

Allocation of Treatment Responsibility and Adherence to Hydroxyurea Among Adolescents With Sickle Cell Disease

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Abstract

Objective Adolescents with sickle cell disease (SCD) are at increased risk for complications. Hydroxyurea is a medication that can ameliorate risk but to benefit, adolescents must adhere to treatment. Study aims were to describe how adolescents and their caregivers decided who was responsible for treatment tasks, to describe adolescents' and caregivers' responsibility for these tasks, and to examine if hydroxyurea adherence was associated with younger adolescent age, less discrepancy between adolescents' and caregivers' reports of adolescent responsibility, and higher caregiver involvement. **Methods** Twenty-nine dyads completed treatment responsibility measures. A combination of laboratory and electronic prescription data were used to determine hydroxyurea adherence and electronic medical records were used to determine appointment adherence. **Results** Few dyads agreed or planned how to complete treatment tasks. Adolescents shared responsibility with caregivers for medication-taking tasks. Adolescents perceived caregivers and caregivers perceived adolescents were overall responsible for treatment, especially for appointment tasks. Half of adolescents were adherent to hydroxyurea and half were adherent to appointments but medication adherence was not associated with age, discrepancy between adolescents' and caregivers' responses, or caregiver involvement. **Conclusions** Despite frequent hydroxyurea and appointment nonadherence, few adolescents and caregivers plan how to manage adolescents' SCD treatment or perceive they are overall responsible. Future studies are needed to determine the factors that influence these perceptions and if increasing adolescent and caregiver treatment planning improves adherence and clinical outcomes.

Key words: sickle cell disease; adherence; parent-adolescent communication.

Introduction

Sickle cell disease (SCD) is the most common inherited blood disorder, affecting approximately 100,000 individuals in the United States (Center for Disease

Control, 2017). SCD is characterized by multiple morbidities, including frequent debilitating pain episodes and an increased risk of stroke, and only 50% of patients survive into their fifth decade (Platt et al., 1991,

1994; Ohene-Frempong et al., 1998). Hydroxyurea is one of the few preventative and disease modifying therapies available for SCD. With multiple studies showing that this once daily medication increases patients' quality of life (Ballas et al., 2006) and reduces hospitalizations (Wang et al., 2011), treatment costs (Wang et al., 2013), and mortality (Lobo et al., 2013; Voskaridou et al., 2010), hydroxyurea use among children with SCD is increasing (Creary et al., 2016). While hydroxyurea is considered safe and effective, patients receiving hydroxyurea require close monitoring due to the potential for low blood cell counts (e.g., neutropenia and thrombocytopenia) that can necessitate temporary interruption and/or hydroxyurea dose de-escalation. Therefore, it is recommended that patients prescribed hydroxyurea receive frequent (every 2–3 months) laboratory and clinical monitoring. The purpose of this monitoring is to: (1) monitor patients for low blood cell counts and interrupt and/or decrease their hydroxyurea dose if it occurs, (2) escalate patients' dose as it is tolerated to a maximum of 35 mg/kg/day or 2,000 mg daily, and (3) address medication nonadherence if it occurs (Yawn et al., 2014). Despite these clear benefits and recommendations, it is estimated that 50% of children, and maybe as high as 75% of adolescents (Badawy et al., 2017), are nonadherent to hydroxyurea (Thornburg, Calatroni, Telen, & Kemper, 2010) and hydroxyurea nonadherence is associated with worse health outcomes (Candrilli et al., 2011). Furthermore, appointment nonadherence is associated with hydroxyurea nonadherence and worse health outcomes, but only 75% of children on hydroxyurea and only 61% of all children with SCD attend the recommended frequency of appointments annually (Creary et al., 2017; Modi, Crosby, Hines, Drotar, & Mitchell, 2008).

