Pediatr Blood Cancer 2015;62:S818–S828

Assessing Medication Adherence as a Standard of Care in Pediatric Oncology

Ahna L. H. Pai, PhD[1,2]* and Meghan E. McGrady, PhD[1,2]

Poor adherence to pediatric cancer treatment protocols may prevent children and adolescents from realizing the potential benefits of therapy. This paper presents the evidence for a standard of care for supporting medication adherence. Databases were reviewed for articles examining adherence and including children and/or adolescents with cancer. Fourteen articles (i.e., qualitative, quantitative, review, and randomized clinical trials) were evaluated for rigor. There is moderate-quality evidence to support a strong recommendation for adherence to be assessed routinely and monitored throughout the treatment. Integrating the proposed clinical procedures into standard clinical care may improve outcomes for children and adolescents with cancer. Pediatr Blood Cancer 2015;62:S818-S828. © 2015 Wiley Periodicals, Inc.

Key words: adherence; adolescent; cancer; child; oncology; self-management

INTRODUCTION

Children and adolescents are diagnosed with cancer and their families are often required to self-manage a complex treatment regimen including multiple medications administered at varied dosing schedules. In other chronic medical conditions, the complexity and prolonged duration characteristic of many pediatric oncology protocols are associated with high rates of nonadherence.[1] Children and adolescents with cancer, thus, may be at particular risk for medication nonadherence.

Consistent with findings from the World Health Organization citing medication nonadherence as one of the greatest threats to suboptimal health outcomes and treatment failure among patients with a chronic medical condition,[2] poor medication adherence among children and adolescents with cancer is associated with adverse health outcomes (i.e., increased risk of relapse).[3,4] While these findings suggest that anticipating, assessing, and promoting treatment adherence are critical components of comprehensive clinical care,[5] few empirically based guidelines exist for providers seeking to incorporate these procedures into their practice. To address this critical gap, the purpose of this paper was to review the literature examining medication adherence among pediatric cancer patients and develop evidence-based guidelines for supporting medication adherence in clinical care.

METHODS

This review was performed as a part of the collaborative Standards for Psychosocial Care of Children with Cancer and Their Families effort. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria were used to assess the quality of evidence in the identified studies.[6] For a full description of the methods used to develop each standard, the reader can refer to Wiener and colleagues in this special issue.[7]

Literature Search

PubMed, PsycINFO, Google Scholar, OVID, and EBSCO HOST (i.e., Academic Search Premier, CINAHL, ERIC, MasterFILE Premier, MEDLINE, Psychology and Behavioral Sciences Collection, TOPIC search) were searched for research articles published in English from March 1, 1995 to March 1, 2015. Search strategies included a combination of terms and MeSH headings related to adherence and neoplasm (see Supplementary Table I). Articles obtained via the database searches were supplemented with relevant articles included in the bibliographies of systematic reviews. The inclusion and exclusion criteria for the larger standards project were used with one exception. As predictors and correlates of nonadherence among young adults may have implications for patients under 18 years of age, articles with an age range extending into the young adult period (19–29 years of age) were not excluded as long as the majority of patients were under 18 years of age. Data detailing the study design, sample, and primary findings were extracted by the authors using an abstraction form developed for this study. A total of 14 articles met inclusion criteria and then used to develop clinical standards for supporting medication adherence (see Fig. 1).

Psychosocial Standard of Care

Adherence should be assessed routinely and monitored throughout the treatment.

External Reviews

The proposed standard and supporting evidence were then reviewed by external reviewers through the Second Think Tank for the Development of Psychosocial Care Standards for

Abbreviations: 6MP, 6-mercaptopurine

[1]Patient and Family Wellness Center, Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio [2]Division of Behavioral Medicine and Clinical Psychology, Center for Adherence and Self-Management, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Conflict of Interests: Nothing to declare.

*Correspondence to: Ahna L. H. Pai, Division of Behavioral Medicine and Clinical Psychology, Center for Adherence and Self-Management, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave., MLC 7039 Adherence Center, Cincinnati, OH 45229. E-mail: ahna.pai@cchmc.org

Received 1 July 2015; Accepted 10 September 2015

DOI 10.1002/pbc.25795
Published online in Wiley Online Library (wileyonlinelibrary.com).

Children with Cancer and Their Families. Minor editorial changes were recommended and incorporated.

RESULTS

There is an emerging body of evidence supporting routine adherence assessment, monitoring, and intervention into standard clinical care in pediatric oncology ($n = 14$ studies and reviews). A summary of evidence is presented in Table I, indicating a strong recommendation based on the quality of evidence and the GRADE system.[6] Study methodology varied across included studies, with four prospective studies, three cross-sectional studies, one qualitative, one randomized clinical trial, three systematic literature reviews, one narrative review, and one guideline developed by experts. Detailed results from the articles meeting inclusion criteria are presented in Supplementary Table II. Selected studies are reported below to highlight the importance of assessing medication adherence throughout the treatment trajectory.

