

Strategies to improve adherence to treatment in adolescents and young adults with cancer: a systematic review

Eden G Robertson^{1,2}
 Claire E Wakefield^{1,2}
 Kate H Marshall²
 Ursula M Sansom-Daly¹⁻³

¹Discipline of Paediatrics, School of Women's and Children's Health, UNSW Medicine, University of New South Wales, Kensington, NSW, Australia; ²Behavioural Sciences Unit, Kids Cancer Centre, Sydney Children's Hospital, ³Sydney Youth Cancer Service, Prince of Wales/Sydney Children's Hospital, Randwick, NSW, Australia

Purpose: Adolescents and young adults (AYAs) with cancer have higher rates of nonadherence to treatment relative to younger and older cancer patients. Efforts to improve adherence in this population are therefore increasing. This review aimed: 1) to synthesize recommendations and strategies used to improve treatment adherence in AYAs with cancer, and 2) to summarize the available evidence supporting the efficacy of adherence-promoting strategies for AYAs with cancer.

Methods: We conducted a systematic review with two stages: 1) a narrative stage, to analyze expert recommendations, and 2) an evaluative stage, to summarize quantitative evidence for interventions. Four electronic databases were searched for studies involving AYAs, aged 10–39 years, with cancer, published from 2005 to 2015. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to ensure quality of the review. The Delphi list was used to assess study quality.

Results: Nine articles were identified in the narrative stage of the review. For the evaluative stage, out of 113 screened abstracts, only one eligible intervention was identified. Common themes of adherence-promoting strategies were grouped into five domains: developmental, communication, educational, psychological well-being, and logistical/management strategies. Strategies to address developmental stage and to improve communication were the most highly recommended to improve adherence. Few strategies focused on the role of the patient in adherence. One intervention found that a behaviorally targeted computer game could significantly improve adherence to prescribed oral medication in AYAs with cancer.

Conclusion: Although numerous studies report challenges to treatment adherence in AYAs with cancer, little research has systematically evaluated the impact of implementing recommended strategies and interventions in this age group. The present review extends the current literature through its focus on strategies recommended to improve adherence, rather than focusing on barriers and risk factors for nonadherence. There is now a need for more rigorous research to systematically assess the effect of implementing strategies to improve AYAs' adherence to cancer treatment.

Keywords: neoplasms, emerging adulthood, interventions, communication, psychosocial

Correspondence: Eden G Robertson
 Behavioural Sciences Unit proudly supported by the Kids with Cancer Foundation, Kids Cancer Centre, Sydney Children's Hospital, Level 1, High St, Randwick, NSW 2031, Australia
 Tel +61 2 9382 3120
 Fax +61 2 9382 1789
 Email eden.robertson@unsw.edu.au

Introduction

Each year there are more than one million new cancer diagnoses worldwide among 15–39 year olds.¹ Despite improved prognoses in this population, there remain a significant number of relapses and deaths.^{2,3} Nonadherence to treatment is one factor that may contribute to the lower rates of survival improvement among adolescents and young adults (AYAs), relative to other age groups.^{2,4,5} With the rise of efficacious self-administered medications for a range of cancer diagnoses,⁶ it is increasingly important

to ensure that young patients are able to properly adhere to their treatment regimens. Despite this, suboptimal adherence to treatment, oral chemotherapy in particular, appears considerably more problematic in AYAs than in pediatric and adult/geriatric patients,^{5,7,8} with up to 60% of AYAs failing to adhere to the recommendations of their medical team.^{4-6,9}

Adherence, also referred to as “compliance”, is most commonly defined as “the extent to which a person’s behavior (with regards to medication, diet, or lifestyle) corresponds with agreed recommendations from health care providers”.¹⁰ In cancer, nonadherence may present as inconsistent medication use (including oral chemotherapy), failure to attend clinic appointments, and failure to engage in self-care behaviors.¹¹ Researchers and clinicians define acceptable medication adherence as 80% or more.¹²

The impact of nonadherence to cancer treatment on survival in AYAs has not yet been fully explored.^{11,13} Medication nonadherence can increase relapse risk and reduce survival in pediatric cancer patients.^{14,15} It can also cause increased mortality among older populations, such as adult women with breast cancer,¹⁶ and can lead to hospitalization and death for cancer patients through overdosing.¹⁷ In the context of research, nonadherence can also invalidate results of trials, and prevent adequate evaluation of treatment efficacy.¹⁸

A variety of factors have been attributed to AYAs’ poor adherence, including developmental factors, interpersonal/support-related factors, and informational factors. Regarding developmental factors, AYAs with cancer are faced with unique challenges as they enter cancer treatment. AYAs may have underdeveloped coping skills and a more concrete thinking style than older adults.⁵ Factors such as reduced autonomy during treatment, an inability to conceive the long-term consequences of their illness, and emerging communication skills also have the potential to negatively affect adherence in this population.^{19,20}

Across AYAs with other chronic illnesses, factors such as the desire for “normality” and “freedom”,^{21,22} a lack of control and lack of participation in usual activities,^{21,23,24} and exploratory risk taking behaviors²⁵ may all contribute to poor adherence. Like any chronic illness, cancer has reciprocal effects on adolescent development, with effects impacting AYAs biologically, psychologically, and socially.²⁵ Developmental factors can also influence AYAs’ behavior in response to the illness; for example, AYAs’ less well-developed abstract thinking and capacity to imagine the future, as well as associated health risk behaviors (eg, alcohol and drug use, and poor nutrition) pose additional challenges to adherence.²⁵