Understanding how adolescents with SCD on hydroxyurea and their caregivers distribute responsibility for hydroxyurea (e.g., taking the pills, obtaining refills, obtaining laboratory testing, and scheduling and attending clinic appointments) could inform interventions to improve medication adherence and SCD-management. First, adolescence is a vulnerable developmental period. Adolescents are seeking independence and autonomy and caregivers are providing less supervision, especially around medical tasks (Modi, Crosby, Hines, Drotar, & Mitchell, 2008) and it is notable that this is the period when hydroxyurea adherence rates are likely to be lowest (Badawy et al., 2017). Second, with increasing hydroxyurea use among younger children with SCD, it is expected that the number of adolescents who will eventually experience hydroxyurea adherence challenges will continue to increase. Third, because adolescents with SCD experience more complications and have a threefold higher risk of mortality compared to younger children (Quinn, Rogers, McCavit, & Buchanan,

2010), ineffective disease management and medication nonadherence consequences become even more impactful compared to when these children were younger. Finally, prior studies suggest that adolescents frequently lack disease self-management skills (Speller-Brown et al., 2015), such as knowing their insurance information or being able to communicate with medical providers, that are necessary to be able to be adherent to treatment. While caregivers of children with SCD report being actively involved in their children's SCD management (Oliver-Carpenter, Barach, Crosby, Valenzuela, & Mitchell, 2011), it is unclear how responsibility for medical treatment tasks are allocated, shared, and transitioned as these children transition to adulthood.

Pai and colleagues developed the allocation of treatment responsibility (ATR) measure to quantify adolescent and caregiver responsibility for the tasks required for chronic medical treatment of adolescents with renal transplants (Pai et al., 2010). The ATR was adapted and subsequently validated among adolescents with epilepsy and their caregivers (Ryan, Arnett, Pai, & Modi, 2014). Combined, these studies suggest that adolescent age, discrepancy between adolescents' and caregivers' reports of adolescent responsibility, and caregiver involvement are associated with medication adherence. Because of the unique features of SCD and of hydroxyurea treatment, the ATR results from these other chronically ill adolescent populations, however, may not apply to adolescents with SCD. For example, most adolescents with SCD in the United States are diagnosed shortly after birth (Center for Disease Control, 2017) and this early diagnosis necessitates early parental dependence that could significantly impact how responsibility for treatment is distributed as children with SCD become adolescents. Thus, the objectives of our study were to describe how adolescents with SCD who are prescribed hydroxyurea and their primary caregivers decided who was responsible for treatment tasks and to describe adolescents' and caregivers' responsibility for these tasks. We hypothesized that adolescents and caregivers would report that they planned how they would complete treatment tasks and that adolescents would have some responsibilities for treatment but caregivers would be overall responsible. We also hypothesized that hydroxyurea adherence would correlate with younger adolescent age, less discrepancy between adolescents' and caregivers' reports of adolescent responsibility, and increased caregiver involvement.

Methods

Participants, Study Design, and Recruitment

We performed an Institutional Review Board approved prospective study of adolescents with SCD and

their primary caregiver at two large, Midwestern pediatric SCD centers, Nationwide Children's Hospital (NCH) and Cincinnati Children's Hospital Medical Center (CCHMC). At NCH, English speaking patients with SCD (all genotypes) were eligible if they were 12–20 years old, initiated hydroxyurea at least 6 months before study entry, and had an English speaking primary caregiver who also agreed to complete the study surveys. At CCHMC, the baseline ATR results of a subset of adolescents with SCD and their caregivers who enrolled on a separate chronic disease self-management intervention study (ClinicalTrials.gov Identifier: NCT02851615) were included in these analyses if the adolescents and caregivers were English-speaking, and if the adolescent had SCD (Hemoglobin SS, SB⁰Thalassemia, SB⁺Thalassemia, or SC genotypes), was 13–21 years of age, and initiated hydroxyurea at least 6 months before study entry. Prospective adolescent participants were identified using electronic medical records (EMR) and mailed a recruitment letter before a trained clinical research coordinator approached them and their caregivers at a clinical or research appointment for study participation. Additional EMR review was completed on enrolled adolescent participants to collect baseline demographic data (including age, gender, SCD genotype, and race), laboratory results [mean corpuscular volume (MCV) and hemoglobin F%], duration of hydroxyurea therapy, and electronic hydroxyurea prescribing information. Caregiver participants self-reported their demographic information (age, relationship to the adolescent, and educational status). Adolescents and caregivers completed surveys electronically and independently and received a small monetary gift card for their time.

