Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Samantha Stacks Date

Caregiver distress and medication errors in pediatric leukemia maintenance therapy

By

Samantha Stacks

Master of Public Health

Master of Science in Nursing

Department of Global Health

Cari Jo Clark, ScD, MPH

Committee Chair

Jordan Gilleland Marchak, PhD, ABPP

Committee Member

Caregiver distress and medication errors in pediatric leukemia maintenance therapy

By

Samantha Stacks

Bachelor of Science in Nursing

University of Toledo

2013

Thesis Committee Chair: Cari Jo Clark ScD, MPH

Thesis Committee Member: Jordan Gilleland Marchak, PhD, ABPP

An abstract of a thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health in Global Health
2018

Abstract

Caregiver distress and medication errors in pediatric leukemia maintenance therapy

By Samantha Stacks

Background and Objective: Caregivers of children with chronic illness are predisposed to increased levels of distress due to many factors including the complex nature of medication management. Our objective was to assess the relationship between caregiver distress and medication administration errors in the home in pediatric leukemia patients.

Methods: Using baseline data from participants in a prospective observational study on factors leading to medication error and injury in pediatric leukemia patients in maintenance therapy, a multivariate Poisson regression model was created to analyze the relationship between caregiver distress and the number of medication administration errors that occurred.

Results: In 34 patients, 64.71% committed at least one medication administration error and 17.65% of caregivers were categorized as distressed. Patients with more medication errors were prescribed more medications ($p=0.05$) and were younger in age ($p=0.07$). Caregiver distress was not found to be significantly associated with number of medication errors ($p=0.89$).

Conclusions: Medication administration errors in the home may be influenced by child age and number of medications prescribed. A larger sample size and further research is needed to determine the relationship between parental distress and medication error.

Caregiver distress and medication errors in pediatric leukemia maintenance therapy

By

Samantha Stacks

Bachelor of Science in Nursing

University of Toledo

2013

Thesis Committee Chair: Cari Jo Clark ScD, MPH

Thesis Committee Member: Jordan Gilleland Marchak, PhD, ABPP

A thesis submitted to the faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health in Global Health
2018

Acknowledgements

I would first like to thank my thesis advisor, Dr. Cari Jo Clark of the Department of Global Health of the Rollins School of Public Health at Emory University. Her expertise, contributions, support, and mentorship were vital to this thesis.

I would also like to thank my thesis committee member Dr. Jordan Gilleland Marchak of the Department of Pediatrics at the Emory University School of Medicine and Aflac Cancer & Blood Disorders Center of Children's Healthcare of Atlanta for her guidance, input, and insight as well as the opportunity to work as a research nurse on this study.

Finally, I would like to thank Dr. Kathleen Walsh of the James M. Anderson Center for Health Systems Excellence at Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, as well as all those who participated in Dr. Walsh's study on medication adherence in the *Human and System Factors Contributing to Pediatric Medication Error and Injury* study. Without them, this thesis would not have been possible.

Thank you,
Samantha Stacks

Table of Contents

Introduction

Despite great advances in pediatric cancer research and treatment, malignant neoplasms remain the 2nd leading cause of death in children 5 to 14 years old in the United States (The National Center for Health Statistics, 2015). Acute lymphoblastic leukemia (ALL) comprises up to 25% of all pediatric cancer diagnoses, making it the most common childhood malignancy (Ries et al., 2003). But with appropriate treatment, ALL now has an 85% five-year survival rate (Jemal et al., 2009).

Recommended therapy for ALL consists of three stages of treatment. First is 4 to 6 weeks of inpatient remission induction utilizing high intensity chemotherapy, followed by 6 to 9 months of outpatient consolidation with combination chemotherapy, concluded with 2 to 3 years of outpatient maintenance chemotherapy agents (Pui et al., 2015). This maintenance therapy course is designed to prevent relapse and allows patients to be treated out of the hospital. However, when medication administration is done outside a hospital setting, medication errors become more likely (Kathleen E. Walsh et al., 2009).

Medication errors are not only a problem for children with ALL, they can occur with any medication prescription. According to the Centers for Disease Control and Prevention, 23.5% of children have taken a medication within the last 30 days (National Center for Health, 2016). These mostly encompass antibiotic and other acute illness prescriptions, however 8 to 11% of persons under the age of 18 in the United States are living in chronic diseases states (National Center for Health, 2017). Patients with cancer as well as cystic fibrosis, asthma, and organ transplant recipients all have complex medication regimens needing to be managed by a

caregiver in the home. With the advancement of treatment modalities for complex pediatric diseases and the rising number of children treated in the outpatient setting, medication error root cause analysis and prevention is imperative (Cohen et al., 2011; Kathleen E. Walsh et al., 2009).

Medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use." (The National Coordinating Council for Medication Error Reporting and Prevention, 2018). When looking at outpatient chemotherapy medication errors in adults and children, pediatric patients were more than twice as likely to experience a medication error when compared to adults; 41% of these errors had potential for harm (Kathleen E. Walsh et al., 2009). To complicate things further, children are at increased risk of harm from medication errors due to the frequent mistakes that come with weight based dosing (Institute of Medicine Committee on Quality of Health Care in, 2000). These actors make childhood medication errors a particular area of concern.

In a meta-analysis on the level of care at which pediatric medication errors occur, prescribing accounted for 3-37% of errors, dispensing 5-58%, documenting 17-21%, and administering 72-75% (Miller, Robinson, Lubomski, Rinke, & Pronovost, 2007). Medication errors often happen in the inpatient setting of the hospital or pharmacy and there have been numerous studies, policies, and interventions implemented to monitor and prevent these types of errors (Landier et

al., 2012; Rinke et al., 2014; Kathleen E. Walsh et al., 2009; Kathleen E Walsh et al., 2011; Kathleen E. Walsh et al., 2013). However, while a child with ALL is in the maintenance therapy phase being treated in the outpatient setting, medication administration is most often in the hands of the patient's caregiver. In a study of outpatient organ transplant patients, it was found that the vast majority of medication errors were due to mistakes made by the patient, rather than by the doctor or pharmacy (Friedman et al., 2007). Furthermore, Walsh et al. (2013), found that 63% of outpatient medication errors for pediatric cancer patients happened during drug administration. These errors ranged from forgetting to fill prescriptions, to missing doses, or failing to adjust to new doses prescribed by the physician (Kathleen E. Walsh et al., 2013).