Interpersonal factors can also contribute to adherence. Across chronic illnesses, poor communication and relationships, between the AYA, health care professionals (HCPs), and family, is associated with adherence challenges.^{21,26} In particular, overly controlling relationships with parents or HCPs,²⁷ conflict between AYAs and their parents, family stress, and difficulty in delegation of treatment responsibilities can be triggers for nonadherence.^{24,28,29} The nature of AYAs’ peer relations and social support may also contribute to adherence.^{21,24,30}

Education/information regarding the illness, treatment, and side effects also appear to impact adherence in AYAs with a chronic illness. Several educational interventions have been implemented, with significant effects, although small, on adherence outcomes.³¹ Knowledge about treatment and illness appear essential for effective AYA health care but is not necessarily sufficient,²¹ with one review showing that chronic illness education alone failed to demonstrate any beneficial effects on adherence.³²

Although research suggests psychological well-being plays a role in adherence for AYAs with a chronic illness, there has been little cancer-specific research. The AYA years are a time of psychological vulnerability,³³ and AYAs with a chronic illness appear to be less treatment-adherent when they are experiencing high levels of stress and poor mental health.^{24,34} High levels of anger and low self-esteem have also been associated with greater nonadherence in adolescents.³⁵ Depression has also been shown to be a significant risk factor for treatment nonadherence in adult and pediatric populations.³⁶ Nonadherence in adolescents with a chronic illness may also be due to a lack of motivation. Across numerous chronic illnesses, other logistical/management factors, such as the complexity of the regimen, inability to recall instruction, poor time management, forgetfulness, treatment side effects, or inability to afford treatment, are also reported reasons for nonadherence in AYAs.³⁴

Although AYAs with cancer face a multitude of unique challenges that are not as prevalent in other chronic illnesses, numerous common psychosocial challenges exist. Research in chronic illness therefore offers a window into understanding the AYA cancer experience. This includes translatable research in areas such as treatment adherence, as well as the role of peer interactions, therapeutic alliance and psychological impact of illness,³⁷ and illness self-management.³⁸ Despite medical advances, cancer remains a life-threatening illness. Given the potential for nonadherence to significantly interfere with curative cancer treatment, it is critical that evidence regarding “best practice” recommen-

dations and interventions to improve treatment adherence in AYAs be examined. Several reviews have reported that adherence-promoting interventions can improve treatment adherence in chronic illness in AYAs,^{32,39–41} in particular, in AYAs with diabetes,⁴² asthma,^{43–45} inflammatory bowel disease,⁴⁶ and human immunodeficiency virus (HIV).⁴⁷ However, less research exists that specifically addresses nonadherence among AYA cancer patients. Several unique aspects of the AYA cancer diagnosis and treatment trajectory warrant cancer-specific interventions. In particular, cancer in AYAs is fairly uncommon,⁴⁸ potentially resulting in greater isolation of patients, and clinicians may have less AYA-specific skills.

To our knowledge, there are no systematic reviews available that address strategies to improve AYA adherence to cancer treatment. The primary focus of this review was therefore to synthesize the current evidence base regarding strategies that may be effective in improving treatment adherence for AYAs with cancer, in order to contribute to clinical practice and the development of evidence-based interventions in this area. In doing so, this review aimed to address two key questions:

1. What strategies have been recommended in the clinical-research literature to improve treatment adherence among AYAs with cancer?
2. What evidence exists to support the efficacy of adherence-promoting strategies among AYAs with cancer?

Methods

We conducted a two-staged systematic review to address our main aims. Due to the known limited research in this population,⁴⁹ a narrative approach was taken to the first stage of the review, in order to synthesize current recommendations and guidelines for HCPs to improve AYAs' adherence to treatment. The second stage of the review drew together published evidence for the efficacy of adherence-promoting interventions. We followed “gold standard” systematic review procedures, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, to ensure the review was high quality, transparent, and comprehensive.⁵⁰

The terms “adherence” and “compliance” have been used interchangeably across the literature,⁵¹ with adherence differentiated by a greater level of collaboration and agreement between patient and HCP.¹⁰ Due to the common use of these terms, we decided a priori to include articles that addressed either adherence or compliance to treatment. Given current research suggesting that the term “adherence” was most

appropriate,^{52,53} this term is used throughout the remainder of this review.

Inclusion criteria

Types of strategies

Articles were included regardless of the type of strategy used or recommended (ie, interpersonal, intrapersonal, or a combination of both). Interpersonal-level strategies are those between individual patients and others. In our study, this included the relationship and communication between the patient and doctors, friends, and family.⁵⁴ Intrapersonal strategies focus on individual factors such as health literacy, attitudes, self-efficacy, and motivation.⁵⁵ Strategies that were directed toward the AYA, their parent(s), or their HCPs were included.

Types of interventions

A range of interventions have been used previously to enhance adherence in chronic illness (eg, behavioral interventions, involving strategies designed to influence behavior), informational interventions (strategies designed to educate and motivate), and family and social interventions (strategies designed to improve social support).⁵⁶ Due to the paucity of intervention research addressing adherence in AYAs with cancer, all categories of interventions were eligible, and data were analyzed together. All interventions that aimed to improve adherence to any type of cancer treatment in AYAs were included (eg, medication-taking behavior, side-effect management, and nonmedical supportive care programs).⁵ Interventions were included irrespective of the way in which adherence was assessed (eg, observation, bioassay of serum/urine/saliva, patient self-report, and pill counts).⁴

Types of studies

Studies published in peer-reviewed journals that had a focus on recommendations or strategies to improve adherence were included in the first stage of the review. Studies published in peer-reviewed journals that presented results of an intervention to improve adherence to treatment in AYAs with cancer were included in the second stage.