Allocation of Treatment Responsibility

The original validated ATR measure (Pai et al., 2010) was slightly modified to be specific to adolescents with SCD and their caregivers by removing items that were not expected of patients with SCD (e.g., bringing medications to every clinic visit). It contained 33 total items (see Supplementary) and was scored using the same methods used in previous studies (Holbein, Smith, Peugh, & Modi, 2019; Pai et al., 2010; Ryan, Arnett, Pai, & Modi, 2014).

Responsibility Planning

The introductory items asked participants to identify the people that assist the adolescent with their health and if the participant had experienced any recent major life changes. To describe how responsibility for treatment was decided, participants were asked to select from the following list: (a) My caregiver/child decided, (b) I decided, (c) We planned who was responsible for each task, (d) We just do it, (e) My

caregiver does/I do it all so there were no decisions to be made, and (f) Other (open response).

Adolescents' and Caregivers' Responsibilities

The remaining 15 ATR items were divided into four different categories of tasks: oral medications, clinic appointments, laboratory tests, and other tasks. Responses to these items were used to determine adolescents' and caregivers' responsibility for treatment. For each of the 15 items, participants first rated their responsibility for each item (e.g., calling the pharmacy when a refill is needed, planning how to get to clinic appointments, remembering to have labs done, making sure medication is available if not at home) on a 4-point Likert scale (1 = none of the time to 4 = all of the time) and then reported their adolescents'/caregivers' responsibility for these same 15 items.

Responsibility scores were calculated for each participant and were used to determine who the participant perceived was most responsible for each category of tasks and overall. Responsibility scores were calculated using the following formula: participants' report of their adolescents'/caregivers' responsibility minus their report of their own responsibility. Responsibility scores could range from –45 to +45 overall, from –18 to +18 for the oral medication tasks, from –12 to +12 for the clinic appointment tasks, from –9 to +9 for the laboratory tasks, and from –6 to +6 for the other tasks. A negative responsibility score indicated the participant perceived the other member of the dyad was more responsible, a positive responsibility score indicated the participant perceived he/she was more responsible, and a responsibility score of 0 indicated shared responsibility between both members of the dyad. For example, if an adolescent reported being responsible “none of the time” for each of the 15 items (score of 15) and his/her caregiver was responsible “all of the time” for each of the 15 items (score of 60), the adolescent's overall responsibility score would be –45 and this would indicate that the adolescent perceived his/her caregiver was solely responsible for all treatment tasks.

Caregiver Involvement

Similar to previous studies (Holbein, Smith, Peugh, & Modi, 2019), caregiver involvement was defined by the adolescents' reported overall responsibility score and larger negative scores indicated higher caregiver involvement.

Discrepancy Scores

Adolescent discrepancy scores were used to identify if there was inconsistency between adolescents' and caregivers' reports of adolescents' responsibility for treatment. Adolescent discrepancy scores were calculated using the following formula: the absolute value

of the adolescents' report of their overall responsibility minus the caregivers' report of their adolescents' overall responsibility. These scores could range from 0 to 45 and larger adolescent discrepancy scores indicated more inconsistency between adolescents' and caregivers' reports of the adolescents' overall responsibility for treatment.

Internal Reliability

Cronbach alpha was used to assess the internal reliability of participants' ATR responses and was 0.86 and 0.67 for adolescent participants and caregiver participants, respectively.

Electronic Prescriptions

In the year prior to study enrollment, clinicians at both study centers exclusively used electronic hydroxyurea prescribing and these prescriptions were available for review within the EMR. Using the same method used in a previous hydroxyurea adherence study (Creary et al., 2017), all hydroxyurea prescriptions written in the EMR during the 210 days prior to the adolescent completing the ATR survey were reviewed. If these prescriptions indicated that, if filled, the participant would have had access to hydroxyurea on at least 80% of the 180 days immediately prior to survey completion, the participant was considered to have evidence of adherence by prescription data. The 80% threshold was used since this was the level of adherence that was achieved by most participants during the phase III, randomized, clinical trial of hydroxyurea in children (Thornburg et al., 2010).