An administration medication error equates to decreased medication adherence. Adherence is defined by the World Health Organization as, "the extent to which a person's behavior - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (Sabaté, 2003). Medication adherence is a common problem for many disease states, but with leukemia in particular nonadherence is considered one of the greatest predictors of relapse (Landier et al., 2017). Up to 20% of ALL patients relapse, which greatly decreases their probability of long-term survival (Landier et al., 2012; Nguyen et al., 2008). During the maintenance phase, it is vital to dose chemotherapy targeting specific therapeutic blood levels; both under-dosing and overdosing can have adverse effects (Landier et al., 2012). Though there is a wide spectrum in severity (i.e. never taking any of the prescribed medications, only missing an occasional dose, inconsistent timing of medications, taking a medication with agents that affect its absorption taking extra doses, etc.), all nonadherence has the potential for harm (Landier et al., 2012; Partridge, Avorn, Wang, &

Winer, 2002). In fact, one study showed that medication adherence of less than 95% corresponded with a 240% increased risk of relapse in pediatric ALL (Bhatia et al., 2012). Currently, nonadherence with treatment regimens in pediatric ALL is estimated at 5-50% meaning many children are at risk for relapse (Bhatia et al., 2012; Landier et al., 2017; Landier et al., 2012; Partridge et al., 2002; Rinke et al., 2014).

Because medication adherence during maintenance therapy is so vital to the eradication of cancer in ALL, and the most common level at which outpatient medication errors occur is during medication administration, it is important to understand what makes administration in the home difficult and error prone. However, the reasons are numerous and likely multifaceted. Maintenance therapy for ALL is complex, with copious prescriptions of which the dosages and timing of administration frequently change (Landier et al., 2012). Much of the responsibility for care and medication administration is in the hands of the parent or guardian of the child, rather than the hands of a trained and skilled medical provider (Landier et al., 2012). The two-year course of treatment is a large expanse of time during which errors can occur, and adherence tends to wane over time (Rohan et al., 2015). The medication administration times may conflict with work or school schedules; a family vacation or variation in routine can lead to a medication being skipped (Landier et al., 2012). Cultural or personal beliefs about illness, taking medicines, or the severity of a cancer diagnosis could prevent drug administration (Armstrong, Duncan, Stokes, & Pereira, 2014). Coordinating between caregivers can lead to skipped or double doses of medication if there is unclear communication (Kathleen E. Walsh et al., 2013). A family's socioeconomic status may inhibit them from affording expensive medications or finding transportation to pick up prescriptions and or get to clinic appointments (Landier et al., 2012).

Children may refuse or be too sick to take medications (Kathleen E. Walsh et al., 2013). These types of medication errors have been reported by caregivers and reflect the many ways in which adherence can be compromised.

Figure 1. Parental Risk Factors for Medication Nonadherence

- Stress / Strain / Distress
- Depression
- Anxiety
- Single Parent
- Poor caregiver-child communication
- Difficult child behavior
- Family dysfunction

Studies on prevalence and ways in which pediatric ALL outpatient medication errors occur exist, but much less is known about risk factors for nonadherence (Landier et al., 2012; McPhillips et al., 2005; Kathleen E. Walsh et al., 2013). Bhatia et al.(2012) found that single mother households were at increased risk for ALL treatment nonadherence. In children with HIV, poor caregiver-child communication was associated with lower levels of adherence (Mellins, Brackis-Cott, Dolezal, & Abrams, 2004). Difficult child behavior was found to have a negative correlation in asthmatic children's medication adherence in a study by DeMore et al. (2005), but was not found to be contributory by Bender, Milgrom, Rand & Ackerson (1998). Bender et al. (1998) also found that increased family dysfunction was negatively associated with adherence.

Pediatric chronic illness takes a toll on caregivers. A study of children with cystic fibrosis found that caregivers were often overwhelmed and reported extreme stress when tasked with adhering to prescribed treatment plans (Ganong, Doty, & Gayer, 2003). In children with cancer, parents have reported a lower quality of life and increased parental distress, especially for those recently diagnosed or currently undergoing treatment (Cousino & Hazen, 2013; Hirst, 2005). In addition,

the risk of stress increases with the level of care required. More intense care treatment plans that result in more hours spent on care lead to increased stress levels, especially in female caregivers (Hirst, 2005). When compared to the general population, caregivers have increased levels of psychological illnesses; those who look after a spouse or partner, or mothers caring for their child are at highest risk (Hirst, 2005).

Some have suggested that parental stress may play a role in pediatric nonadherence and health outcomes (Barakat et al., 2007). In children on antiretroviral treatment for HIV infection (Mellins et al., 2004) and using dose metered inhalers for asthma (DeMore et al., 2005; Drotar & Bonner, 2009; Graves, Adams, & Portnoy, 2006), higher caregiver reported stress levels are significantly associated with lower levels of medication adherence. Elevated levels of caregiver strain resulted in decreased frequency of glucose monitoring and worsened glycemic control in children with diabetes (Carcone, Ellis, & Naar-King, 2012; Mackey et al., 2014).

Depression and anxiety, closely correlated to stress, may also influence adherence. Missed medication doses in adolescent transplant patients correlated with symptoms of anxiety, depression, and stress (McCormick King et al., 2014). In general, patients with chronic illnesses and depression are 2 to 3 times more likely to miss their prescribed medication doses (DiMatteo, Lepper, & Croghan, 2000; Grenard et al., 2011). Findings also suggest that caregivers with depression are more likely to report lower adherence levels; depressed mothers of asthmatic children were five times more likely to report that their child had trouble using their inhaler, and more than four times more likely to report two or more missed medication doses in the previous two weeks (Bartlett et al., 2004). If stress and depression are similar to other barriers that

decrease medication adherence, it is unlikely they will dissipate without targeted intervention (Lee et al., 2014). The contribution of caregiver stress and depression to medication error and adherence in pediatric leukemia outpatient treatment is a gap in the literature. This relationship should be further explored to identify potential risk factors for medication non-adherence.

To our knowledge, there has not been an examination of the association between caregiver distress and medication adherence in pediatric ALL patients to date. Thus, this analysis sought to answer the following question: What is the contribution of caregiver distress to medication error?