DISCUSSION

Research findings from quantitative, qualitative, and review studies suggest that best practices for promoting medication adherence among children and adolescents with cancer will likely require a multifaceted approach. To achieve this goal, multidisciplinary teams are encouraged to integrate medication adherence-related assessments, education, anticipatory guidance, and documentation into standard clinical care. Each of these recommendations is outlined below.

Self- and parent-reported assessments of medication adherence should be obtained routinely using standardized language that assesses each specific medication for a specific period of time (e.g., In the last 7 days, how many times have you [has your child] missed a dose of [INSERT MEDICATION NAME] by a designated member of a multidisciplinary team?).[8] The high rates of medication nonadherence (19–53%),[4,9–15] especially among adolescents,[9,11,14] support the implementation of routine and standardized assessment of medication adherence. Assessing nonadherence may identify patients at risk for suboptimal treatment outcomes as nonadherence is associated with an increased risk of relapse and mortality. In pediatric acute lymphoblastic leukemia, 6-mercaptopurine (6MP) adherence rates lower than 95% are associated with a significantly increased risk of relapse.[4] Similarly, adolescents with cancer who are nonadherent to trimethoprim/sulfamethoxazole have lower survival rates than adherent adolescents.[11] As self- and parent-reported rates of nonadherence typically differ,[11] providers are encouraged to administer standardized measures of adherence (e.g., medication adherence measure) [8] to patients who are functioning at the developmental equivalent of 12 years of age or older.

Adherence behaviors occur in the context of daily life and an ongoing developmental course and are thus susceptible to changes in daily routines and family systems. Therefore, mediation adherence should be assessed and monitored routinely

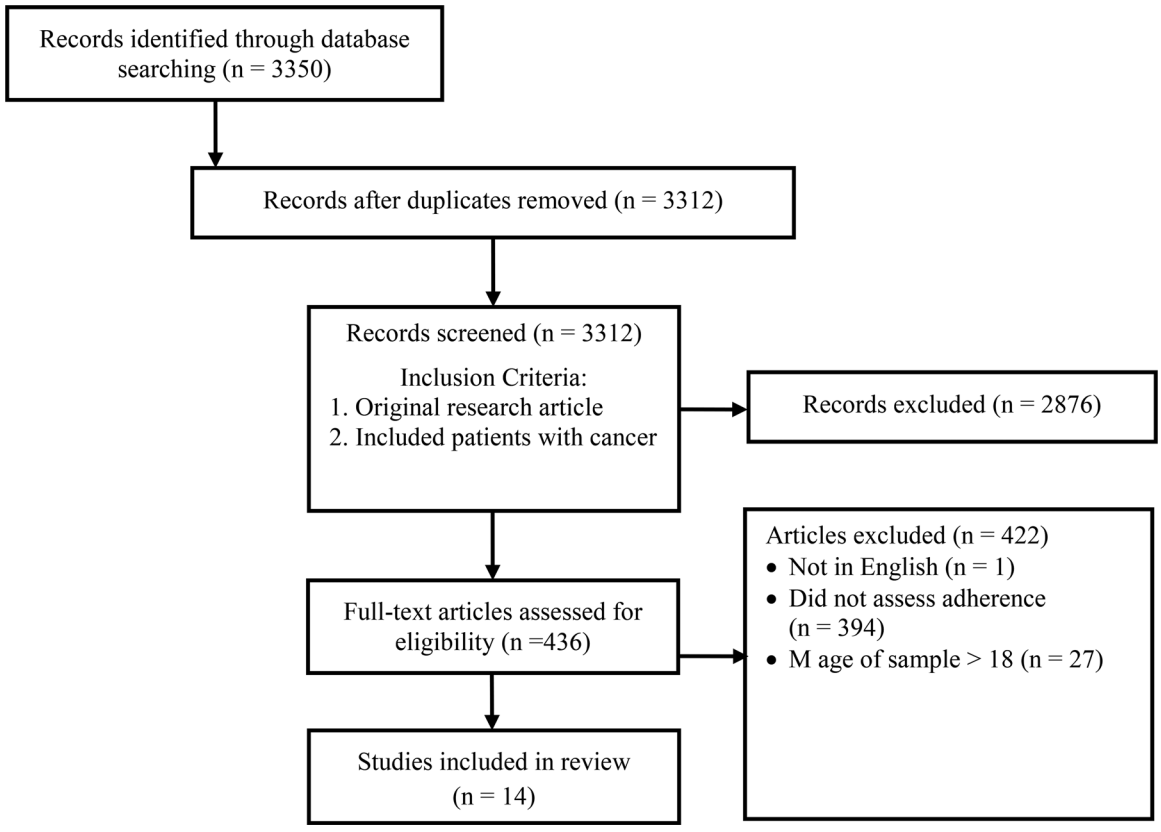

Fig. 1. PRISMA diagram of literature search and article selection.

