to patients or their caregivers and measurement of serum 6-mercaptopurine levels by chromatography (Bhatia)(19) MEMS cap of microelectronic technology to record date/time of each pill bottle opening and red blood cell TGN levels reflecting chronic systemic exposure (1-4 weeks prior) (Bhatia)(5) Methotrexate with three polyglutamate residues (MTXPG3) measured in peripheral red blood cells (Kandikonda)(21) Adherence as the frequency of taking oral medication (Rohan4)
Interventions to promote treatment adherence	Phone calls with the child's caregiver to explore reasons for absence, emphasizing the importance of treatment adherence. Intervention includes education and daily reminders of personalized text messages from the treating oncologist to the patient and parents as encouragement (Salaverria)(10) Interactive multimedia educational program using video shots of patients and parents from diverse sociodemographic backgrounds to address health beliefs, including susceptibility or severity of ALL (Bhatia)(19)

Abbreviations: ALL, acute lymphoblastic leukemia; TNG, thioguanine nucleotide.

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Table 2. Features of the Related Studies

Author's Name Country and Year of Publication	Year	Purpose	Sample Size	Age Distribution	Definition of Patient	Methodology	Level of Adherence	Results
Salaverria El Salvador 2015	2012	Exploring the results of implementing the time-sensitive adherence tracking method	491 children with solid or hematological malignancies	< 15 years	All patient/family absences from pediatric oncology department appointments, whether for chemotherapy or doctor visits.	Data were part of a prospective study. The intervention process involved telephone and one-on-one contact with the child's caregiver to identify reasons for the child's absence, emphasizing the importance of adherence to treatment. It was conducted	The dropout rate decreased from 13% to 3% in the year following the intervention.	Reasons for leaving treatment: Lack of funds was the most common (23%) Home needs category (12%) including the illness of primary caregiver or other family member Unforeseen events category (16%), such as

						over 2 years.		weather and transportation problems
Rohan U.S.A. 2015		Describing patterns of adherence to treatment in the initial maintenance phase for acute leukemia	139	7-19 years with an average of 12 years	Children and adolescents aged 7-19 years diagnosed with ALL or LBL and their primary caregivers enrolled in six centers for pediatric cancer treatment.	Using an objective observational method (electronic monitoring), percentage adherence was measured as the frequency of taking oral medication doses as prescribed. A MEMS electronic monitoring device was used.	The average adherence rate was 86.2%. The adherence rate decreased to 83% at one-month follow-up.	Most patients (75.8%) showed good adherence during the first month of the maintenance phase, while the second group (17.1%) showed deteriorating adherence: Decreased from 100% to 60%, and the third group (7.1%) showed poor adherence: an average of 40%. There were no differences between the pathway groups with respect to patient age.
Rohan U.S.A. 2017	2015	Describing the relationship between pharmacological and behavioral measures of adherence to 6-mercaptopurine (in children with cancer)	139	7-19 years	The participants were 139 patients with ALL or LBL and their caregivers.	This study was a secondary analysis of data from a prospective randomized controlled trial. Pharmacological measures (e.g., metabolite concentrations) assessed 6-MPG intake. Behavioral measures (e.g., electronic monitoring) described adherence patterns over time. Adherence was defined as the frequency of taking prescribed oral medications.	59.2% indicating adequate adherence	Low levels of both metabolites (40.8%) were consistent with non-adherence. Low levels of both metabolites consistently correlated with lower rates of behavioral adherence.
Kandikonda U.S.A. 2019	2012 2015	Determining the reference ranges to identify patients with low MTXPG3 levels showing poor adherence or the risk of high MTXPG3 toxicity	123 samples taken from 76 patients with ALL undergoing maintenance therapy	1.2-21 years	MTXPG3 levels were included from 123 samples in 76 patients with ALL receiving maintenance therapy with oral methotrexate and mercaptopurine	Methotrexate is confirmed by three polyglutamate residues (MTXPG3) measured in peripheral red blood cells. The primary intracellular metabolite is	-------	MTXPG3 values ranged from 6.1 to 78.6 nmol/L. The 5th, 10th, 90th, and 95th percentile values were 0, 8.4, 53, and 64, respectively, with a