Mean Corpuscular Volume and Fetal Hemoglobin

The hydroxyurea clinical trial in children with Hemoglobin SS SCD showed that hydroxyurea exposure increases erythrocyte MCV and fetal hemoglobin (HbF) concentrations (Wang et al., 2011). Hydroxyurea monitoring guidelines that were similar to published recommendations (Yawn et al., 2014) were used at both study centers in the year prior to study enrollment. These guidelines recommended that clinicians routinely measure patients' MCV and HbF if they were prescribed hydroxyurea. Participants' MCV and HbF from their routine hematology appointments that occurred within 90 days of survey completion were abstracted from their EMR. If participants had multiple visits during this time, only data from their most recent visit was used. Similar to a previous study, adolescents with an MCV ≥ 102 fl were considered to have evidence of adherence by MCV and participants with an HbF $\geq 16\%$ were considered to have evidence of adherence by HbF (Badawy et al., 2017).

Hydroxyurea Adherence

There are no validated hydroxyurea adherence measures, but electronic prescriptions, MCV, and HbF have been used to classify patients as adherent or non-adherent in previous studies (Badawy et al., 2017; Creary et al., 2017). Since multimethod adherence measurement is recommended to reduce the inherent limitations that exist with all adherence measures (Quittner, Modi, Lemanek, Levers-Landis, & Rapoff, 2008), adolescents were considered adherent to hydroxyurea if they had evidence of adherence by at least two of the following: electronic prescriptions, MCV, and HbF. Only adolescent participants with Hemoglobin SS ($n = 26$) SCD were included in the hydroxyurea adherence analyses because previous studies suggest that hydroxyurea may not have the same impact on MCV or HbF in patients with Hemoglobin SC or SB⁺Thalassemia SCD (Luchtman-Jones et al., 2016; Zimmerman et al., 2004).

Clinic Appointment Adherence

Hydroxyurea monitoring guidelines at both centers in the year prior to enrollment recommended that adolescents on hydroxyurea attend at least four in-person hematology appointments annually, unless their provider documented a less frequent appointment plan. Adolescent participants' EMR for the year prior to enrollment was reviewed to determine the number of these appointments each participant attended and participants who attended at least four appointments (or the minimum number of appointments required and documented by their provider) were categorized as adherent to their appointments.

Statistical Analysis

Descriptive statistics were used to describe how adolescents and caregivers decided on responsibility for treatment, adolescents' and caregivers' responsibilities for tasks, adolescent discrepancy scores, and hydroxyurea and appointment adherence. Because of our small sample size and non-normally distributed data, Wilcoxon rank sum tests were used to determine if hydroxyurea adherence and appointment adherence were associated with younger adolescent age, less discrepancy between adolescents' and caregivers' reports of adolescent responsibility, and higher caregiver involvement. Effect sizes for these analyses were calculated using Cohen's method. Finally, Wilcoxon rank sum tests were also used to compare ATR results between the two study sites to explore if location of care was associated with participants' perceived responsibility.

Results

Participants

NCH recruited 18 adolescents (78.3%) of those eligible for the survey study and CCHMC recruited 66

Table I. Participant Demographics and Adolescent Patient Demographics

	NCH participants	CCHMC participants	Total participants	Patients ^b at NCH	Patients ^b at CCHMC
Adolescent Patients on hydroxyurea (<i>n</i>)	18	11	29	34	33
Median age, in years (range)	14 (12–18)	16 (13–17)	14 (12–18)	14 (12–18)	16 (12–18)
Female (<i>n</i>)	11	7	18	17	17
SCD genotype (<i>n</i>)					
SS or Sβ ⁰	17	9	26	31	29
Other (e.g., SC, Sβ ⁺)	1	2	3	3	4
Race					
Black/African American	13	11	24	–	–
African	4	0	4		
Black/African American and African	1	0	1		
Caregivers (<i>n</i>)	18	11	29	–	–
Median age, in years (range)	40 (34–68)	40 (33–55) ^a	40 (33–68) ^a	–	–
Relationship to adolescent					
Mother	12	7	19	–	–
Father	5	4	9		
Grandmother	1	0	1		
Education level (<i>n</i>)					
<12th grade	3	1	4		
High school diploma or General Education Diploma	4	1	5		
Some college, no degree	4	3	7	–	–
Associates degree	2	0	2		
Bachelor's degree	3	3	6		
Graduate or professional degree	2	3	5		

^aTwo caregivers did not report their age.