TABLE I. Summary of Evidence—Adherence

Standard	Evidence summary[1]	Methodology[2]	Quality of evidence[3]	Strength of recommendation[4]
Adherence should be assessed routinely and monitored throughout the treatment.	Empirical research for children with cancer indicates prevalent and significant difficulties with adherence to medication regimens. *Evidence gaps*: Additional randomized clinical trials are needed to determine how to best promote adherence to medication regimens among youth with cancer.	Cross-sectional; longitudinal studies; systematic review articles show significant replication of findings; one randomized clinical trial.	Moderate-quality evidence. Evidence from RCTs with important limitations (methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies.	Strong recommendation, given the prevalence of adherence difficulties and relationship between poor adherence and poor disease outcomes. Desirable effects clearly outweigh undesirable effect or vice versa. Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an important effect on our confidence in methods to promote adherence.

[1]Based on the summary of evidence table for that standard; [2]types of studies: for example, randomized clinical trial (RCT), cross-sectional, longitudinal; consensus; systematic review articles; [3]quality of evidence: High, moderate, low, and very low (based on GRADE criteria); [4]strength of recommendation: strong or weak (based on GRADE quality criteria).

throughout the course of treatment. For children and adolescents with leukemia or lymphoma who are prescribed two doses of 6MP per day, adherence decreases as rapidly as 6% per day, with rates falling as much as 40% over time.[15] As children enter adolescence, the variability in the timing of medication administration often increases and nonadherence becomes even more prevalent.[14,15] To capture the anticipated changes in medication adherence over time, providers are encouraged to assess and monitor medication adherence at each follow-up outpatient clinic visit.

Developmentally appropriate education about the purpose, administration, and side effects of each medication and importance of medication adherence should be provided to youth with cancer and/or their family immediately prior to the transfer of self-management responsibilities to the patient and/or family and whenever there is a change in the medication regimen. Adolescents with cancer and their families cite disease knowledge and cancer care skills as the foundation for medication regimen self-management.[16] The critical role of education is further supported by results of a systematic review indicating that patients who receive interventions with an educational component demonstrate higher rates of medication adherence, based on blood tests for metabolites, than patients in control conditions.[17] Therefore, developmentally appropriate regimen education is a core component of adherence care.[18]

Anticipatory guidance including a discussion of common barriers to adherence, previous experiences taking medication, and strategies to improve medication adherence should be provided immediately prior to the transfer of self-management responsibilities to the patient and/or family and whenever there is a change in the medication regimen. Children and adolescents with cancer and their families describe multiple barriers to medication adherence that can be addressed with behavioral intervention including forgetting, being away from home when doses are due, difficulty in swallowing pills, taste of medications, and not feeling well.[19] Observational studies suggest that interventions targeting family support [19] and patient psychosocial functioning (i.e., depressive symptoms) [11] may improve adherence. As behavioral and multicomponent interventions providing such guidance are more effective in improving medication adherence than educational interventions alone [20] and have been shown to improve self-efficacy, cancer-related knowledge, and adherence,[21] clinicians are encouraged to consider partnering with relevant disciplines (i.e., psychology, social work, and child life) to develop procedures for assessing barriers and delivering behavioral interventions as appropriate.

Adherence-related assessments, education, and anticipatory guidance should be documented. Specific and distinct documentation outlining assessment results, the education provided, and interventions to promote medication adherence should occur every visit. This practice facilitates the tracking of patients' adherence, progress toward adherence-related goals, and the supports in place to optimize adherence.[22]

Barriers to integrating adherence care INTO practice. Despite the critical importance of supporting medication adherence, integrating the above recommendations into clinical care has been hindered by several logistical and systemic barriers. Most fundamentally, standardized approaches of obtaining self-reported adherence are rarely used.[2] However, assessing adherence is critical in setting the stage for open dialogue between patients and providers regarding the difficulties inherent to maintaining high levels of adherence.[23] Training providers about the complexity of adherence behaviors, how to assess adherence (e.g., In the last 7 days, how many times have you [has your child] missed a dose of 6MP?), and the importance of routinely assessing adherence can facilitate the delivery of appropriate adherence care.