					and patients suspected of non-adherence to oral chemotherapy.	methotrexate. The data included: mean weekly dose of methotrexate in mg over 4 and 8 weeks, with an average daily dose of mercaptopurine in mg over 4 and 8 weeks. For analysis, MTXPG3 values below the detection limit (< 5 nmol/L) were set to zero. MTXPG3 values below the 5th percentile Showed poor adhesion.		mean of 24.7 nmol/L. The MTXPG3 percentile below 5 reflects six samples from 3 patients aged 16 to 21 years who were considered to be a poor adherent prior to sample collection. There were also two other patients who had MTXPG3 ≤10 and were perceived to be less adherent.
Rifky Egypt 2015	2012-March, 2013 2012-March, 2013	Assessing adherence to oral 6-mercaptopurine maintenance chemotherapy for childhood leukemia and determining predisposing factors	129	Age range of 1.5 to 15 years, average age of 4.9 129 children and adolescents undergoing maintenance treatment for leukemia, Pediatric Oncology Department, Children's Hospital	129 children and adolescents undergoing maintenance treatment for leukemia, Pediatric Oncology Department, Pediatric Hospital.	Design type: Cross-sectional All recruited children received 6-mercaptopurine according to the revised protocol of the Children's Cancer Group (1991). Regular follow-up visits were held weekly, with laboratory tests and medications provided free of charge.	55.81	There was a correlation between non-adherence to the questionnaire and mercaptopurine levels. Non-adherence was associated with low socioeconomic status and low educational level of large families with five or more members. Adolescent age was not significant.
Bhatia Birmingham, 2020	2012 and August, 8, 2018 2012 and August 8, 2018	Determining the effect of a multicomponent intervention, compared to education alone, on adherence to mercaptopurine medication in patients with ALL for all study participants and a comparison between patients younger than 12 years and older than 12 years	Total number of 444 223 in the intervention group and 223 and 214 in the training group	The median age was 8.1 years, with a range of 5.1 to 14.3 years	Children who received mercaptopurine in the maintenance phase of treatment for at least 24 weeks at the first clinical remission.	Design type: Clinical trial Participants were randomly assigned 1:1 to the intervention group or education alone using stratified block randomization by study age (<12 vs. 12 years) and race/ethnicity. Intervention: Web-based message via mobile phone and education group: video images based	In patients younger than 12 years, adherence rates remained at 74% from baseline to post-intervention in the intervention group and decreased from 74% to 65% in the education group.	After adjusting for baseline adherence, time in study, and father's education, the difference in the proportion of patients with mercaptopurine adherence of 95% or higher between the intervention and the education group was not significant.

						on the health belief model. Done over 16 weeks.		For patients 12 years of age and older, the proportion with adherence of 95% or higher decreased from 57% to 52% in the intervention group and from 65% to 50% in the education group.
Bhatia 2014		Describing the prevalence and predictors of adherence to oral 6 mg of erythromycin in children, African Americans, and Asian Americans with ALL	298 Patients 39 803 samples a day	1-19 years	Patients diagnosed with ALL at age 21 or younger and receiving maintenance chemotherapy that included 6 mg orally.	The electronic monitoring device (MEMS TrackCap and MEMS cap) uses microelectronic technology to record the date/time of each pill bottle opening. Red blood cell TGN levels reflect chronic systemic exposure (1-4 weeks prior). The adherence questionnaire was administered at four points in time during the study (days 29, 57, 113, and 141). An adherence rate of <90% was used to define nonadherence.	Adherence to oral 6MP decreased from 95.0% at the end of month 1 to 91.8% at the end of month 5. Of the participants, 20.5% were non-adherent.	نرخ Adherence rates were significantly higher among patients: (1) single-parent/single-child families (96.6% 6:1.4%) when compared to patients in nuclear families (92.3% 6:0.9%) , families whose mothers were full-time caregivers (94.9% 6:0.9%) when compared to families with other caregivers configurations (91.0% 6:1.3%), with adherence rates are significantly lower in patients from low-income families. Self-reported reasons for missing 6MP included forgetfulness, logistical barriers, and active refusal.
Afungchwi Cameroon 2019	2008-2014	Exploring the relationship between poverty and treatment adherence and its effect on patients with Burkitt's lymphoma (BL) survival.	132	8.2	All guardians of children ≤15 years of age treated for BL at Baptist Hospital Banso or Baptist Hospital Mbingo.	This study was part of the BL clinical trial and used a prospective, questionnaire-based survey of socio-economic factors affecting families of children with	8% were late for treatment, 25% were delayed for follow-up by more than a week, and 9.8% dropped out of treatment	Poverty score was not significantly associated with treatment delay, but was significantly associated with follow-up delay.