Types of participants

We included all articles addressing adherence in patients who were aged 10–39 years during treatment, or that specified they were relevant for adolescence and/or AYAs or tailored to the AYA developmental stage. We acknowledge that there are varying definitions of “AYA” and therefore allowed for the most broad definition to cover all relevant research.⁵⁷

Articles that evaluated adherence in AYAs, as well as other populations (ie, pediatric, adult, geriatric) were only included if data was presented separately for each population group. Studies were eligible if the participants were receiving any form of active treatment for any type of cancer, including palliative care.

Narrative synthesis of strategy recommendations

Search strategy and selection criteria

Due to the recency of most contributions in this field, we decided to limit the search to the past 10 years, searching from 2005 to 2015. This was supplemented by reference list and author searches. Given the growing role of Google Scholar in academic work,^{58,59} we utilized this search engine for the narrative stage of the review. Two grey literature databases (OpenGrey and Grey Literature Report) were also searched. The search strategy and selection criteria are summarized in Table 1.

Data collection

Two authors (EGR and KHM) searched the literature and found all eligible articles. Consensus regarding inclusion of articles was achieved by discussion.

Evaluative review of interventions

Search strategy and selection criteria

Three electronic databases were searched (MEDLINE, EMBASE, and PsychInfo), limited to human studies published in English. We limited the search to the past 10 years, searching from 2005 to 2015. A series of searches defining the age group, disease, and outcomes were run, and the results were combined. Search terms were adapted

from previous research^{37,60} to ensure the most complete and accurate coverage of the literature. The search strategy and selection criteria are summarized in Table 1.

Data collection

Two authors (EGR and KHM) reviewed all abstracts and relevant full-text articles. Consensus regarding inclusion of articles was achieved by discussion. Methodological quality was assessed by two authors (EGR and KHM). Study quality was assessed using the Delphi list. The Delphi list is a set of generic core items used to assess whether the design and conduct of a randomized controlled trial is of high quality.⁶¹ The captured intervention is summarized in Table 2.

Results

Study selection

Figure 1 summarizes the search process and reasons for study exclusion. For the first stage of the systematic review, nine articles were reviewed. The interrater reliability, that is, the extent to which the two raters agreed on which articles to include, was 75% (calculated by total number of articles agreed upon, divided by total number of articles agreed upon plus total number of disagreed upon). For the second stage of the review, after deduplication, the search yielded 113 abstracts. Captured articles were screened by two authors (EGR and KHM) using the inclusion criteria described above. Three articles were deemed appropriate for full evaluation. The interrater reliability was 100%. No additional articles were identified after a manual search for additional articles in relevant reviews and journals. Using the search algorithm, we were able to conduct searches with 100% sensitivity (every eligible intervention was captured by the algorithm) and 0.9% specificity (one eligible article was captured out of 113 abstracts).

Table 1 Summary of search algorithms

Review	Search database	Search strategy	Data collection	Inclusion criteria
Narrative stage	Google Scholar, Grey literature databases (OpenGrey and Grey Literature Report)	Relevant publications, reference lists, and author searches	<ul style="list-style-type: none"> Author Year of publication, country Sample characteristics General recommendations Key statements 	<ul style="list-style-type: none"> Published 2005–2015 Participant age range: 10–30 yrs Any active treatment Any recommendation to improve adherence Any adherence measurement
Evaluative stage	MEDLINE, EMBASE, and PsychInfo	[oncol\$ OR neoplasm OR cancer OR tumor OR tumour] AND [adolesc\$ OR young adult OR teen OR AYA.mp OR TYA.mp] AND [adherence OR compliance] AND [intervention OR program] AND [pilot OR trial OR evaluation]	<ul style="list-style-type: none"> Author Year of publication Country Sample/intervention characteristics Study methods Intervention outcomes Methodological quality 	<ul style="list-style-type: none"> Published 2005–2015 Participant age range: 10–30 yrs Any active treatment Any type of intervention to improve adherence Any adherence measurement

Table 2 Summary of captured intervention(s)

Author, country	Study size	Patient population	Intervention (n=195)	Control (n=176)	Study period	Adherence measure	Intervention outcomes
Kato et al. ⁶⁸ United States	371 AYAs aged 13–29 yrs	Malignancy diagnosis (newly diagnosed or relapsed), undergoing treatment (chemotherapy, radiation, or stem cell transplantation)	The intervention was a PC game, “Re-mission”, which addressed behavioral issues of cancer treatment and care for AYAs	A PC version of Indiana Jones and the Emperor’s Tomb served as the control game	Participants were asked to play the game(s) for at least 1 hour per week during the 3-month study period	<ul style="list-style-type: none"> Self-reported adherence Serum metabolite assay Electronic pill-monitoring devices 	<ul style="list-style-type: none"> Results suggest that behaviorally targeted video game intervention can enhance adherence to prescribed oral medication regimens in AYA with cancer Self-efficacy and knowledge together were also shown to mediate improvements that were observed in patient adherence to prescribed oral antibiotics

Abbreviations: AYAs, adolescent and young adults; PC, personal computer.

Research question I: what types of strategies have been recommended in the clinical-research literature to improve treatment adherence among AYAs with cancer?

Description of articles

Nine articles that explored recommendations for treatment adherence among AYAs with cancer were found that met the inclusion criteria. Five articles were narrative reviews,^{4,5,9,62,63} two reported studies involving semistructured interviews,^{64,65} one was an analysis of qualitative focus group data,⁶⁶ and one was a proposed algorithm for adherence risk assessment.¹⁹ Five articles addressed cancer patients in general,^{4,5,9,19,62} three assessed acute lymphoblastic leukemia patients specifically,^{64–66} and one addressed patients with any hematological disorder.⁶³ The articles are summarized in Table 3.