Methods

Population and recruitment

The data for this analysis came from the *Human and System Factors Contributing to Pediatric Medication Error & Injury* study (Project ID R01 HS024390), a multisite observational project designed to explore the factors that precipitate medication errors in pediatric leukemia patients (Cincinnati Children's Hospital Medical Center, 2017). The population for this study is comprised of patients receiving treatment from one of the study site's healthcare systems located in the Southeast United States. This healthcare system utilizes Children's Oncology Group Protocols, although minor variations in individual care plans in number of medications prescribed or frequency of prescription revisions due to provider preference may exist between patients (PDQ Pediatric Treatment Editorial Board, 2018).

Subjects were contacted by the site research coordinator during a clinic visit and consented at time of recruitment. Inclusion criteria for the study consisted of a diagnosis of leukemia or lymphoma, current oral chemotherapy use, with ongoing cancer treatment at an oncology clinic

of the healthcare system, patient under 18 years of age, and with provision of appropriate consent. Participants were excluded from the study if the caregiver was not fluent in English or Spanish, if the patient lived more than a one-hour drive from the study site, and/or if the patient's medical status or condition precluded study completion. For completing surveys and home visits families received graduated stipends totaling $90 over the course of the study.

Data collection

Medication errors, adherence levels, and other data were collected over a 6-month time period from consent. Data sources included chart review, surveys, interviews, direct medication administration observation, and Medication Event Monitoring System® (MEMS) electronic medication bottles.

Families received three home visits from registered nurses over the course of six months. The first home visits were completed within one month of obtaining consent; all three visits were finished within 6 months of consent and before maintenance therapy had concluded. Figure 2 illustrates the time periods at which data were collected.

Basic demographic information was obtained at consent. Initial home visits included an in depth interview exploring factors that make medication administration easier or more difficult for caregivers, an adherence interview, and medication review. Medication preparation and administration were observed. If errors were noted during the home visit, they were recorded on error report forms. During the initial home visit, a MEMS cap was given to each family. These are used to store one of the child's medicines and record a timestamp when its cap is removed to track medication adherence. During subsequent visits, medication review and adherence interviews were again completed, medication administration observed, and MEMS caps scanned.

Figure 2. Data Collection Timeline	Consent	Pre Visit 1	Visit 1	Pre Visit 2	Visit 2	Pre Visit 3	Visit 3	Post Visit 3
Basic Demographic Data	X							
Patient Reported Outcomes Measurement Information System Survey		X		X		X		
Medical Outcomes Study Social Support Survey		X		X		X		
Social Problem-Solving Inventory-Revised: Short		X		X		X		
Behavior Rating Inventory of Executive Function		X		X		X		
Strengths & Difficulties Questionnaire		X		X		X		
Perceived Collective Family Efficacy		X		X		X		
Home Visit Data Collection Form			X		X		X	
Drug Tracking Form			X		X		X	
Medication Adherence Measure			X		X		X	
Photographs of labels, measuring devices, guides, tools, etc.			X		X		X	
Medication Administration Observation			X		X		X	
Medication Log			X		X		X	
Hospitalization Log			X		X		X	
Adverse Event Log			X		X		X	
Error Report Form			X		X		X	
Environmental Scan Audio Recording			X					
Short Test of Functional Health Literacy in Adults			X					
MEMs Cap Scan					X		X	
Chart extraction								X

Corresponding with all visits, caregivers had a number of online surveys to complete including the Patient-Reported Outcomes Measurement Information System fatigue and sleep disturbance scale (PROMIS-29), which was available in English and Spanish. The Medical Outcomes Study Social Support Survey (MOS), Social Problem-Solving Inventory-Revised: Short (SPSI-R:S), Behavior Rating Inventory of Executive Function (BRIEF), Strengths and Difficulties Questionnaire (SDQ), and Perceived Collective Family Efficacy (PCFE) were also administered prior to visits. The analysis used data collected at baseline, prior to visit one, and at the first home visit. Variables pertinent to answering the research question posted in this thesis are subsequently described in detail.

Variables

Figure 3. Data Variables		
Predictor	**Outcome**	**Covariates**
Parental Distress • PROMIS-29 Subscales o Anxiety o Depression	Number of medication administration errors • Error Report Forms o Medication administration direct observation o Caregiver self-report	Demographics • Consent data • Child's age • Primary caregiver sex • Primary caregiver race • Number of primary caregivers Health Literacy score • s-TOFHLA Number of medications

Demographics

Demographic information including the child's age, child sex, number of primary caregivers, primary caregiver relationship to patient, caregiver race, and caregiver preferred language was collected at consent. Other demographics were generated from chart review prior to each visit. These comprised of current prescribed medications as well as the patient's current height, weight, allergies, all medical diagnoses, recent hospitalizations, and adverse events. Caregiver health literacy was measured with the Short Test of Functional Health Literacy in Adults (s-TOFHLA). Developed in 1999, the s-TOFHLA is a tool that tests both reading comprehension and numeracy, and is a widely used measure of health literacy (Baker, Williams, Parker, Gazmararian, & Nurss, 1999). The primary caregiver completed the s-TOFHLA test during the first home visit. Scores from the reading comprehension and numeracy components were summed to produce a final health literacy score on a 0-100 point scale. According to the scoring guidelines, those who scored between zero and fifty-three points have inadequate health literacy; those who score between fifty-four and sixty-six points have marginal health literacy; those who score above sixty-seven have adequate health literacy (Baker et al., 1999).

Distress

The PROMIS-29 v2.1 reliably assesses physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, and sleep disturbance using 5-point scales (Appendix A) (Hays, Spritzer, Schalet, & Cella, 2018). Questions from the PROMIS-29 were scored and interpreted according to the instrument's design (HealthMeasures, 2018). The PROMIS-29 measures each of the 7 domains with 4 questions using a Likert-type scale (1- Never; 2- Rarely; 3-Sometimes; 4- Often; 5- Always) (Hays et al., 2018). Total raw scores are calculated by summing the values of the response to each question. Raw data are then converted into standardized T-scores. The general United States population is represented with a T-score of 50 with a standard deviation of 10. Higher scores correlate to higher amounts of the concept measured (Appendix B) (HealthMeasures, 2018). For the purposes of this analysis, the subscales of anxiety and depression were used as a proxy for caregiver distress. Caregivers who scored greater than or equal to one standard deviation above the general population on either the depression or anxiety subscales were categorized as distressed. Cronbach's alpha statistic was calculated to determine internal reliability (0.94).