						BL. Analyses were done with IBM Statistics 25. Nonadherence was defined as a delay of 1 week or more for chemotherapy or follow-up.	within a year.	
Goh Singapor 2016	------	A systematic review of literature to identify factors associated with non-adherence to treatment in pediatric oncology patients	39 articles	------	Articles with participants under 18 years of age.	In a systematic review, 1036 articles were retrieved, 960 articles from PubMed and 76 from PsycINFO. A hand search was also performed using references from relevant articles. A total of 46 articles met the inclusion criteria. After removing duplicates, 39 articles were retained.	----------	The most important factor associated with non-adherence to treatment is a financial problem. The second factor is the patient's personality. The patient's age group has been identified as one of the main factors affecting treatment adherence. The fourth is the perception of the disease and treatment. The fifth commonly mentioned factor is its adverse effect.

Abbreviations: ALL, acute lymphoblastic leukemia; LBL, lymphoblastic lymphoma; MEMS, *medication monitoring system*.
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Prevalence of Treatment Adherence

It is well established that treatment is key to achieving maximum benefits, including relapse prevention and outcome-free survival. The prevalence of treatment adherence ranged from 59% to 87% across the studies reviewed. In a review by Pritchard on adherence to mercaptopurine during maintenance therapy in children with ALL, adherence to the treatment regimen was found to be 90%-80% [21]. However, the adherence rates do not exceed 90%, suggesting the importance of measures to increase adherence in children younger than 12 years of age with cancer.

Risk Factors for Treatment Adherence

Only a few studies focused on adherence's mechanisms and potential psychosocial determinants [26]. Several bio-psychosocial factors influence the rate of treatment adherence. In a literature review, three factors were found: socio-economic factors, patient and caregiver factors, and environmental factors. The foremost factor associated with non-adherence to treatment is financial problems. Low socioeconomic status, low educational level, and large family size were associated with non-adherence to treatment [30]. However, a study in Cameroon showed that medication adherence was not correlated with poverty [31]. Poverty was associated with follow-up periods, reflecting the role of financial problems.

Patient-Caregiver Factors

An influential factor is the patient's age. In Rohan's study, no difference in adherence patterns was found with patient age [27]. However, in Bhatia's study, treatment adherence was 74% at baseline among children younger than 12 years, versus 54% among children older than 12 years [32]. Bonilla (2001) reported that younger children and children with higher functioning are more likely to experience nonadherence, especially about procedure-based treatments, such as oral care and central line care [33]. Many children also need medical care at home. Many families have difficulty performing the complex medical tasks they

need to do [26, 34]. Regarding oral medication, various factors affect parental behavior, including low parental education and understanding of the disease. In a review, seven studies with 503 participants showed that information about the disease, knowledge of the disease, and participants' personality can influence caregivers' and patients' behaviors [18, 35]. However, this discrepancy could be due to the measurement instrument for treatment adherence. The use of objective measures instead of parent and child behaviors in self-care for medication side effects could be due to the objective nature of these measures. In another study, Salaverria showed that some reasons for discontinued treatment were related to domestic needs, such as the disease of the primary caregiver (53%) or another family member (22%), and the conflicting responsibilities of the primary caregiver and other family members, which could affect treatment adherence in children [16]. In Pritchard's study, the most common reason for missing medication doses by patients and families were human error, including forgetfulness, mental obsession, and inadequate medication supply [21]. Adolescents may experience lower adherence due to developmental features. One study showed that patients who disregarded or underestimated the severity of their disease were less likely to adhere to treatment. This was particularly true in adolescents who perceived themselves as invulnerable or used defense mechanisms such as denial [36].