Another barrier to adherence assessment in pediatric oncology is the concern that assessing adherence behaviors could compromise the patient–provider relationship. One method of addressing this concern is to incorporate standardized adherence assessments into each clinic visit. This practice reduces the stigma associated with discussing medication adherence. When providers acknowledge the common barriers to medication poor adherence and importance of an open dialogue from the onset of treatment, patients and families may be more likely to disclose adherence difficulties and as a result, receive the support and resources they need to address any concerns.

Finally, effective interventions to target barriers to medication nonadherence require predetermined systems for adherence care and well-coordinated care plans. Providers lacking a specific plan for identifying and intervening on the factors contributing to poor adherence may be less likely to assess adherence. To overcome this barrier, providers are encouraged to work with members of the multidisciplinary team (i.e., physicians, nurses, psychology, social workers, and child life specialists) to establish a plan for supporting adherence and intervening when there are adherence difficulties. Plans should include identifying the specific team members responsible for providing interventions for specific adherence barriers. For example, a team could have a nurse or care manager to address patient lack of medication regimen knowledge by providing education, a psychologist to address emotional or behavioral barriers to adherence using cognitive and or behavioral therapies, and child life therapists to address pill-swallowing difficulties contributing to poor adherence. This example is far from comprehensive as each institution will assign roles in adherence care based on local resources and in some cases may need to utilize community agencies to provide support for adherence behaviors.[24]

While this review demonstrates that the existing quality of evidence is moderate, we strongly recommend the integration of routine adherence monitoring into the standard of care in pediatric oncology given the consistencies in evidence between pediatric oncology and the larger pediatric literature to date.[18] Moreover, poor adherence is common and can have adverse and life-threatening outcomes for youth with cancer. Therefore, adherence to oral medication regimens should be assessed routinely and monitored throughout the treatment in youth with cancer. The integration of these recommendations into standard clinical care could optimize treatment adherence and ultimately the health outcomes of youth with cancer.

REFERENCES

1. DiMatteo MR. Patient adherence and medical treatment outcomes: A meta-analysis. Med Care 2002;40:794–811.
2. Sabaté E. Adherence to long-term therapies: Evidence for action. Geneva, Switzerland: World Health Organization; 2003.
3. Butow P, Palmer S, Pai ALH, Goodenough B, Luckett T, King M. Review of adherence-related issues in adolescents and young adults with cancer. J Clin Oncol 2010;28:4800–4809.
4. Bhatia S, Landier W, Shangguan M, Hageman L, Schaible AN, Carter AR, Hanby CL, Leisenring W, Yasui Y, Kornegay NM, Mascarenhas L, Ritchey AK, Casillas JN, Dickens DS, Meza J, Carroll WL, Relling MV, Wong FL. Nonadherence to oral mercaptopurine and risk of relapse in hispanic and non-hispanic white children with acute lymphoblastic leukemia: A report from the children's oncology group. J Clin Oncol 2012;30:2094–2101.
5. Drotar D. Psychological interventions in childhood chronic illnesses. Washington, DC: American Psychological Association; 2006.
6. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–394.
7. Wiener L, Kazak AE, Noll RB, Patenaude AF, Kupst MJ. Standards for psychosocial care of children with cancer and their families: An introduction to the special issue. Pediatr Blood Cancer 2015;62(Suppl 5):419–424.
8. Zelikovsky, N, Schast AP, Palmer J, Meyers KEC. Perceived barriers to adherence among adolescent renal transplant candidates. Pediatr Transplant 2008;3:300–308.
9. Partridge A, Avorn J, Wang PS, Winer EP. Adherence to therapy with oral antineoplastic agents. J Natl Cancer Inst 2002;94:652–661.
10. Spinetta JJ, Masera G, Eden T, Oppenheim D, Martins AG, van Dongen-Melman J, Jankovic M. Refusal, non-compliance, and abandonment of treatment in children and adolescents with cancer: A report of the SIOP Working Committee on Phychosocial Issues in Pediatric Oncology. Med Pediatr Oncolol 2002;38:114–117.
11. Kennard BD, Stewart SM, Olvera R, Bawdon RE, hAilin OA, Lewis CP, Winick NJ. Nonadherence in adolescent oncology patients: Preliminary data on psychological risk factors and relationships to outcome. J Clin Psychol Med Settings 2004;11:31–39.
12. Lau RCW, Matsui D, Greenberg M, Koren G. Electronic measurement of compliance with mercaptopurine in pediatric patients with acute lymphoblastic leukemia. Med Pediatr Oncol 1998;30:85–90.
13. Davies HA, Lilleyman JS. Compliance with oral chemotherapy in childhood lymphoblastic leukaemia. Cancer Treat Rev 1995;21:93–103.
14. Pai ALH, Drotar D, Kodish E. Correspondence between objective and subjective reports of adherence among adolescents with acute lymphoblastic leukemia. Child Health Care 2008;37:225–235.
15. Rohan JM, Drotar D, Alderfer M, Donewar CW, Ewing L, Katz ER, Muriel A. Electronic monitoring of medication adherence in early maintenance phase treatment for pediatric leukemia and lymphoma: Identifying patterns of nonadherence. J Pediatr Psychol 2015;40:75–84.
16. Stinson LN, Sung L, Gupta A, White ME, Jibb LA, Dettmer E, Baker N. Disease self-management needs of adolescents with cancer: Perspectives of adolescents with cancer and their parents and healthcare providers. J Cancer Surviv 2012;6:278–286.
17. Beale IL, Bradlyn AS, Kato PM. Psychoeducational interventions with pediatric cacner patients: Part II. Effects of information and skills training on health-related outcomes. J Child Fam Stud 2003;12:385–397.
18. Modi AC, Pai AL, Hommel KA, Hood KK, Cortina S, Hilliard ME, Guilfoyle SM, Gray WN, Drotar D. Pediatric self-management: A framework for research, practice, and policy. Pediatrics 2012;129:e473–e485.
19. Hullmann SE, Brumley LD, Schwartz LA. Medical and psychosocial associates of nonadherence in adolescents with cancer. J Pediatr Oncol Nurs 2015;32:103–113.
20. Kahana S, Drotar D, Frazier T. Meta-analysis of psychological interventions to promote adherence to treatment in pediatric chronic health conditions. J Pediatr Psychol 2008;33:590–611.
21. Kato PM, Cole SW, Bradlyn AS, Pollock BH. A video game improves behavioral outcomes in adolescents and young adults with cancer: A randomized trial. Pediatrics 2008;122:e305–e317.
22. Patenaude A, Pelletier W. Staff training, communication, and documentation. Pediatr Blood Cancer 2015;62(Suppl 5):870–894.
23. Drotar D. Physician behavior in the care of pediatric chronic illness: Association with health outcomes and treatment adherence. J Dev Behav Pediatr 2009;30:246–254.
24. Pai ALH, Drotar D. Medication adherence in pediatric oncology, In: Weiner LS, Pao M, Kazak AE, Kupst M, Patenaude AF, Holland JC, editors. Quick reference for pediatric oncology clinicians: The psychiatric and psychological dimensions of pediatric cancer symptom management. Charlottesville, VA: IPOS Press; 2014:157–163.