In terms of participants’ ages at the time of treatment, five articles discussed AYAs,^{4,5,19,63,66} two articles discussed adolescents only,^{9,62} one article discussed children, adolescents, and adults,⁶⁴ and one article discussed children and adolescents.⁶⁵

Findings

The nine reviewed articles described a range of strategies to be implemented by the AYA, parent, and/or HCP. The identified strategies targeted a range of underlying factors, and we categorized these strategies into five domains that affect adherence: developmental, communication, educational, psychological well-being, and logistical/management difficulties. Articles that discussed strategies taking a developmental approach were the most prevalent (n=9),^{4,9,11,19,62–66} while strategies relating to communication were identified in six articles.^{9,11,19,62,65,66} Table 4 provides an overview of the strategies recommended to address each underlying factor, for AYA patients, parents, and HCPs.

Developmental strategies

All nine articles highlighted the role that developmental stage might play in impeding treatment adherence among AYAs with cancer. Development-focused recommendations appeared to take two forms. Firstly, some strategies focused on how parents and HCPs can present, and discuss treatment information in a developmentally appropriate manner. Taking the developmental stage and maturity of the patient into consideration when developing treatment plans may assist in improving adherence outcomes.^{19,64–66} In particular, providing AYAs with a greater sense of control and allowing them to maintain independence throughout treatment may

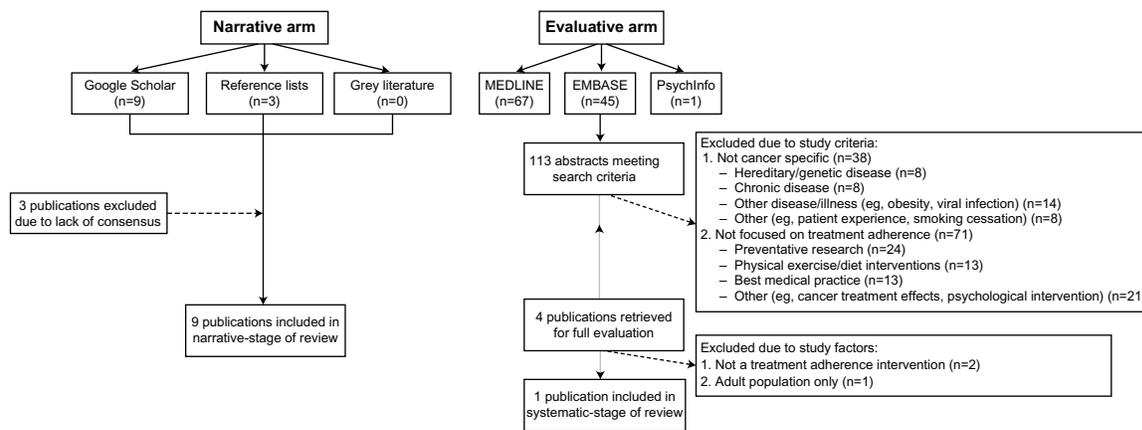


Figure 1 Reasons for exclusion of publications resulting from the database search.

improve adherence.^{62,65} Secondly, other strategies focused on how AYA milestones, such as school formals, graduations, and 18th birthdays, should be addressed through collaboration of the AYA, their parents, and HCPs.¹¹ Recommendations were that active discussions between the three parties should focus on how the AYA can continue to meet important milestones whilst meeting an adequate level of treatment adherence;^{63,66} by acknowledging the developmental importance of such social events and allowing for flexibility in the treatment schedule, these strategies promote adherence in the context of the unique developmental issues in AYAs.^{19,66}

Communication-related strategies

Six articles emphasized the important role that communication has in treatment adherence among AYAs with cancer,^{9,11,19,62,63,65} highlighting that AYAs, parents, and HCPs need to work together throughout the treatment process to ensure good adherence.

Articles recommended strategies in which the HCP tailors communication style to the individual patient, with the aim of achieving open and trustworthy communication.^{9,67} Additionally, positive family relationships and good communication between AYAs and parents is also important for adherence.^{4,11,63} Agreement with parents about treatment, medication, and the doctor's instructions is especially important.⁶² Role delineation about medication administration also needs to be clarified between AYAs and their parents in the early stages of treatment.^{4,9,65}

Educational and informational strategies

The role of education and information about the illness and treatment was emphasized in three articles.^{11,63,65} Adherence may be improved when the patient understands the treatment procedures, and the effects of treatment and medications.⁶³

The literature identified that HCPs need to provide AYAs with knowledge about the disease, treatment, and future health outcomes, and provide them with confidence in the possibility of their recovery.⁹ Articles highlighted the importance of AYAs understanding the life-threatening nature of their disease.^{19,65} Personal health beliefs and locus of control may also influence adherence.^{4,11} The most important strategy discussed was providing education about medication, the therapeutic effects of the lifesaving treatment, and the importance of taking medication when advised.^{11,65} Articles also suggested that HCPs and parents need to be responsible for teaching AYAs basic adherence strategies, and encouraged strategies such as the use of reminder tools and instilling medication routines.^{11,65} Further recommendations are that AYAs should also seek information by raising any concerns or questions with their clinician; in response, HCPs should aim to provide a safe and nonjudgmental environment for the AYA's concerns to be raised, and as well remain open-minded and willing to discuss or offer alternative treatment options when appropriate.⁶² Parents' knowledge about cancer and its treatment is also associated with adherence.⁶⁵ Articles also focused on HCPs, arguing that they are responsible for ensuring they are up to date with current chronic illness adherence strategies for AYAs.^{9,11}

Psychological strategies

Several articles discussed the importance of psychological well-being in treatment adherence among AYAs with cancer.^{4,19,63} Nonadherence can be seen as a sign of distress.⁴ Specifically, psychological factors such as parental depression,⁶² anxiety,⁶³ and self-esteem⁴ were identified as potentially affecting AYAs' treatment adherence. Articles argued that HCPs and parents must acknowledge the potential for psychological distress, and minimize the risk by providing