Medication errors

Medication errors were determined by comparing the medication prescription in the EMR to medication labels, parental report of medication administration, and observation of medication administration during a nurse home visit. The focus of this analysis was the total number of medication errors made in the home and/or by the caregiver (or child if self-administration). These medication administration errors were categorized as missed doses, wrong dose or frequency, using expired medication, inappropriate technique, or other uncategorized errors. All

potential errors were recorded on a standardized Error Report Form. Nurses were trained prior to the home visits to ensure inter-observer reliability. Medication administration errors used for analysis were extracted from the Error Report Forms.

Analysis

Demographic information was analyzed with descriptive statistics. Descriptive statistics were calculated to examine the distribution of study variables. Bivariate analyses were calculated for covariates and the exposure variable, distress, to assess potential relationships to the medication error outcome. Due to the small sample size, distress, the main exposure of interest and covariates with a p-value of ≤ 0.25 were retained in the model to ensure numeric stability (Hosmer & Lemeshow, 2005). Multivariate analysis was completed using Poisson regression. Predicted mean number of medication errors was calculated for variables retaining significance in the multivariate model. Statistical tests used the 10% level of significance due to the small population size.

Ethical considerations

Human and System Factors Contributing to Pediatric Medication Error & Injury was approved by Cincinnati Children's Hospital Medical Center (IRB #2015-1775). Risk of breach of confidentiality and research risks were mitigated by maintaining data confidentiality unless immediate dangers (hazardous medication error, child abuse or neglect, mental health emergencies) were identified by the home nurse. Data collected were stored in locked offices or on password protected computers. Subjects were assigned unique identifiers and keys were not

shared between sites. Statistical analyses were performed in aggregate. All study personnel completed human subjects' protection training modules.

Results

63 children with leukemia were consented for the study. At the time of this analysis, 39 patients had completed visit 1; 28 had completed visit 2; 23 had completed visit 3. Eleven patients dropped out. Nine patients were lost to follow up. This recruitment rate of 68% is comparable to other home visit studies (Hommel, Denson, & Baldassano, 2011; Kathleen E. Walsh et al., 2013). Reported reasons for study withdraw included not wanting someone visiting the home and having a busy schedule; participants were also removed if they had not responded to at least three phone calls and emails. The age between participants in the study and those who withdrew were similar, 7.17 and 7.68 years old respectively. 70% of those who withdrew were male as compared to 59% that participated in the study. 35% of those who withdrew from the study listed Spanish as their preferred language compared to only 6% of those who participated. Only those who had completed the PROMIS-29 survey were included in the final analysis. Of the 34 home visit 1s included in this analysis, 280 medications were reviewed and 46 medication errors were identified. Of these errors, 32 were determined to be medication administration errors (69.57%).

Table 1 presents the demographics of the study participants. Of the 34 study participants, all (100%) were diagnosed with leukemia (not tabulated). The mean child age was 7.17 years old. Most patients had only one primary caregiver (73.5%) and 85% of primary caregivers were the patient's mother. 94% of the primary caregivers spoke English. Primary caregivers' identified ethnicities were white (47.06%), black (31.18%), and other (11.76%). The average health literacy score on the s-TOFHLA was 91.93%. All primary caregivers who completed the s-

TOFHLA (82.45%) scored in the Adequate Health Literacy Range. Six (17.65%) primary caregivers did not complete the s-TOFHLA. Patients took an average of 9.4 prescribed medications (range 4-19). The average number of medication errors per caregiver was 0.94. Twenty-two caregivers made one or more medication errors (64.71%, n=22). Six of the caregivers reported levels of distress greater than one standard deviation above the US average anxiety and / or depression levels (17.65%).

Table 1. Demographic Data

	N	%	mean	SD
Child age			7.17	4.11
Child Sex				
Female	14	41.18		
Male	20	58.82		
Number of primary caregivers				
1	25	73.53		
2	9	26.47		
Primary caregiver relationship				
Mother	29	85.29		
Other	5	14.71		
Primary caregiver race				
White / Caucasian	16	47.06		
Other	18	52.94		
s-TOFHLA Health Literacy Scores				
Adequate Health Literacy	28	82.35	91.93	9.26
Missing	6	17.65		
Number of prescribed medications			8.24	3.12
Medication Administration Errors			0.94	0.92
0	12	35.29		
1	15	44.12		
2	4	11.76		
≥3	3	8.82		
Level of Distress				
No distress	28	82.35		
≥1 SD	6	17.65		

Table 2 presents the findings of the bivariate analyses. Distress, child sex, number of primary caregivers, primary caregiver relationships, primary caregiver race, and health literacy were not

shown to be independently significantly associated with medication errors. Child age was inversely associated with medication errors while number of medications was positively associated with medication errors. Neither child age nor number of medications correlated with distress in this analysis. These variables had p values <0.25 and were included with distress in the multivariate model.

Table 2. Poisson Model Bivariate Analysis

	Estimate	95% Confidence Interval	$\chi 2$	p value
Distress				
No distress	-0.07	(-0.96, 0.81)	0.03	0.87
≥1 SD	ref			
Child Age	-0.08	(-0.18, 0.02)	2.24	0.13
Child Sex				
Male	0.02	(-0.68, 0.73)	0.00	0.95
Female	ref			
Number of Primary Caregivers				
1	0.44	(-0.44, 1.33)	0.96	0.33
2	ref			
Primary Caregiver Relationship				
Mother	-0.29	(-1.18, 0.60)	0.41	0.52
Other	ref			
Primary Caregiver Race				
White / Caucasian	-0.26	(-0.97, 0.44)	0.53	0.47
Other	ref			
Health Literacy				
Adequate	0.07	(-0.81, 0.96)	0.03	0.87
Missing	ref			
Number of medications	0.09	(-0.02, 0.19)	2.65	0.10

In the multivariate analysis (Table 3), having a higher number of medications was associated with a higher log count of medication errors (p =0.05) while greater child age was associated with a lower log count of medication errors (p=0.07). The mean number of errors increased as the number of prescribed medication increased; a child with two medications had a mean of 0.45 medication errors while a child with 14 medications had a mean of 1.73 errors. The mean

number of medication errors decreased as age increased; the mean number or errors for a two-year-old child was 1.49, as compared to 0.34 in a 17-year-old child. Parental distress was not found to be significantly associated with an increased log count of medication administration errors (p=0.89). The Goodness of Fit Chi Squared Test was indicative of good fit evidenced by a p-value well in excess of 0.05 (p=0.55).