SUPPLEMENTARY INFORMATION

SUPPLEMENTAL TABLE I. Search Terms

01.	exp Intervention/
02.	((cogniti* or family* or behavior* or psychological*) adj5 (intervention* or treatment* or therap*)).ti, ab, hw
03.	1 or 2
04.	(child* or infant* or adolescent* or caregiver* or family or parent* or mother* or father* or care-giver or care-givers or families or youth).ti, ab, hw
05.	(compliance or adherence or self-care or self-management).ti, ab, hw
06.	(cancer* or childhood cancer or transplant* or sarcoma* or tumor* or tumour* or (amlor AND b cell) or carcinoma* or ewing* or gliom* or hematolo* or hematooncolog* or hemato oncolog or hepatoblastom* or hepatom* or Hodgkin* or leukaemi* or leukemi* or lymphoma* or malignan* or medulloblastom* or meningioma* or neoplasm* or nephroblastom* or neuroblastom* or non Hodgkin or oncolog* or osteosarcoma* or pnet* or retinoblastoma* or rhabdomyosarcoma* or sarcom* or t cell or teratom* or wilms*).ti, ab, hw
07.	((chronic* or longterm or long-term) adj5 (condition* or ill* or disease*)).ti, ab, hw
08.	6 or 7
09.	3 and 4 and 5 and 8
10.	limit 9 to English language
11.	limit 10 to yr = "1995 – Current"