Table 3 Description of articles addressing strategies to improve treatment adherence

Author	Country	Main aim of paper	Sample	Main proposed causes and risk factors for nonadherence in AYAs	Conclusion
Abrams et al ⁶²	United States	Review discussing psychological issues in adolescents with cancer, including treatment compliance	Adolescents with cancer (age not specified)	<ul style="list-style-type: none"> Developmental stage Low socioeconomic status Barriers to communication Psychological distress Poor communication Shift in responsibility from AYA to parent Frequent disagreements between patients and parents 	<ul style="list-style-type: none"> There is a need to identify nonadherence issues early, to address any issues openly, and to overcome any adherence issues by following the recommendations of the SIOP Working Committee on Psychosocial Issues in Pediatric Oncology
Butow et al ¹¹	Australia	Review providing an overview of issues and clinical challenges of nonadherence in AYAs with cancer	AYAs with cancer (15–25 yrs)	<ul style="list-style-type: none"> Poor family relationships Overly controlling relationships Poor communication Lack of involvement in decision making process Lack of social support Difficulty with attendance at rite of passage events 	<ul style="list-style-type: none"> Discusses two frameworks used to define adherence – as an interaction between patient and medical team, or as a cognitive-motivational process If any adherence issues arise or any patient presents with multiple risk factors for nonadherence, increased monitoring should be employed Definite need for studies to evaluate interventions to promote adherence in AYAs with cancer
Kondryn et al ¹⁴	United Kingdom	Review to identify adherence challenges faced by AYAs with cancer	TYAs with cancer (13–24 yrs)	<ul style="list-style-type: none"> Demographics (eg, low socioeconomic status) Psychological distress (depression, low self-esteem) Perceived illness severity Family structure and dynamics Therapy and treatment factors (eg, complexity of regimen, side effects) 	<ul style="list-style-type: none"> Understanding the patient's reason for nonadherence, and considering potential factors associated with nonadherence is integral Future research needs to assess whether it is possible to identify AYAs at risk of nonadherence Interventions need to be evaluated to determine which programs are most effective
Landier et al ⁶⁵	United States	Semistructured interviews to develop and validate a model to explain adherence to oral chemotherapy in children and adolescents with ALL	22 children and adolescents with ALL (age range at diagnosis, 2–18 yrs; age range at study entry, 6–28 yrs)	<ul style="list-style-type: none"> Low socioeconomic status Family structure and dynamics Relationship with the HCPs Patient personality and developmental stage Health beliefs Knowledge about medications, treatments, and disease Therapy and treatment factors (eg, complexity of regimen, duration of treatment, negative side effects) 	<ul style="list-style-type: none"> Developed a 3-step process of adherence: recognition of the serious health threat, taking control of the situation, and managing adherence for the duration of the treatment Additional research is needed to further explore the role of contextual factors in adherence

(Continued)

Table 3 (Continued)

Author	Country	Main aim of paper	Sample	Main proposed causes and risk factors for nonadherence in AYAs	Conclusion
Leader and Raanani ⁶⁵	Israel	Review addresses prevalence, definitions, causes, and clinical implications of nonadherence of AYAs with hematological disorders, and then strategies to improve adherence	AYAs with hematological disorders (age not specified)	<ul style="list-style-type: none"> Difficulties transitioning from pediatric to adult care Disease and treatment factors (eg, severity, complexity of regimen, duration of treatment, negative side effects) Knowledge about medications, treatments, and disease Interaction between AYA, HCPs, and family members Perceived illness severity Unintentional nonadherence: forgetfulness Lack of appropriate social support Psychological distress (depression, low self-esteem) 	<ul style="list-style-type: none"> Interventions to improve treatment adherence should be designed based on AYAs with other chronic diseases, or from different age groups with hematological disorders Further research in evaluating strategies will improve our ability to better manage this aspect of treatment regimen
Malbasa et al ⁶⁶	United States	Secondary analysis of focus group interviews to understand the role of adolescent perception on adherence to treatment, and factors affecting adherence	Six AYAs with leukemia (aged 16–23 yrs)	<ul style="list-style-type: none"> Disease and treatment course Adolescent cognitive development, in particular, egocentrism and concrete thinking Parental support 	<ul style="list-style-type: none"> Identified four themes that emerged as pertinent to adherence in adolescents: a desire for normalcy, egocentrism, concrete thinking, and parental involvement Emphasis on adherence in the developmental context There is a need to incorporate these four themes into clinical practice to improve adherence Likelihood of nonadherence increased with age. Special attention should be given to adolescents to detect nonadherence risks early Screening for adherence should be systematic. Caregivers and physicians should address repeated evidence of nonadherence with special note of risk factors and potential causes
Mancini et al ⁶⁴	France	Semistructured interviews and self-report questionnaires to determine factors associated with nonadherence	31 parents of children, 12 parents of adolescents, 12 adolescents (aged 11–17 yrs), and nine adult patients (aged >17 yrs) with leukemia	<ul style="list-style-type: none"> Patient age Unintentional nonadherence: forgetfulness Lack of consistent treatment schedule Negative side effects of the treatment Fewer numbers of family members at home Socioeconomic status 	<ul style="list-style-type: none"> Risk of nonadherence should be assessed by considering the patient's developmental stage and maturity, psychosocial challenges, and unmet needs. Clear assessment enables tailored interventions to address adherence concerns Questions the generalizability of strategies to improve adherence to treatment of other chronic diseases, due to the specific nature of cancer – in particular, requires dramatic life changes Preventative measures are most effective when acknowledging the complexity of the issues faced by AYAs with cancer. Unique developmental characteristics can be predictive of nonadherence Preemptive strategies to be put in place to reduce nonadherence; however, significant shifts need to be made in current practice to better enable AYAs to make informed adherence decisions
Rosenberg et al ¹⁹	United States	Presents a theoretical model of risk assessment of adherence among AYA cancer patients	AYAs with cancer (15–39 yrs)	<ul style="list-style-type: none"> Perceived illness severity Perceived lack of control Sociodemographics AYA personality Social support Doctor–patient communication Psychological distress (depression, stress, anxiety) Financial stress 	<ul style="list-style-type: none"> Perceived lack of control Psychological distress Misunderstanding the effect of treatment and medication Low health literacy Family dysfunction Financial stress
Windebank and Spinetta ⁷	United Kingdom	An overview of the challenges in AYA treatment adherence. Outlines how health clinicians can increase likelihood of adherence	Adolescents with cancer (aged 13–18 yrs old)	<ul style="list-style-type: none"> Perceived lack of control Psychological distress Misunderstanding the effect of treatment and medication Low health literacy Family dysfunction Financial stress 	<ul style="list-style-type: none"> Preventative measures are most effective when acknowledging the complexity of the issues faced by AYAs with cancer. Unique developmental characteristics can be predictive of nonadherence Preemptive strategies to be put in place to reduce nonadherence; however, significant shifts need to be made in current practice to better enable AYAs to make informed adherence decisions