Table 3. Poisson Model Multivariate Analysis

	Estimate	95% Confidence Interval	$\chi 2$	p value
Distress				
No distress	0.07	(-0.82, 0.95)	0.02	0.89
≥1 SD	ref			
Child Age	-0.10	(-0.20, 0.01)	3.30	**0.07**
Number of medications	0.11	(0.00, 0.22)	3.98	**0.05**

Discussion

Nearly a quarter of children in the US have taken a medication in the last 30 days (National Center for Health, 2016) and with better treatment techniques more children with chronic illnesses are surviving and being treated at home with complex medication schedules (Cohen et al., 2011; Kathleen E. Walsh et al., 2009). Parents of children with chronic illness have been shown to have increased levels of psychological problems and stress when compared to the general population (Cousino & Hazen, 2013; Ganong et al., 2003; Hirst, 2005). With this in mind, it is important to consider the implications of unchecked parental distress on medication error and ultimately the health outcomes and survival of pediatric patients.

This analysis aimed to examine the relationship between caregiver stress and medication administration errors in pediatric ALL patients on maintenance therapy being treated at home. It was expected that there would be a positive correlation between increased levels of stress and

increased medication administration errors. However, this analysis showed no correlation between stress and number of medication administration errors. These results are not entirely surprising due to the small sample size of the study population and relatively small number of patient caregivers in the sample who reported clinically significant levels of distress. There is also limited literature available to truly contextualize and corroborate the findings. In studies on children with HIV, asthma, and diabetes, increased parent stress led to decreased medication adherence (Barakat et al., 2007; Carcone et al., 2012; DeMore et al., 2005; Drotar & Bonner, 2009; Graves et al., 2006; Mackey et al., 2014; Mellins et al., 2004). However, in a systematic review by Cousino and Hazen (2013), there was not a clear answer as to whether a correlation exists between parental stress and medication adherence in all children with chronic illness. In a small study of preschool-aged asthmatic patients, there was no correlation found between parenting stress and medication adherence (Armstrong et al., 2014). This could be because stress affects people differently, and while increased stress in one caregiver could lead to missed doses or incorrect administration of medication, in another it could be extremely motivating and create a state of hypervigilance when it comes to their child's medicines (Cousino & Hazen, 2013). Similarly, though anxiety and depression in this analysis were highly correlated with one another to create the exposure variable, distress, anxiety and depression separately can affect medication adherence differently. While depression is often shown to be detrimental to adherence (Bartlett et al., 2004; DiMatteo et al., 2000; Grenard et al., 2011; McCormick King et al., 2014), anxiety can sometimes have the opposite effect and lead to fewer missed (Belaiche et al., 2017; Wu, Aylward, & Steele, 2010). Due to the small number of participants who were distressed and the close correlation between the two variables, potential differences were unable to be parsed out in this analysis.

It could be argued that if there is any evidence that increased levels of distress negatively impacts medication adherence, it would be worthwhile to identify and create interventions for this phenomenon. In a literature review of behavioral interventions for medication adherence in pediatric patients with asthma, juvenile rheumatoid arthritis (JRA), and type 1 diabetes, behavioral interventions where shown to increase medication adherence (Lemanek, Kamps, & Chung, 2001). Psychosocial interventions have also been found to be effective in increased medication adherence in children with chronic conditions (Kahana, Drotar, & Frazier, 2008).

Knowing how parental distress affects medication adherence has a number of implications for childhood leukemia and other pediatric chronic conditions. Caregivers are already at increased risk of distress when compared to the general population and suffer negative health outcomes as a result (Cousino & Hazen, 2013; Ganong et al., 2003; Hirst, 2005). They also may unknowingly jeopardize their children's health in the form of medication administration errors. If this barrier to medication adherence is similar to others studied, it has been shown that it will likely continue to hinder adherence for the duration of the child's illness (Lee et al., 2014). Parents at high risk of distress should be identified early in treatment plans and routinely monitored. Early identification of those at risk could help to inform and allocate resources towards targeted behavioral or psychosocial interventions and other forms of support. If in place, behavioral or psychosocial interventions could be done to reduce the number of medication errors during maintenance therapy and ultimately lead to improved outcomes for children. This information would be valuable to parents, clinicians, case managers, as well as insurance agencies. Protocols

for early and routine identification of parental distress should be part of a pediatric leukemia treatment plan.

Child age was found to be associated with medication error in the analysis. This fits in with the findings of a meta analysis by Belaiche et al. (2017) on medication adherence in kidney transplantation. Younger children may be more likely to refuse medications and rely completely on caregivers to track and administer medicine, while older children with more autonomy may take on more responsibility in following the treatment plan. Interestingly, adolescents have been shown to be less adherent with chemotherapy agents in previous research (Kondryn, Edmondson, Hill, & Eden, 2011; Landier et al., 2012; Partridge et al., 2002). Caregivers of younger patients may need additional strategies and tools to bolster medication management for their children. The number of medications prescribed also was found to be associated with medication errors. This could be due to the fact that there is simply more opportunity for error with more medicines or that children with more medications may have comorbidities or associated symptoms that complicate their treatment plans (Belaiche et al., 2017; Landier et al., 2012). Reducing unnecessary prescriptions or extra caregiver education on medication administration may be necessary interventions for patients with higher nonadherence.