SUPPLEMENTAL TABLE II. Summary of Included Articles

Quantitative Studies									
				Study Bias*					
Study	Design	Sample	Findings	Adequate Sample Size	Appropriate Blinding	Free of selective reporting	Analyses appropriate for question	Incomplete outcome data addressed	Level of Evidence**
Beale [1]	Systematic literature review Adherence to a variety of therapeutic regimens (i.e., oral chemotherapy) assessed via multiple methods (i.e., blood metabolites)	Children and young adults† with cancer††	• Evidence suggests the interventions with behavioral training can improve adherence among children and young adults	NA	NA	NA	NA	NA	5
Bhatia [2]	Prospective cohort Adherence to oral mercaptopurine assessed via electronic monitoring device (MEMS TrackCap)	Children (ages 1–19 years) with acute lymphoblastic leukemia (n = 327)	• 44% of patients had adherence rates <95% • Patients with an adherence rate of <95% were at an increased risk of relapse (reference: adherence ≥95; 94.9–90%: HR = 4.1, $p = .02$; 89.9–85%: HR = 4.0, $p = .04$; <85%: HR = 5.7, $p = .002$) • Cumulative risk of relapse was higher among Hispanics than non-Hispanic whites (HR = 2.6, $p = .02$) but was non-significant after adjusting for adherence and socioeconomic status (HR = 1.8, $p = .26$)	+	NA	+	+	+	4
Butow [3]	Systematic literature review Adherence to a variety of therapeutic regimens (i.e., oral chemotherapy) assessed via multiple methods (i.e., self-report, blood metabolites)	Adolescents and young adults (ages 12–24 years) with cancer††	• Rates of non-adherence range from 27–60% • The following variables are associated with non-adherence: ◦ Poorer prognosis ◦ Orally administered chemotherapy ◦ Longer treatment duration ◦ More complex treatment regimens ◦ Increased impact of treatment on daily living ◦ Perceived inadequacy of facilities and expertise ◦ Divergence from guidelines or best practice ◦ Perceived lack of involvement in decision-making ◦ Perceived negative attitudes of healthcare providers	NA	NA	NA	NA	NA	5

(*Continued*)

SUPPLEMENTAL TABLE II. (*Continued*)

Quantitative Studies									
				Study Bias*					
Study	Design	Sample	Findings	Adequate Sample Size	Appropriate Blinding	Free of selective reporting	Analyses appropriate for question	Incomplete outcome data addressed	Level of Evidence**
Davies [4]	Narrative literature review Adherence to oral mercaptopurine or prednisolone assessed via multiple methods (i.e., self-report, blood metabolites)	Children† with acute lymphoblastic leukemia	• Rates of non-adherence range from 10–42% • It is recommended that medication non-adherence be identified via ongoing assays of 6MP or measurement of urinary 17-ketogenic steroids	NA	NA	NA	NA	NA	5
Hullmann [5]	Cross-sectional Adherence to "all" cancer-related medications assessed via adolescent- and parent-report	Adolescents (ages 13–19 years) with cancer (leukemia, lymphoma, solid tumor, or brain tumor, n = 103)	• 57% of patients reported less than perfect adherence • 46% of parents reported that their child had less than perfect adherence • Patient-reported adherence was lower than but correlated with parent-reported adherence ($r = .33$, $p = .001$; patient M(SD) = 8.72(1.87); parent M(SD) = 9.08(1.47)) • The most common patient-reported barriers included: forgetting (n = 39, 38%), not being home (n = 12, 12%), difficulties swallowing pills (n = 11, 11%), and hating the taste (n = 10, 10%) • The most common parent-reported barriers included: forgetting (n = 23, 22%), not being home (n = 5, 5%), difficulties swallowing pills (n = 6, 6%), and hating the taste (n = 7, 7%) • Lower family social support ($p = .02$), lower parent overprotection ($p = .04$), and fewer future-oriented goals ($p = .02$) predicted non-perfect adherence	+	NA	+	+	+	4

(*Continued*)

SUPPLEMENTAL TABLE II. (*Continued*)

Quantitative Studies									
				Study Bias*					
Study	Design	Sample	Findings	Adequate Sample Size	Appropriate Blinding	Free of selective reporting	Analyses appropriate for question	Incomplete outcome data addressed	Level of Evidence**
Kato [6]	Randomized clinical trial Adherence to oral mercaptopurine assessed via blood metabolites of 6MMP and 6-TG	Adolescents and young adults (ages 13–29 years) with cancer (leukemia, lymphoma, brain tumor, osteosarcoma, ewing sarcoma, or "other", n = 375)	• Patients in the intervention group maintained significantly higher chemotherapy metabolite levels over time than patients in the control group ($p = .002$) • Patients in the intervention group demonstrated a significantly greater increase in cancer-related knowledge ($p = .035$) and self-efficacy ($p = .011$) than patients in the control group	+	+	+	+	+	2
Kennard [7]	Cross-sectional Adherence to trimethoprim/sulfamethoxazole assessed via direct serum levels and parent- and patient-report	Adolescents (ages 13–17 years) with cancer (acute lymphoblastic leukemia, Hodgkin's disease, non-Hodgkins lymphoma, bone sarcoma, ependymoma, primitive neuroectodermal tumor, or chronic myelogenous leukemia, n = 44)	• 27% of patients were non-adherent (serum sulfamethoxazole level < 2.0 mcg/ml) • Adolescent-reported adherence ($\rho = .34$, $p < .03$) but not parent-reported adherence ($\rho = .09$, $p < .57$) was correlated with adherence per serum assay • Greater patient depressive symptoms ($r = .39$, $p < .05$) and lower patient self-esteem ($r = -.30$, $p < .05$) were associated with higher levels of non-adherence per serum assay • Adherence per serum assay was associated with an increased likelihood of survival (OR = 4.62, $p = .04$)	–	NA	+	+	+	4
Lau [8]	Prospective cohort Adherence to oral mercaptopurine assessed via electronic monitoring device (MEMS TrackCap)	Children (ages 2–17 years) with acute lymphoblastic leukemia (n = 24)	• 33% of patients had adherence rates of <90% • 17% of patients had adherence rates <80% • While not statistically significant, adherence rates during the evening were higher than adherence rates in the morning ($p = .12$)	–	NA	+	+	+	4