^bPrescribed hydroxyurea and were 12–18 years of age at the beginning of enrollment.

adolescents (85.7%) of those eligible for the larger self-management intervention study. Of these, survey responses from 29 adolescents and their caregivers (18 dyads from NCH and 11 dyads from CCHMC) were included in these analyses. All of the enrolled adolescents initiated hydroxyurea at least 1 year prior to survey completion and were between 12 and 18 years. Participants' demographics and the demographics of the patients with SCD that were 12–18 years and were prescribed hydroxyurea at the start of enrollment at each center are shown in Table I.

Responsibility Planning

Most adolescents (96.6%) and caregivers (86.2%) listed at least one, and up to four additional people that assist the adolescent with medications and treatments. The adolescent's mother was the most frequently listed person by both adolescents and caregivers. Many dyads (65.5%) did not agree how the treatment responsibility was decided. Of the dyads who agreed, only two dyads reported that they planned who was responsible for each task. The most common response for adolescents (31%) and caregivers (51.7%) when asked how responsibility was decided was "We just do it."

Caregiver and Adolescent Responsibility

Twenty-five (86.2%) of the adolescents had negative overall responsibility scores, indicating that most

adolescents perceived their caregivers were more responsible for treatment (Table II). Fifteen (51.7%) caregivers had a negative overall responsibility score, indicating that approximately half of caregivers perceived their adolescents were more responsible overall for treatment. Adolescents' and caregivers' perceived shared responsibility for taking oral medication and other tasks, but neither adolescents nor caregivers perceived personal responsibility for clinic appointment tasks (Table II). Comparing study sites, adolescents' responsibility scores were not significantly different (median –15 at NCH vs. –6 at CCHMC, $p = .22$), but caregivers' responsibility scores were significantly different (median –23 at NCH vs. 17 at CCHMC, $p < .0001$).

Hydroxyurea Adherence

Electronic prescriptions showed that participants had access to hydroxyurea for a median of 75.8% (range 0–100%) of the 180 days prior to survey completion (Table III). The median MCV and HbF for the 26 participants with Hemoglobin SS SCD was 93.7 fl (range 76.8–123.8) and 21% (range 3.2–40%), respectively. Fourteen (53.8%) of the adolescents with Hemoglobin SS were classified as adherent to hydroxyurea because they had evidence of hydroxyurea adherence by two or three of the following: electronic prescriptions, MCV, and HbF.

Table II. *Participants' Responsibility Scores*

Responsibility score	Adolescent report		Caregiver report	
	Median score	Range	Median score	Range
Taking oral medications	0	-12 to 12	-3	-18 to 16
Clinic appointments	-10	-12 to 2	-7	-12 to 12
Laboratory tests	-3	-9 to 4	-3	-9 to 9
Other tasks	0	-6 to 5	0	-6 to 6
Overall	-11	-37 to 10	-8	-45 to 41

Hydroxyurea Adherence versus Age, Discrepancy Score, and Caregiver Involvement

The median adolescent discrepancy score was 14 (range 1–38). Adolescent age (median 14 vs. 15 years, $p = .28$, Cohen's $d = .34$), adolescent discrepancy score (median 13.5 vs. 16 points, $p = .92$, Cohen's $d = .06$), and caregiver involvement (median -13 vs. -13 points, $p = .8$, Cohen's $d = .15$) were not significantly different between hydroxyurea adherent and nonadherent adolescents.

Appointment Adherence versus Age, Discrepancy Score, and Caregiver Involvement

Adolescents attended a median of 3 (range 1–10) clinic appointments in the year prior to survey completion (Table III). Adolescent age (median 13 vs. 15 years, $p = .11$, Cohen's $d = .53$), adolescent discrepancy score (median 22 points vs. 11 points, $p = .06$, Cohen's $d = 0.72$), and caregiver involvement (median -15 points vs. -7 points, $p = .36$, Cohen's $d = .23$) were not significantly different between appointment adherent and non-adherent adolescents.