Abbreviations: ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; HCP, health care professional; SIOP, International Society of Pediatric Oncology; TYA, teenager and young adult.

Table 4 Strategies to improve adherence to treatment in AYAs with cancer

Context	Individual to implement strategy	Health care professionals	Parent/support person
Developmental	Patient <ul style="list-style-type: none"> • Need for developmental milestones to be met.^{1,3} <ul style="list-style-type: none"> – Voice concerns regarding desire for normal activities – Collaborate with HCPs and parents/support person on meeting important milestones and treatment requirements 	<ul style="list-style-type: none"> • Provide individualized guidance based on developmental stage¹ <ul style="list-style-type: none"> – Discuss what strategies other young people have found useful – Get a young person who has completed their cancer treatment to talk to the AYA • Allow developmental milestones to be met by having open discussions with AYA about what aspects of treatment are, and are not, flexible and open to negotiation.^{1,3} <ul style="list-style-type: none"> – For < 18 year olds, actively address need to meet developmental milestones with them • Promote a smooth transition from pediatric to adult care⁴ <ul style="list-style-type: none"> – Provide information about transition and what is to be expected; consider having a key HCP accompany AYA to initial appointments – Maintain hospital relationships from pediatric care into an adult setting – For > 18 year olds, support and assist AYA to identify and engage with a good GP to help with transition to outpatient and survivorship care 	<ul style="list-style-type: none"> • Normalize medication taking by assisting young person to integrate into a routine aspect of their daily self-care³ <ul style="list-style-type: none"> – Provide routines, such as taking medications at breakfast • Allow developmental milestones to be met.^{1,3} <ul style="list-style-type: none"> – Have open conversations with AYA about their hopes and goals for treatment and life outside of treatment • Support usual activities in regards to friends and extracurricular activities⁴ <ul style="list-style-type: none"> – Provide AYA with a schedule that allows them to participate in activities and social events, discuss what aspects of treatment are flexible (so that the AYA may have some autonomy to schedule) and which aspects are nonnegotiable or “fixed”
Communication	<ul style="list-style-type: none"> • Discuss issues and concerns with parents/support person and HCPs^{9,11} <ul style="list-style-type: none"> – Attend meetings together with parents/support person and HCPs – Write down list of questions for HCP before the appointment and discuss questions and concerns with parents/support person beforehand 	<ul style="list-style-type: none"> • Encourage an increased level of open communication by prompting the AYA to ask questions, and write down questions between appointments^{2,4,5} • Provide more certainty and information around health status and need for medication by providing regular updates, regularly reviewing what AYA understands about their treatment progress and the purpose of different aspects of treatment, and the overall treatment goals³ <ul style="list-style-type: none"> – For > 18 year olds, ask AYA at outset who they would like their support person to be, and if/when they would like them involved in consultations, etc 	<ul style="list-style-type: none"> • Be wary of certain parental/support person behaviors (eg, controlling or disagreement between patient and parent/support person), which may cause nonadherence⁴ <ul style="list-style-type: none"> – Try to discuss any issues openly and calmly, whilst remaining nonjudgmental – Attempt to reach agreement about role delineation at diagnosis by negotiating some decisions that the AYA can decide for themselves, or allow more autonomy in deciding⁶ • Improve family/caregiver communication by providing AYA with opportunities to ask questions and clarify understanding⁴ <ul style="list-style-type: none"> – Parent/support person should ask questions on how best to support the AYA • Gain knowledge of the disease and treatment.^{6,3} <ul style="list-style-type: none"> – Talk with HCPs and clarify any misunderstandings
Educational	<ul style="list-style-type: none"> • Understand effects of treatment and medication⁷ <ul style="list-style-type: none"> – Ask questions and remain engaged during meetings with HCPs when discussing treatment and medications 	<ul style="list-style-type: none"> • Learn from other chronic conditions^{29,11} • Provide AYA with knowledge about the disease, treatment, future health outcomes, and confidence in recovery¹ <ul style="list-style-type: none"> – Discuss how AYA learns best (eg, verbal, written, images) and provide information consistent with their preference – Ask how much information the AYA would like to receive (eg, enough to understand treatment vs information on all options available) • Address any concerns from the AYA and offer alternative treatment options when appropriate⁵ • Be open-minded⁵ 	

(Continued)

Table 4 (Continued)