(*Continued*)

Pediatr Blood Cancer DOI 10.1002/pbc

SUPPLEMENTAL TABLE II. (*Continued*)

Quantitative Studies									
				Study Bias*					
Study	Design	Sample	Findings	Adequate Sample Size	Appropriate Blinding	Free of selective reporting	Analyses appropriate for question	Incomplete outcome data addressed	Level of Evidence**
Lennard [9]	Cross-sectional Adherence to oral mercaptopurine assessed via blood cell concentration of thioguanine nucleotides and methylmercaptopurine metabolites	Children (ages 1–15 years) with lymphoblastic leukemia (n = 327)	• 32 patients (10%) demonstrated thioguanine nucleotide and methylmercaptopurine metabolite levels in the lower quartile ◦ Only one metabolite (thioguanine nucleotides or methylmercaptopurine metabolites) was detected in four patients ◦ Neither metabolite (thioguanine nucleotides and methylmercaptopurine metabolites) was detected in six patients • When these 32 patients were removed from the analysis, the correlation between thioguanine nucleotide levels and methylmercaptopurine metabolites was significant ($r = -0.26$, $z = 4.46$, $p < .001$)	+	NA	+	+	+	4
Pai [10]	Prospective cohort Adherence to oral mercaptopurine assessed via serum levels and patient-report	Adolescents (ages 12–19 years) with acute lymphoblastic leukemia (n = 51)	• 53% of patients had serum levels suggestive of non-adherence at ≥1 of 3 time points during the 4 month study period • On average, patients reported missing medication doses 1.6–2.2 days per week • Patient-reported adherence predicted future, but not concurrent adherence via serum level	+	NA	+	+	+	4
Partridge [11]	Systematic literature review Adherence to oral chemotherapy assessed via multiple methods (i.e., blood metabolites)	Children† with cancer (leukemia, lymphoma, Hodgkin's disease, "other malignancies")	• Rates of non-adherence range from 10–52% • Non-adherence is highest among adolescents • Non-adherence is clinically important, at least in patients with ALL • Parental involvement is hypothesized to impact non-adherence	NA	NA	NA	NA	NA	5

(*Continued*)

SUPPLEMENTAL TABLE II. (*Continued*)

Quantitative Studies									
				Study Bias*					
Study	Design	Sample	Findings	Adequate Sample Size	Appropriate Blinding	Free of selective reporting	Analyses appropriate for question	Incomplete outcome data addressed	Level of Evidence**
Rohan [12]	Prospective cohort Adherence to oral mercaptopurine assessed via electronic monitoring device (MEMS TrackCap)	Children (ages 7–19 years) with acute lymphoblastic leukemia or lymphoblastic leukemia (n = 139)	• 44% of patients had adherence rates < 95% • 76% of patients demonstrated adherence rates starting at 100% and decreasing .01% per day • 17% of patients demonstrated adherence rates at 100% and decreasing 3.3% per day to an average of 60% by the end of the first month • 7% of patients demonstrated adherence rates ≤ 40% and decreasing 5.6% per day	+	NA	+	+	+	4
Spinetta [13]	Guidelines Adherence not assessed	Children and adolescents† with cancer††	• Healthcare providers should engage in open, honest, and thorough communication with all patients and include them in decision-making • Factors predictive of non-adherence should be identified at diagnosis • Providers should intervene to prevent non-adherence when possible by providing support to families	NA	NA	NA	NA	NA	7
Stinson [14]	Qualitative Adherence not assessed	Adolescents (ages 12–18 years) with cancer (brain tumor, leukemia, lymphoma, or solid tumor, n = 29) and their parents (n = 30) and healthcare providers (n = 22)	• The self-management needs of adolescents with cancer include: ◦ "Disease knowledge and cancer care skills" ◦ "Knowledge and skills to support effective transition to adult healthcare" ◦ "Delivery of accessible healthcare services" ◦ "Supports for the adolescent with cancer"	+	+	+	+	+	6