Discussion

Hydroxyurea is an effective medication for adolescents with SCD, but to effectively utilize this treatment, patients must be closely monitored and successfully complete many treatment tasks (Yawn et al., 2014). Adolescents and their caregivers have awareness that responsibility for SCD must shift from caregivers to adolescents (Porter, Graff, Lopez, & Hankins, 2014), but overall, our data suggest, few adolescents or their caregivers plan how to manage the adolescents' treatment or perceive they are personally overall responsible for treatment. Additional studies are needed to determine if our findings are related to adolescents and caregivers not knowing what tasks need to be completed, not being capable (e.g., cognitive difficulties) of completing the required tasks, not recognizing the potential benefits of treatment planning, not communicating well, or if there are other factors that influence these perceptions that could inform interventions to improve treatment planning and adherence.

Adolescents with SCD and their caregivers reported more shared responsibility for taking oral medications

Table III. *Adolescents' Hydroxyurea and Clinic Appointment Adherence*

Hydroxyurea adherence measures	Participants $n = 26$ ($n, \%$)
% of days the participant had access to hydroxyurea by electronic prescription data	
<20%	5 (19.2)
20–39%	0 (0)
40–59%	5 (19.2)
60–79%	4 (15.4)
80–100% ^a	12 (46.2)
Participants' MCV	
<80 fl	1 (3.8)
80–101 fl	19 (73.1)
≥102 fl ^a	6 (23.1)
Participants' HbF	
<10%	1 (3.8)
10–15%	3 (11.5)
≥16% ^a	22 (84.6)
Multi-method hydroxyurea adherence	
None of the measures met the threshold	3 (11.5)
1 of the measures met the threshold	9 (34.6)
≥2 of the measures met the threshold ^a	11 (42.3)
All 3 of the measures met the threshold ^a	3 (11.5)
Appointment adherence	Participants $n = 29$ ($n, \%$)
Number of appointments attended in the year prior to study entry	
1	1 (3.4)
2 or 3	14 (48.3)
≥4 (or at least as many as required by his/her provider) ^a	14 (48.3)

^aThreshold used to define adherence.

and other tasks. This could suggest that these tasks may be an opportunity for adolescents to begin to become increasingly involved with their treatment, especially since most of these tasks do not require financial resources to complete (e.g., taking the medication out of the bottle; knowing when it is time to take the medication). In contrast, adolescents' and caregivers' perceptions about their own responsibility for clinic appointment tasks, or lack thereof, was striking. Adolescents may not have perceived responsibility for appointment tasks because transportation resources are required to attend an appointment and because younger patients (those less than 18 years of age) usually must attend appointments with consenting adults. Since caregivers' contact information

is typically used to schedule appointments for younger patients and caregivers typically manage transportation logistics and the family's schedule, caregivers' perception that they were not responsible for appointment tasks was unexpected. Our exploratory analyses did not show that adolescent age, discrepancy between adolescents' and caregiver' reports of adolescent responsibility, or higher caregiver involvement were correlated with appointment adherence but, we may have been underpowered to detect these associations. Considering appointment non-adherence is common and associated with worse health outcomes (Creary et al., 2017; Modi, Crosby, Hines, Drotar, & Mitchell, 2008), interventions, potentially facilitated by clinicians, that encourage caregivers and/or adolescents to take responsibility for appointment tasks are especially needed. These appointments could also provide opportunities to identify other adherence barriers and to facilitate adolescent and caregiver SCD-management planning.

We anticipated that caregivers would report more overall personal responsibility for treatment than their children because this was what was observed in prior ATR studies that included adolescents with renal transplants and epilepsy (Holbein, Smith, Peugh, & Modi, 2019; Pai et al., 2010). Unlike these other chronically ill adolescents, however, our adolescents were minorities and this may suggest that cultural differences or parenting styles differences that may vary by culture (Dearing, 2004) have the potential to influence how caregivers' allocate treatment responsibility. Given low caregiver internal reliability, however, additional studies are needed to confirm this finding and should also consider including caregivers of younger children to determine when caregivers of children with SCD may begin to report having less responsibility.