Context	Individual to implement strategy	
	Patient	Health care professionals
Psychological well-being and social support	<ul style="list-style-type: none"> Minimize psychological distress by attending support services when offered^{2,3} <ul style="list-style-type: none"> Be aware of potential for psychological distress and request help if necessary 	<p>Parent/support person</p> <ul style="list-style-type: none"> Acknowledge potential for psychological distress and normalize help-seeking with individuals (eg, friends) and HCPs (eg, social worker or psychologist) outside of the family unit⁴ <ul style="list-style-type: none"> Provide access to mental health support throughout treatment
Other	<ul style="list-style-type: none"> Use reminder systems (eg, alarms, pill-monitoring system)⁴ Collaborate with parent/support person about responsibilities in regards to medication administration⁵ 	<ul style="list-style-type: none"> Be aware of potential emotional distress in AYAs and encourage social support networks¹ <ul style="list-style-type: none"> Provide access to a range of support networks and services that may be of interest to certain AYAs and families throughout treatment Regularly assess for distress^{3,5} <ul style="list-style-type: none"> Involve psychologists/mental health workers throughout treatment Normalize the experience of distress and talk about the common experiences of AYAs with cancer going through similar treatment milestones <ul style="list-style-type: none"> For < 18 year olds, provide option to discuss issues without parent available Provide ongoing adherence-risk assessment¹ <ul style="list-style-type: none"> Regularly discuss adherence barriers, assess for nonadherence (via self-report, pill counts, etc) Decrease negative side effects^{2,4} <ul style="list-style-type: none"> Ensure AYA is comfortable and offer treatment options Identify predictive factors and risk of nonadherence at diagnosis to allow preemptive strategies^{2,5} <ul style="list-style-type: none"> Ask about potential barriers to nonadherence prior to treatment Assess adherence throughout treatment via the "Brief Medications Questionnaire"⁷⁷

Note: Strategies in italics have been recommended by the authors based on the findings/suggestions from the papers reviewed.

Abbreviations: AYA, adolescent and young adult; GP, general practitioner; HCP, health care professional.

the AYA with access to further psychosocial support services.^{4,62} By maintaining a positive attitude, being aware of their own psychological states, and accepting support when offered, AYAs can also reduce the risk of any psychological distress and counter any potential adherence issues.⁶⁵

Other strategies

Finally, other factors regarding the logistics and management of treatment, complex regimens, and treatment side effects were also highlighted as potentially impairing AYAs' capacity to adhere to treatment.^{4,5,19,63,64,66} Articles argued that HCPs need to tailor treatment plans to meet individual patient needs⁶⁶ and that parents and AYAs should assess what treatment routines work best and establish a treatment management schedule that both parties agree on.^{4,65}

Research question 2: what evidence exists to support the efficacy of adherence-promoting strategies among AYAs with cancer?

Description of intervention(s)

Only one intervention met criteria for inclusion in this systematic review. It assessed the effectiveness of a computer game intervention for improving treatment adherence and other behavioral outcomes for AYAs with cancer. The game addressed issues including common treatment-related adverse effects (eg, bacterial infection and nausea), and positive self-care behaviors (eg, taking oral chemotherapy and practicing good mouth care). The intervention translated behavioral objectives into the game, based on principles of the self-regulation model of health and illness, social cognitive theory, and learning theory.

Methodological quality of intervention(s)

Two investigators (EGR and CEW) evaluated the intervention: the Delphi score was 7 (from a possible range of 0–9), indicating moderate–high methodological quality (interrater reliability of the Delphi scores was 100%). However, Delphi items regarding concealment of treatment allocation and blinding of patients were not met.

Intervention outcomes

Results showed that although both groups of AYAs (those who participated in the game and those who did not) described themselves as highly treatment-adherent across time points, there was a significant 16% increase in antibiotic adherence for the intervention group. Oral chemotherapy adherence also remained significantly higher in the intervention group than

in the control group. Increases in cancer-related knowledge and cancer-specific self-efficacy were also reported, with these changes mediating improvements observed in AYA adherence to oral antibiotics. Less than 30% of AYAs fully adhered to the intervention requirements; however results still indicated significant benefits on medication adherence, despite suboptimal game play (less than 50% of the requested game time).

Discussion

Research in AYA adherence to cancer treatment is lacking. With recent research focusing on the barriers affecting adherence in AYAs with cancer, published recommendations have increasingly focused on adherence-promoting strategies for these patients, parents, and HCPs. The present review synthesized recommendations for improving cancer treatment adherence within AYA populations, and summarized the evidence for adherence-promoting interventions. While some recommendations were extracted from the existing literature, the review highlights the dearth of fully tested strategies available to improve adherence outcomes in AYAs affected by cancer, with the description of only one evidence-based intervention.

Several commonalities in barriers to adherence and strategies to improve nonadherence were found across the reviewed articles and were categorized according to five domains: developmental, communication, education, psychological well-being, and logistical/management difficulties. Key to the present findings was the acknowledgment of the AYA developmental stage and the unique challenges it presents. Strategies supporting AYAs' need for "normalcy" were most prevalent.⁶⁶ Open and nonjudgmental communication between HCPs, patient, and family was also strongly recommended to improve adherence. Providing the AYA and parent with information about the disease, treatment procedures, and medications is also important. HCPs also need to be aware of strategies to improve adherence in AYAs with chronic illness as a starting point for addressing adherence in AYAs with cancer. Minimizing psychological distress, providing support services, and improving social support networks may also lead to improved adherence. Other strategies, such as reducing treatment side effects, identifying patients at risk for adherence problems at diagnosis, and reminder systems for commonly cited forgetfulness, may also lead to improved adherence.

