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Greater number of perceived barriers to hydroxyurea associated with poorer health-related quality of life in youth with sickle cell disease

Arlene Smaldone[1,2], **Deepa Manwani**[3], and **Nancy S. Green**[4]

[1]Columbia University School of Nursing, New York, New York

[2]College of Dental Medicine, Columbia University Medical Center, New York, New York

[3]Department of Pediatrics, Albert Einstein College of Medicine, New York, New York

[4]Department of Pediatrics, Columbia University Medical Center, New York, New York

Abstract

Background: Despite medical benefits, hydroxyurea adherence in adolescents is often poor. As part of a baseline assessment of 28 youth (10–18 years) parent dyads who participated in a 6-month feasibility trial to improve hydroxyurea adherence, we measured the relationship between greater barriers to adherence and health-related quality of life (HRQL) from youth and parent perspectives.

Procedure: Barriers were measured using the Adolescent and Parent Medication Barriers Scales with nine hydroxyurea items added. Barriers reported by ≥25% of the sample were considered common. Generic and disease-specific HRQL were measured by PedsQL and PedsQL Sickle Cell Disease modules. Data were analyzed using descriptive statistics, Cronbach alpha, Spearman correlation coefficients, and paired *t* tests.

Results: Fifty-six subjects (28 dyads) participated. Youth reported greater barriers compared with parents (5.0 ± 3.9 and 3.5 ± 3.2; $P = 0.03$), with >80% of respondents reporting ≥1 barriers. Twelve barriers were reported by ≥25% of adolescents, whereas six were reported by ≥25% of parents. Of these, only two were common to both dyad members. Approximately one-third of youth had generic and disease-specific HRQL scores that fell at or below cutoff scores, suggesting being at risk for impaired HRQL. Greater barriers were inversely associated with poorer generic (parent $r = -0.43$, $P = 0.03$; youth $r = -0.44$, $P < 0.001$) and disease-specific HRQL (parent $r = -0.53$, $P = 0.005$; youth $r = -0.53$, $P < 0.001$).

Conclusions: Hydroxyurea barriers were frequently reported but differed by dyad members' perspective. Greater barriers were associated with poorer generic and disease-specific HRQL. To reduce barriers to hydroxyurea in youth with sickle cell disease, perspectives of both dyad members should be addressed.

Correspondence Arlene Smaldone, Columbia University School of Nursing, 560 West 168th Street, New York, NY 10032. ams130@columbia.edu.

CONFLICT OF INTEREST

The authors have no conflicts to disclose.

Keywords

hydroxyurea; medication barriers; quality of life; sickle cell disease

1 | INTRODUCTION

Sickle cell disease (SCD), an inherited disorder affecting red blood cells, affects approximately 100 000 people in the United States, including African Americans, Caribbean Latinos, and other underserved ethnicities.[1,2] SCD is characterized by fatigue, pain, organ damage,[3] reduced health-related quality of life (HRQL),[4,5] high health-care costs,[6,7] and premature mortality.[8,9] Offering hydroxyurea, a daily oral medication, is now recommended as standard practice in the treatment of youth with SCD.[10] The drug's induced dose-dependent increase in fetal hemoglobin (HbF) is largely responsible for its impact.[11,12] Hydroxyurea markedly reduces symptoms, morbidity and mortality,[13] improves HRQL,[14] decreases healthcare cost,[15] and may protect against cumulative disease burden. Despite these therapeutic benefits, adherence in adolescents and young adults with SCD is often poor.[16–22]

Barriers to medication adherence are common in youth across chronic health conditions[20,23,24] and are a source of racial/ethnic disparities.[25–27] Although parents are often the decision-makers regarding the initiation and continued use of hydroxyurea therapy, adolescents may have a different perspective from their parents regarding what difficulties exist for adherence to therapy. Research examining hydroxyurea barriers in samples of parents who decided either for or against hydroxyurea for their youth with SCD[28,29] demonstrates that parents frequently expressed fearfulness about starting hydroxyurea, lack of understanding of SCD and the therapeutic benefits of hydroxyurea, concerns about long-term toxicities, and thought their child was not sick enough to warrant its use. In a recent sample of 34 adolescents/young adults with SCD prescribed hydroxyurea,[30] approximately one-third reported no barriers, with only a small minority reporting multiple barriers to hydroxyurea use. Of those reporting barriers, forgetfulness, negative beliefs about hydroxyurea, and cost and/or failure to obtain timely prescription refills were most frequently reported; greater barriers were associated with poorer self-reported adherence.