Our results showed that caregivers at NCH reported having significantly less responsibility for treatment compared to caregivers at CCHMC. This may be related to differences between these two clinics' structures. For example, NCH schedules patients with SCD who are ≥ 14 years old into an adolescent-focused SCD clinic instead of a standard SCD clinic appointment. This adolescent-focused structure was designed to facilitate separating adolescents from their caregivers for part of the appointment to provide adolescents with privacy and to give adolescents an opportunity to report their own health information and concerns. This clinic structure is supported by the American Academy of Pediatrics to promote confidentiality (American Academy of Pediatrics, 2018), but further study is needed to determine how to implement it among adolescents with chronic illnesses who may still require significant caregiver involvement and oversight. Selection bias may have also contributed to the difference in caregivers' reported responsibility for treatment between the two study sites, since the

caregivers at NCH only agreed to complete surveys, whereas the caregivers at CCHMC agreed to complete surveys and to participate in an ongoing self-management intervention with their adolescents.

Consistent with previous hydroxyurea adherence studies (Badawy et al., 2017; Candrilli et al., 2011; Thornburg, Calatroni, et al., 2010), our results suggest that approximately half of adolescents with SCD are nonadherent to hydroxyurea. Because all of the tasks on the ATR measure must be completed to be able to be adherent to hydroxyurea, failure to plan for how these tasks were going to be completed may have contributed to hydroxyurea nonadherence. In contrast to prior studies, we did not observe that hydroxyurea adherence was associated with younger adolescent age, lower discrepancy between adolescents' and caregivers' reports of adolescent responsibility (Pai et al., 2010), or higher caregiver involvement (Holbein, Smith, Peugh, & Modi, 2019; Landers, Friedrich, Jawad, & Miller, 2016). Since our medication adherence measure was not validated, our sample size was small, and only a few adolescents reported low caregiver involvement, larger studies are needed to confirm these findings or if high discrepancy for specific tasks (i.e., clinic appointment tasks) and caregiver discrepancy scores may also be associated with adherence.

This is the first study to describe the distribution of treatment responsibility among adolescents with SCD and their caregivers, however, there are several limitations. First, while our adolescent sample appeared to be representative of patients followed at two large pediatric SCD programs, because of our cross-sectional study design, low recruitment rate, and small sample size these results may not be generalizable and should be confirmed in larger studies. These future studies should also consider assessing if cerebral infarcts and executive functioning deficits that occur commonly in patients with SCD (Hensler et al., 2014) impact how responsibility is allocated. Second, the hydroxyurea adherence measure that was used has limitations and may not be valid, for example, if patients did not fill and/or take all of the doses that were electronically prescribed. Third, the low internal consistency of our caregivers' responses suggests that future studies may also need to evaluate the ATR's psychometric properties in SCD and if modifications could improve its reliability in this population. Fourth, this study measured perceived responsibility for treatment tasks but actual task completion was not measured. Finally, while it is our experience that few caregivers attend appointments with their adolescents who are 18 years of age or older, patients who did not attend an appointment with their caregiver were not eligible. Therefore, it remains uncertain if treatment responsibility is completely transitioned to adolescents once they attend clinic appointments independently or if their

caregivers continue to have some responsibilities. To overcome some of these limitations, alternative recruitment strategies, such as approaching participants outside of their appointments should be considered and may provide opportunities to enroll more adolescents who are nonadherent to their appointments and older adolescents who may not attend appointments with their caregiver. Also, since time and perceived burden are barriers for children with SCD to participate in research studies (Lebensburger et al., 2013), recruiting participants outside of appointments when adolescents and their caregivers may have more time and be less preoccupied by the other aspects of their SCD care could increase participant recruitment.

Overall, this study suggests adolescents with SCD perceive their caregivers and caregivers perceive their adolescents are overall responsible for treatment, but adolescents share some responsibility with their caregivers for oral medication-taking tasks. Additional studies to identify the factors that influence adolescents' and caregivers' perceptions of responsibility for treatment and result in effective adolescent-caregiver treatment planning are warranted. In the future, however, the ATR could also be a useful tool to identify specific treatment tasks that are challenging for adolescents and caregivers to complete and the appropriate target(s) (adolescents, caregivers, or both) for hydroxyurea adherence interventions.

Supplementary Data

Supplementary data can be found at: <https://academic.oup.com/jpepsy>

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