NOTE. HR = hazard ratio; OR = odds ratio; *† = age range of included participants not reported; †† = cancer diagnosis of included participants not reported; + = study meets criteria; − = study does not meet criteria; NA = not applicable to study; **1 = systematic review or meta-analysis of controlled studies, or evidence-based clinical practice guidelines; 2 = individual experimental studies (randomized clinical trial); 3 = quasi-experimental studies (non-randomized); 4 = non-experimental studies (case-control, cohort); 5 = systematic reviews of descriptive or qualitative studies; 6 = individual descriptive or qualitative study; 7 = opinions of respected authorities and expert committees

REFERENCES-SUPPLEMENTARY TABLE II

1. Beale IL, Bradlyn AS, Kato PM. Psychoeducational interventions with pediatric cancer patients: part II. Effects of information and skills training on health-related outcomes. J Child Fam Stud 2003;12(4):385–397.
2. Bhatia S, Landier W, Shangguan M, Hageman L, Schaible AN, Carter AR, Hanby CL, Leisenring W, Yasui Y, Kornegay NM, Mascarenhas L, Ritchey AK, Casillas JN, Dickens DS, Meza J, Carroll WL, Relling MV, Wong FL. Nonadherence to oral mercaptopurine and risk of relapse in hispanic and non-hispanic white children with acute lymphoblastic leukemia: A report from the children's oncology group. J Clin Oncol 2012;30(17):2094–2101.
3. Butow P, Palmer S, Pai A, Goodenough B, Luckett T, King M. Review of adherence-related issues in adolescents and young adults with cancer. J Clin Oncol 2010;28(32):4800–4809.
4. Davies HA, Lilleyman JS. Compliance with oral chemotherapy in childhood lymphoblastic leukaemia. Cancer Treat Rev 1995;21(2):93–103.
5. Hullmann SE, Brumley LD, Schwartz LA. Medical and psychosocial associates of nonadherence in adolescents with cancer. J Pediatr Oncol Nus 2015;32(2):103–113.
6. Kato PM, Cole SW, Bradlyn AS, Pollock BH. A video game improves behavioral outcomes in adolescents and young adults with cancer: A randomized trial. Pediatrics 2008;122(2):e305-e317.
7. Kennard BD, Stewart SM, Olvera R, Bawdon RE, O hAilin A, Lewis CP, Winick NJ. Nonadherence in adolescent oncology patients: Preliminary data on psychological risk factors and relationships to outcome. J Clin Psychol in Med Settings 2004;11(1):31–39.
8. Lau RCW, Matsui D, Greenberg M, Koren G. Electronic measurement of compliance with mercaptopurine in pediatric patients with acute lymphoblastic leukemia. Med Pediatr Oncol 1998;30(2):85–90.
9. Lennard L, Welch J, Lilleyman JS. Intracellular metabolites of mercaptopurine in children with lymphoblastic leukaemia: A possible indicator of non-compliance? Br J Cancer 1995;72(4):1004–1006.
10. Pai ALH, Drotar D, Kodish E. Correspondence between objective and subjective reports of adherence among adolescents with acute lymphoblastic leukemia. Child Health Care 2008;37(3):225–235.
11. Partridge AH, Avorn J, Wang PS, Winer EP. Adherence to therapy with oral antineoplastic agents. J Natl Cancer Inst 2002;94(9):652–661.
12. Rohan JM, Drotar D, Alderfer M, Donewar CW, Ewing L, Katz ER, Muriel A. Electronic monitoring of medication adherence in early maintenance phase treatment for pediatric leukemia and lymphoma: Identifying patterns of nonadherence. J Pediatr Psychol 2015;40(1):75–84.
13. Spinetta JJ, Masera G, Eden T, Oppenheim D, Martins AG, van Dongen-Melman J, Jankovic M. Refusal, non-compliance, and abandonment of treatment in children and adolescents with cancer: A report of the SIOP Working Committee on Psychosocial Issues in Pediatric Oncology. Med Pediatr Oncol 2002;38(2):114–117.
14. Stinson LN, Sung L, Gupta A, White ME, Jibb LA, Dettmer E, Baker N. Disease self-management needs of adolescents with cancer: Perspectives of adolescents with cancer and their parents and healthcare providers. J Cancer Surviv 2012;6:278–286.