Environmental Factors:

Salaverria's study showed that missed appointments increased during the rainy season. Throughout one year, 23% of absences occurred when a tropical storm hindered public transportation for two weeks [16]. One reason can be the climatic conditions prevailing in El Salvador, which require health policymakers to consider climate-related issues in this population.

Measurement Instruments

Adherence to treatment can be measured through objective or subjective methods [37]. The latter includes direct measures, such as biological measurements or clinical observation of medication use, and indirect measures, such as self-report or parent report. The former contains more objective measures, such as medical chart review to record observed adherence, pill counts, or electronic monitoring. Many studies have used adherence measures or pill counts reported by physicians, parents, or patients, often overestimating adherence levels [12].

Various instruments were used, including missed appointments for chemotherapy or follow-up or counseling, measurements of drug metabolite levels, questionnaires, and electronic monitoring using a microelectronic device placed on top of the medication bottle that recorded the time the bottle cap was removed. Lau et al. evaluated adherence to Mercaptopurine in 24 pediatric ALL patients using a medication monitoring system (MEMS). The MEMS provided information on all dates and times the pill container was opened over a 4- to 6-week period. The results showed that 33% of patients consumed less than 90% of the prescribed mercaptopurine and 17% consumed less than 80% of the prescribed dose [38]. Although electronic devices are more accurate, they have certain disadvantages, such as opening the bottle but not taking the medicine, or failing or forgetting to take the medicine, which can mislead findings. In Rifky's study [30], a questionnaire specific to patients or their caregivers and a measurement of serum 6-mercaptopurine levels by chromatography were used. The questionnaire included age at diagnosis and recovery, number of siblings, socioeconomic status, place of residence, cost of hospital visits, and the time spent on each visit. The details of the caregiver included the level of education, knowledge of the disease, what would happen if the patient did not receive their maintenance treatment, as well as written instructions about maintenance treatment. The details of maintenance medication included timing, regularity, time and frequency of missing a dose, and what to do if so. A significant correlation was found between the results of non-adherence to treatment through the questionnaire and mercaptopurine levels [30]. However, Rifky's study suggests that assessment by both instruments is valid and that one can be used based on the existing facilities. In Kandikonda's study, the lower 5th percentile of the three-residue polyglutamate metabolite represented a sample of six of three patients aged 16-21 years with poor adherence prior to the sample selection. The three-residue polyglutamate is the primary intracellular metabolite of methotrexate that persists until the end of the life of red blood cells, providing an estimate of drug exposure over time that may provide helpful information for monitoring patient adherence or methotrexate toxicity during maintenance chemotherapy in ALL [39].

Interventions to Promote Adherence to Treatment

In the present study, the implemented interventions primarily focused on health centers and health systems, with positive results. In the study by Salaverria et al., a phone call was made with the caregiver when the patient did not attend the clinic. Calling the caregiver was considered an intervention, considering the significant impact a clinician's attention can have on ordinary parents in this context. The results also pointed to the effectiveness of this intervention [12, 17]. In Bhatia's study, the intervention included daily training and reminders as personalized text messages sent by the visiting oncologist to the patient and parents. The intervention also included an interactive multimedia educational program of video images of patients and parents from different sociodemographic backgrounds to address health beliefs, such as susceptibility or

severity of ALL [32]. This is consistent with Hudson's study, in which cancer survivors were randomly assigned to telephone counseling by an advanced practice nurse plus standard care versus standard care alone (the intervention-only group). The latter had greater adherence to screening with echocardiography in those receiving telephone counseling. The estimated rates were 52.2% versus 22.3% [40]. Kana et al. conducted a meta-analysis of 70 adherence-promoting interventions among young people with a chronic disease, none of which included children with cancer. Educational interventions were associated with a slight increase in adherence [29], consistent with Bhatia's study. Larger effect sizes were observed with behavioral and multicomponent interventions, and technology-based interventions were not associated with positive effects [29, 41].