Highlighting the paucity of adherence interventions, this review identified only one study that systematically evaluated the role of an intervention on adherence behaviors.⁶⁸

The study showed a behaviorally targeted computer game could improve adherence to oral antibiotics and chemotherapy. Cancer-related self-efficacy and knowledge was also shown to mediate adherence. This intervention took an educational approach and focused on the AYA patient developing specific knowledge about their cancer, the role of treatment and common side effects, and the importance of adherence, with no involvement of the parents or HCPs in the intervention. Given the reviewed evidence indicating the importance of communication, support, and interactions with parents and HCPs, future interventions might build on this study. Combining the efficacious education strategies for AYAs used in this intervention, with other strategies (eg, communication-focused strategies) may achieve even stronger effect.

AYA adherence: implications for future interventions

Even with a growing evidence base documenting the challenges AYAs face with adherence to cancer treatment, few studies provide evidence-based advice surrounding strategies to improve adherence, and only one rigorously tested intervention has been described in the literature in the last 10 years. The results of this review also indicate that the majority of the recommended strategies in this area are interpersonal, focusing on communication between patients and HCPs, rather than focusing on strategies that AYAs can implement themselves. Future interventions work may draw on the broader chronic illness literature to implement more communications-focused strategies among AYAs with cancer.

Strategies recommended to improve adherence were for implementation by the patient, parent, or a HCP. Adherence, by definition, involves the patient actively working to maintain their health.²¹ In understanding nonadherence, the interaction between patients and others, and the patients cognitive-motivational processes both need to be taken into consideration.⁵ To better manage issues of nonadherence, research focusing on both intrapersonal strategies and the cognitive-motivational processes of AYAs is necessary. In addition to strategies for parents and HCPs, interventions for AYAs that address coping strategies, health beliefs, understanding and managing treatment, and motivation may improve adherence further.

Although AYA adherence to cancer treatment requires further exploration, it may be beneficial to build upon the literature among AYAs with other chronic illnesses and cancer in other age groups, where similar adherence challenges exist.^{4,11,63} Research has highlighted the similar psychosocial

challenges that face AYAs living with chronic illnesses across various conditions;^{37,69} existing adherence-promoting interventions for AYAs with other chronic illnesses may be used to develop targeted interventions for AYAs with cancer. Many strategies to improve adherence recommended for AYAs with cancer correspond to strategies for AYAs with a chronic illness, including balancing AYA life priorities and the treatment regimen, decreasing side effects,³⁰ and using reminders to reduce forgetfulness.³⁴

The World Health Organization has argued that increasing the effectiveness of adherence interventions may have a greater impact than improvement in specific medical treatments for chronic illnesses.⁷⁰ One review that assessed the effects of 182 interventions to enhance chronic illness patients' medication adherence, however, found effects were somewhat inconsistent from study to study.⁷¹ The authors concluded that the current methods for improving adherence in chronic illness are overly complex (reducing the ability to replicate studies) and not very effective.⁷¹ However, another review found adherence-promoting interventions were effective, although effects had limited longevity.⁷² Across chronic illnesses in children and adolescents, behavioral and multicomponent interventions appear to be most effective at improving adherence, with medium effect sizes.³¹ An education program for parents of childhood cancer patients also had a positive outcome on adherence, with a significant decrease in treatment refusal.⁷³ Future interventions should also consider being guided by the Adolescent Resilience Model, specifically developed as a model for understanding the process of resilience and quality of life outcomes in adolescents with cancer.^{74,75} Motivational Enhancement Therapy, which focuses on trying to understand an adolescent's view, rather than coercing them to change their behaviors, and may also be of use in improving adherence in children and adolescents.⁴¹

Limitations

To our knowledge, this was the first systematic review to synthesize the evidence base for adherence-promoting strategies among AYAs with cancer. This addresses a significant gap in the literature and outlines individual strategies researchers and clinicians may implement, highlighting important methodological "next steps" for interventions research in this field. The results of this review should be interpreted in reference to a number of limitations, however. Although a strength of this paper is that it broadly covers the spectrum of adherence issues in AYAs, this is also a limitation, in that specific subgroups of AYAs, such as those aged between 10 and 15 years old, were not commonly addressed

throughout this paper. This is also a limitation in the literature, due to minimal research differentiating subgroups within the AYA population.⁶⁰ As only articles that separately analyzed a subset of AYA participants were included, an additional limitation of our paper is the potential of having missed data from the broader adult oncology literature. As the aim of the study was to review strategies to improve current treatment adherence in AYAs, only articles published since 2005 were included due to improvements in cancer treatment. Although this methodological decision was to identify the strategies based on current medical treatment, it may have resulted in exclusion of appropriate, older, articles. Another limitation was the single intervention identified in the review. Although this reflects the paucity of literature in this field, the examination of only one intervention limited our ability to examine adherence strategies across studies and draw conclusions.

Conclusion and future directions

With the gap widening between potential and actual patient health, there is an increasing need to address malleable factors that improve AYA health outcomes, such as treatment adherence. This review found that effective treatment adherence is best promoted through a collaborative approach involving patients, parents, and HCPs. Emphasis was placed on improving communication, addressing developmental concerns for the AYA, and reducing patient distress. Based on the findings of this review, the authors recommend that more effort be devoted to developing interventions with specific strategies that aim to improve adherence in AYAs. Development of targeted interventions and adherence strategies could be adapted from those identified in research of chronic illness in AYAs. Future research should also consider the wide variability of experiences within the AYA stage, such as the role of parents as opposed to spouses or of attendance at school versus work, and the relationship between these individual variables on adherence. Regardless, the strategies adopted should be individually tailored for each patient, given their unique developmental needs and individual risk or resilience factors. By addressing individual barriers to care, more appropriate strategies can be implemented. Improving adherence in AYAs with cancer has the potential to ultimately improve health outcomes, reduce patient distress, provide more sound clinical trials results, and lead to a more cost-effective health care system.

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