Limitations

There are several limitations that need to be addressed. First and foremost, due to the small sample size, the relatively small number of patient caregivers reporting clinically significant levels of distress, and the number of covariates that needed to be included, the analysis was severely underpowered to be able to detect the relationship between distress and medication error. The study was not complete at the time of this writing and so not all study participants' data could be used. Study site demographics may not be representative and treatment protocols

vary. Study enrollment may not have been representative of the population of pediatric ALL patients, as eligible caregivers may not have wanted someone visiting their home or recording their medication errors. The study is unlikely to have caught all errors: errors that occurred when nurses were not present, errors not disclosed by parents, or the limitations of the interview questions could have led to errors being missed or under-reported. Observation of medication preparation and administration may not have been reflective of normal behavior due to the Hawthorne effect. Though all nurses were trained prior to the study, individual differences in how errors are perceived and characterized may have influenced reporting. The medication errors at the time of this analysis were unable to be validated by two-physician review, as is study protocol. Additionally, there may be other confounding factors that influence medication adherence undetected by the study.

Conclusions

Medication administration errors are common during the maintenance phase of acute lymphoblastic leukemia, a disease in which risk of relapse is directly related to medication adherence. Younger child age and higher numbers of prescribed medications were shown to have an association with increased medication error in this analysis. Caregivers of children with chronic disease are more likely to be distressed and although not illustrated here, the literature has shown this could have an effect on medication adherence. Further research is needed to determine the influence of parental distress on medication error. In any regard, strategies to identify and support caregivers in distress should be part of a comprehensive acute lymphoblastic leukemia treatment plan.

Appendices

Appendix A: PROMIS-29 Survey

PROMIS–29 Profile v2.1

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS–29 Profile v2.1

	Fatigue **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9	How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities? .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS–29 Profile v2.1

Pain Intensity

In the past 7 days…

Global07	How would you rate your pain on average?.....	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

Appendix B: PROMIS-29 Scoring Tables

Adult v1.0 - Physical Function 4a

Short Form Conversion Table

Raw Summed Score	T-score	SE*
4	22.9	3.9
5	26.9	2.7
6	29.1	2.4
7	30.7	2.2
8	32.1	2.2
9	33.3	2.1
10	34.4	2.1
11	35.6	2.1
12	36.7	2.1
13	37.9	2.2
14	39.1	2.2
15	40.4	2.2
16	41.8	2.3
17	43.4	2.4
18	45.3	2.6
19	48.0	3.1
20	56.9	6.7

*SE = Standard Error on T-score metric

Adult v1.0 - Anxiety 4a

Short Form Conversion Table

Raw Summed Score	T-score	SE*
4	40.3	6.1
5	48.0	3.6
6	51.2	3.1
7	53.7	2.8
8	55.8	2.7
9	57.7	2.6
10	59.5	2.6
11	61.4	2.6
12	63.4	2.6
13	65.3	2.7
14	67.3	2.7
15	69.3	2.7
16	71.2	2.7
17	73.3	2.7
18	75.4	2.7
19	77.9	2.9
20	81.6	3.7

*SE = Standard Error on T-score metric

Adult v1.0 - Depression 4a

Short Form Conversion Table

Raw Summed Score	T-score	SE*
4	41.0	6.2
5	49.0	3.2
6	51.8	2.7
7	53.9	2.4
8	55.7	2.3
9	57.3	2.3
10	58.9	2.3
11	60.5	2.3
12	62.2	2.3
13	63.9	2.3
14	65.7	2.3
15	67.5	2.3
16	69.4	2.3
17	71.2	2.4
18	73.3	2.4
19	75.7	2.6
20	79.4	3.6

*SE = Standard Error on T-score metric

Adult v1.0 - Fatigue 4a

Short Form Conversion Table

Raw Summed Score	T-score	SE*
4	33.7	4.9
5	39.7	3.1
6	43.1	2.7
7	46.0	2.6
8	48.6	2.5
9	51.0	2.5
10	53.1	2.4
11	55.1	2.4
12	57.0	2.3
13	58.8	2.3
14	60.7	2.3
15	62.7	2.4
16	64.6	2.4
17	66.7	2.4
18	69.0	2.5
19	71.6	2.7
20	75.8	3.9

*SE = Standard Error on T-score metric

Adult v1.0 - Sleep Disturbance 4a

Short Form Conversion Table

Raw Summed Score	T-score	SE*
4	32.0	5.2
5	37.5	4.0
6	41.1	3.7
7	43.8	3.5
8	46.2	3.5
9	48.4	3.4
10	50.5	3.4
11	52.4	3.4
12	54.3	3.4
13	56.1	3.4
14	57.9	3.3
15	59.8	3.3
16	61.7	3.3
17	63.8	3.4
18	66.0	3.4
19	68.8	3.7
20	73.3	4.6

*SE = Standard Error on T-score metric

Adult v1.0 – Ability to Participate in Social Roles and Activities 4a

Short Form Conversion Table

Raw Summed Score	T-score	SE*
4	27.5	4.1
5	31.8	2.5
6	34.0	2.3
7	35.7	2.2
8	37.3	2.1
9	38.8	2.2
10	40.5	2.3
11	42.3	2.3
12	44.2	2.3
13	46.2	2.3
14	48.1	2.2
15	50.0	2.2
16	51.9	2.2
17	53.7	2.3
18	55.8	2.3
19	58.3	2.7
20	64.2	5.1

*SE = Standard Error on T-score metric

References

Armstrong, M. L., Duncan, C. L., Stokes, J. O., & Pereira, D. (2014). Association of caregiver health beliefs and parenting stress with medication adherence in preschoolers with asthma. *J Asthma, 51*(4), 366-372. doi:10.3109/02770903.2013.876431

Baker, D. W., Williams, M. V., Parker, R. M., Gazmararian, J. A., & Nurss, J. (1999). Development of a brief test to measure functional health literacy. *Patient Educ Couns, 38*(1), 33-42.

Barakat, L. P., Patterson, C. A., Weinberger, B. S., Simon, K., Gonzalez, E. R., & Dampier, C. (2007). A prospective study of the role of coping and family functioning in health outcomes for adolescents with sickle cell disease. *J Pediatr Hematol Oncol, 29*(11), 752-760. doi:10.1097/MPH.0b013e318157fdac

Bartlett, S. J., Krishnan, J. A., Riekert, K. A., Butz, A. M., Malveaux, F. J., & Rand, C. S. (2004). Maternal depressive symptoms and adherence to therapy in inner-city children with asthma. *Pediatrics, 113*(2), 229-237.