Discussion

One of the significant challenges in the treatment process is treatment adherence, which is particularly crucial in children with cancer and can affect treatment outcomes and disease-free survival. The results of the present study showed that the rate of treatment adherence in children with cancer varied between 59% and 87%, indicating a significant gap in the provision of medical care. In a study by Pritchard et al., the rate of treatment adherence and mercaptopurine use in the maintenance phase of ALL was reported to be 80%-90%. These results indicate the need for greater attention to factors affecting treatment adherence, especially in children under 12 years of age [21].

This study identified three key categories of factors affecting adherence to treatment: socioeconomic factors, patient- and caregiver-related factors, and environmental factors. Poor economic status, low parental education, and large family size were the most important socioeconomic factors [42]. However, contradictory results were also observed. In a study in Cameroon, no significant relationship was observed between poverty and adherence to treatment. This could be due to the free access of individuals to health services in this country, indicating the role of health institutions in promoting adherence to treatment [31, 43].

Regarding patient and caregiver factors, the patient's age, the child's functional abilities, and parental knowledge and beliefs about the disease were influential. Some studies have shown that children under 12 years of age may be more compliant [8]. However, other studies have suggested that children with higher performance in daily activities may be more negligent in specific care tasks, such as caring for intravenous lines or taking oral medications [33]. Family problems, such as the illness of the primary caregiver, multiple parental responsibilities, and psychological disorders, such as forgetfulness or denial of disease in adolescents, can reduce compliance [44, 45].

Environmental factors include weather conditions, heavy rainfall, and seasonal storms, which can disrupt access to treatment centers and cause missed treatment sessions. This is especially important in countries with poor transportation infrastructure [44].

In the field of adherence measurement tools, although objective methods, such as blood drug level measurement or electronic monitoring, are more accurate, questionnaires and patient or parent self-report remain common, which can lead to overestimation of adherence [46]. In a study by Lau et al. (2015) using a MEMS system, about one-third of patients took less than 90% of the prescribed medication dose [47]. This finding highlights the importance of using objective and subjective tools simultaneously for more accurate estimation [48].

Finally, interventions to promote adherence have been implemented mainly at the individual health and health system levels [49, 50]. Telephone calls to parents, personalized reminder messages, interactive multimedia education, and telephone counseling were among the most effective interventions [8, 51]. A systematic review by Kahana et al. (2008) also showed that educational interventions alone have limited effects, while behavioral and multicomponent interventions have a greater impact on improving adherence [29]. Contrary to expectations, technology-based interventions were not significantly effective.

According to this review's findings, multilevel and multicomponent approaches, including educational, behavioral, psychosocial, and health policy interventions, should be used to improve treatment adherence in children with cancer.

Limitations of the Study

The present review had certain limitations, including a focus solely on English-language literature and the use of only three databases. The review results highlighted the role of financial problems in non-adherence, which requires further meta-analyses. Other limitations include the variety of designs, which compromised the integrity of the findings.

Conclusions

Treatment adherence in children does not reach the ideal 95%, but interventions have shown they can improve it. Treatment adherence is multifactorial, and especially for children, the role of the family is of utmost importance. This review is helpful for health policymakers in pediatric cancer and the chronic diseases of children. It can also be used to provide better care for these children. It is recommended that more studies be conducted on increasing treatment adherence

in children under 12 years of age, emphasizing the family.

Ethical Considerations

Compliance with ethical guidelines

This article is the result of a research project approved by Gonabad University of Medical Sciences and has been approved by the Research Ethics Committee of Gonabad University of Medical Sciences. (IR.GMU.REC.1403.066).

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Authors' contributions

Study conception and organization: ME and MI;

Execution and data collection of the study: MR, NE, and ME;

Statistical analysis design and/or execution: ME, MI, NE, and HI.

All authors contributed to the preparation, critical review, and approval of the final manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

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