Belaiche, S., Décaudin, B., Dharancy, S., Noel, C., Odou, P., & Hazzan, M. (2017). Factors relevant to medication non-adherence in kidney transplant: a systematic review. *International Journal of Clinical Pharmacy, 39*(3), 582-593. doi:10.1007/s11096-017-0436-4

Bender, B., Milgrom, H., Rand, C., & Ackerson, L. (1998). Psychological Factors Associated with Medication Nonadherence in Asthmatic Children. *Journal of Asthma, 35*(4), 347-353. doi:10.3109/02770909809075667

Bhatia, S., Landier, W., Shangguan, M., Hageman, L., Schaible, A. N., Carter, A. R., . . . Wong, F. L. (2012). 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. *Journal of Clinical Oncology, 30*(17), 2094-2101. doi:10.1200/JCO.2011.38.9924

Carcone, A. I., Ellis, D. A., & Naar-King, S. (2012). Linking Caregiver Strain to Diabetes Illness Management and Health Outcomes in a Sample of Adolescents in Chronically Poor Metabolic Control. *J Dev Behav Pediatr, 33*(4), 343-351. doi:10.1097/DBP.0b013e31824eaac8

Cincinnati Children's Hospital Medical Center. (2017). Grants, Contracts, and Industry Agreements. *James M Anderson Center for Health Systems Excellence.* Retrieved from https://www.cincinnatichildrens.org/research/divisions/j/anderson-center/grants

Cohen, E., Kuo, D. Z., Agrawal, R., Berry, J. G., Bhagat, S. K. M., Simon, T. D., & Srivastava, R. (2011). Children With Medical Complexity: An Emerging Population for Clinical and Research Initiatives. *Pediatrics, 127*(3), 529-538. doi:10.1542/peds.2010-0910

Cousino, M. K., & Hazen, R. A. (2013). Parenting stress among caregivers of children with chronic illness: a systematic review. *J Pediatr Psychol, 38*(8), 809-828. doi:10.1093/jpepsy/jst049

DeMore, M., Adams, C., Wilson, N., & Hogan, M. B. (2005). Parenting Stress, Difficult Child Behavior, and Use of Routines in Relation to Adherence in Pediatric Asthma. *Children's Health Care, 34*(4), 245-259. doi:10.1207/s15326888chc3404_1

DiMatteo, M. R., Lepper, H. S., & Croghan, T. W. (2000). Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med, 160*(14), 2101-2107.

Drotar, D., & Bonner, M. S. (2009). Influences on adherence to pediatric asthma treatment: a review of correlates and predictors. *J Dev Behav Pediatr, 30*(6), 574-582. doi:10.1097/DBP.0b013e3181c3c3bb

Friedman, A. L., Geoghegan, S. R., Sowers, N. M., Kulkarni, S., Formica, R. N., & Jr. (2007). Medication errors in the outpatient setting: Classification and root cause analysis. *Archives of Surgery, 142*(3), 278-283. doi:10.1001/archsurg.142.3.278

Ganong, L., Doty, M. E., & Gayer, D. (2003). Mothers in postdivorce families caring for a child with cystic fibrosis. *Journal of Pediatric Nursing, 18*(5), 332-343. doi:https://doi.org/10.1016/S0882-5963(03)00105-2

Graves, M. M., Adams, C. D., & Portnoy, J. M. (2006). Adherence in young children with asthma. *Curr Opin Allergy Clin Immunol, 6*(2), 124-127. doi:10.1097/01.all.0000216856.85021.11

Grenard, J. L., Munjas, B. A., Adams, J. L., Suttorp, M., Maglione, M., McGlynn, E. A., & Gellad, W. F. (2011). Depression and Medication Adherence in the Treatment of Chronic Diseases in the United States: A Meta-Analysis. *J Gen Intern Med, 26*(10), 1175-1182. doi:10.1007/s11606-011-1704-y

Hays, R. D., Spritzer, K. L., Schalet, B. D., & Cella, D. (2018). PROMIS®-29 v2.0 profile physical and mental health summary scores. *Quality of Life Research, 27*(7), 1885-1891. doi:10.1007/s11136-018-1842-3

HealthMeasures. (2018). PROMIS Adult Profile Instruments: PROMIS® Scoring Manuals.

Hirst, M. (2005). Carer distress: a prospective, population-based study. *Soc Sci Med, 61*(3), 697-708. doi:10.1016/j.socscimed.2005.01.001

Hommel, K. A., Denson, L. A., & Baldassano, R. N. (2011). Oral medication adherence and disease severity in pediatric inflammatory bowel disease. *Eur J Gastroenterol Hepatol, 23*(3), 250-254. doi:10.1097/MEG.0b013e328344019c

Hosmer, D. W., & Lemeshow, S. (2005). Model-Building Strategies and Methods for Logistic Regression. In W. A. Shewhart, S. S. Wilks, D. W. Hosmer, & S. Lemeshow (Eds.), *Applied Logistic Regression*.

Institute of Medicine Committee on Quality of Health Care in, A. (2000). In L. T. Kohn, J. M. Corrigan, & M. S. Donaldson (Eds.), *To Err is Human: Building a Safer Health System*. Washington (DC): National Academies Press (US)

Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., & Thun, M. J. (2009). Cancer Statistics, 2009. *CA Cancer J Clin, 59*(4), 225-249. doi:10.3322/caac.20006

Kahana, S., Drotar, D., & Frazier, T. (2008). Meta-Analysis of Psychological Interventions to Promote Adherence to Treatment in Pediatric Chronic Health Conditions. *Journal of Pediatric Psychology, 33*(6), 590-611. doi:10.1093/jpepsy/jsm128

Kondryn, H. J., Edmondson, C. L., Hill, J., & Eden, T. O. (2011). Treatment non-adherence in teenage and young adult patients with cancer. *Lancet Oncol, 12*(1), 100-108. doi:10.1016/s1470-2045(10)70069-3

Landier, W., Chen, Y., Hageman, L., Kim, H., Bostrom, B. C., Casillas, J. N., . . . Bhatia, S. (2017). Comparison of self-report and electronic monitoring of 6MP intake in childhood ALL: a Children's Oncology Group study. *Blood, 129*(14), 1919-1926. doi:10.1182/blood-2016-07-726893

Landier, W., Hughes, C. B., Calvillo, E. R., Anderson, N. L. R., Briseño-Toomey, D., Dominguez, L., . . . Bhatia, S. (2012). "Doing Our Part" (Taking Responsibility): A Grounded Theory of the Process of Adherence to Oral Chemotherapy in Children and Adolescents with Acute Lymphoblastic Leukemia. *J Pediatr Oncol Nurs, 28*(4), 203-223. doi:10.1177/1043454211409582

Lee, J. L., Eaton, C., Gutiérrez-Colina, A. M., Devine, K., Simons, L. E., Mee, L., & Blount, R. L. (2014). Longitudinal Stability of Specific Barriers to Medication Adherence. *Journal of Pediatric Psychology, 39*(7), 667-676. doi:10.1093/jpepsy/jsu026

Lemanek, K. L., Kamps, J., & Chung, N. B. (2001). Empirically supported treatments in pediatric psychology: regimen adherence. *J Pediatr Psychol, 26*(5), 253-275.

Mackey, E. R., Struemph, K., Powell, P. W., Chen, R., Streisand, R., & Holmes, C. S. (2014). Maternal depressive symptoms and disease care status in youth with type 1 diabetes. *Health Psychol, 33*(8), 783-791. doi:10.1037/hea0000066

McCormick King, M. L., Mee, L. L., Gutiérrez-Colina, A. M., Eaton, C. K., Lee, J. L., & Blount, R. L. (2014). Emotional Functioning, Barriers, and Medication Adherence in Pediatric Transplant Recipients. *Journal of Pediatric Psychology, 39*(3), 283-293. doi:10.1093/jpepsy/jst074

McPhillips, H. A., Stille, C. J., Smith, D., Hecht, J., Pearson, J., Stull, J., . . . Davis, R. L. (2005). Potential medication dosing errors in outpatient pediatrics. *J Pediatr, 147*(6), 761-767. doi:10.1016/j.jpeds.2005.07.043

Mellins, C. A., Brackis-Cott, E., Dolezal, C., & Abrams, E. J. (2004). The role of psychosocial and family factors in adherence to antiretroviral treatment in human immunodeficiency virus-infected children. *Pediatr Infect Dis J, 23*(11), 1035-1041.

Miller, M. R., Robinson, K. A., Lubomski, L. H., Rinke, M. L., & Pronovost, P. J. (2007). Medication errors in paediatric care: a systematic review of epidemiology and an evaluation of evidence supporting reduction strategy recommendations. *Quality & Safety in Health Care, 16*(2), 116-126. doi:10.1136/qshc.2006.019950

National Center for Health, S. (2016). Health, United States *Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities*. Hyattsville (MD): National Center for Health Statistics (US).

National Center for Health, S. (2017). Health, United States *Health, United States, 2016: With Chartbook on Long-term Trends in Health*. Hyattsville (MD): National Center for Health Statistics (US).

Nguyen, K., Devidas, M., Cheng, S. C., La, M., Raetz, E. A., Carroll, W. L., . . . Loh, M. L. (2008). Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. *Leukemia, 22*, 2142. doi:10.1038/leu.2008.251

Partridge, A. H., Avorn, J., Wang, P. S., & Winer, E. P. (2002). Adherence to therapy with oral antineoplastic agents. *J Natl Cancer Inst, 94*(9), 652-661.

PDQ Pediatric Treatment Editorial Board. (2018). *Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®): Health Professional Version*. National Cancer Institute, Bethesda (MD) Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK65763/.

Pui, C.-H., Yang, J. J., Hunger, S. P., Pieters, R., Schrappe, M., Biondi, A., . . . Mullighan, C. G. (2015). Childhood Acute Lymphoblastic Leukemia: Progress Through Collaboration. *Journal of Clinical Oncology, 33*(27), 2938-2948. doi:10.1200/jco.2014.59.1636

Ries, L., D, H., M., K., A., M., B.A., M., E.J., F., . . . BK, E. (2003). *SEER Cancer Statistics Review, 1975-2003*. Retrieved from Bethesda, MD: http://seer.cancer.gov/csr/1975_2003/,

Rinke, M. L., Bundy, D. G., Velasquez, C. A., Rao, S., Zerhouni, Y., Lobner, K., . . . Miller, M. R. (2014). Interventions to reduce pediatric medication errors: a systematic review. *Pediatrics, 134*(2), 338-360. doi:10.1542/peds.2013-3531

Rohan, J. M., Drotar, D., Alderfer, M., Donewar, C. W., Ewing, L., Katz, E. R., & Muriel, A. (2015). Electronic monitoring of medication adherence in early maintenance phase treatment for pediatric leukemia and lymphoma: identifying patterns of nonadherence. *J Pediatr Psychol, 40*(1), 75-84. doi:10.1093/jpepsy/jst093

Sabaté, E., & World Health Organization,. (2003). *Adherence to long-term therapies: Evidence for action*. Retrieved from

The National Center for Health Statistics. (2015). *Deaths: Leading Causes for 2015*. Retrieved from https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_05_tables.pdf

The National Coordinating Council for Medication Error Reporting and Prevention. (2018). About Medication Errors.

Walsh, K. E., Dodd, K. S., Seetharaman, K., Roblin, D. W., Herrinton, L. J., Worley, A. V., . . . Gurwitz, J. H. (2009). Medication Errors Among Adults and Children With Cancer in the Outpatient Setting. *Journal of Clinical Oncology, 27*(6), 891-896. doi:10.1200/jco.2008.18.6072

Walsh, K. E., Mazor, K. M., Stille, C. J., Torres, I., Wagner, J. L., Moretti, J., . . . Gurwitz, J. H. (2011). Medication errors in the homes of children with chronic conditions. *Arch Dis Child, 96*(6), 581-586. doi:10.1136/adc.2010.204479

Walsh, K. E., Roblin, D. W., Weingart, S. N., Houlahan, K. E., Degar, B., Billett, A., . . . Mazor, K. M. (2013). Medication Errors in the Home: A Multisite Study of Children With Cancer. *Pediatrics, 131*(5), e1405-e1414. doi:10.1542/peds.2012-2434

Wu, Y. P., Aylward, B. S., & Steele, R. G. (2010). Associations Between Internalizing Symptoms and Trajectories of Medication Adherence Among Pediatric Renal and Liver Transplant Recipients. *Journal of Pediatric Psychology, 35*(9), 1016-1027. doi:10.1093/jpepsy/jsq014