To date, the identification of hydroxyurea barriers from the perspective of parent–youth dyads has not been reported. The purpose of this study was to examine barriers to hydroxyurea adherence and the relationship between barriers and HRQL from both dyad perspectives in a sample of youth ages 10–18 years, who met criteria for poor adherence to hydroxyurea, and their parents who participated as a dyad in the Hydroxyurea Adherence for Personal Best in Sickle Cell Disease (SCD), "HABIT," a six-month feasibility trial[31] to improve hydroxyurea adherence (NCT02029742). We hypothesized that a greater number of barriers would be associated with poorer HRQL.

2 | METHODS

The study protocol has been reported elsewhere.[31] Of relevance to this report, youth more than one grade level below that expected for age were excluded from study participation.

Further, as a clinical standard for hydroxyurea-induced HbF to assess adherence is lacking,[12,17,19,32,33] we employed a personal best HbF defined as the child's highest historical HbF assessed at maximum stable dose since the initiation of hydroxyurea therapy. In the HABIT feasibility trial, poor adherence was defined as an average HbF value of ≥10% below personal best over the past year.[34] Institutional review board approval was obtained at each participating site prior to study initiation. All measures reported here were assessed at study entry.

3 | STUDY VARIABLES AND MEASURES

3.1 | Barriers to hydroxyurea use

The Parent Medication Barriers (PMBS) and Adolescent Medication Barriers (AMBS) scales[35] were adapted for use in this study by adding nine items to capture hydroxyurea knowledge and beliefs.[28] Two of the added items about contraception and concern about future childbearing potential were completed by girls and their parents only. The adapted parent and adolescent scales contained 25 and 26 items, respectively. Each item was rated on a 5-point Likert scale. A subject's response of 4 or 5 to an item was considered endorsement of the barrier. Three subscales are common to both scales: disease frustration/adolescent issues (7-item parent scale; 8-item adolescent scale), regimen adaptation/cognitive (5 items both scales), ingestion issues (3-item parent scale; 4-item adolescent scale) and parent reminder (1 item, parent scale only).[35] The nine added items were included as a knowledge/belief subscale. Barriers reported by ≥25% of youth or parents were considered to be common. The presence of three or more barriers was considered high on the basis of the cutoff scores developed for both scales.[36]

3.2 | Health-related quality of life

Generic and disease-specific HRQL was measured using the PedsQL[37] (23 items) and PedsQL SCD module[38] (43 items), respectively. Both scales employ a 5-point Likert scale, measure HRQL from a parent-proxy and youth perspective, with scores ranging from 0 to 100. In this study, total HRQL scores were measured. A total PedsQL generic HRQL score at or below 69.7 (for child self-report) and 65.4 (parent-proxy report) can be interpreted as being at risk for impaired HRQL.[39] PedsQL disease-specific HRQL scores 60 and lower, particularly for pain-related subscales, can be interpreted as impaired HRQL, while scores 80 and higher are consistent with good HRQL in youth with SCD.[40]

3.3 | Data analysis

An internal consistency reliability or Cronbach alpha coefficient was computed for each barrier total score measure and its subscales to determine scale reliability in the current sample. An alpha of 0.70 or higher was considered adequate reliability.[41] Descriptive statistics were used to profile outcome measures at baseline for the parent and youth sample. The total number of reported barriers and generic and disease-specific HRQL scores reported by parents and youth at study entry were compared using the paired *t* test. The relationship between barriers and total HRQL scores was computed using a Spearman correlation coefficient. Data were analyzed using SAS 9.4 (Cary, NC) statistical software.

4 | RESULTS

Fifty-six subjects participated as 28 parent–youth dyads (youth age, 14.3 ± 2.6 years; 43% female; 50% Latino; 26 of 28 participating parents were mothers). At study entry, the decline from personal best HbF for this sample was, on average, 27.2%. Table 1 compares internal reliability and average number of barriers by a dyad member. The internal reliability of the barrier scale was high for parent (alpha = 0.88) and youth (alpha = 0.91) total scores and most subscales. On average, the total number of reported barriers were greater for youth compared with parents (5.0 ± 3.9 and 3.5 ± 3.2, $P = 0.03$). Self-report of generic (70.5±20.8 vs 76.8 ± 17.0, $P = 0.05$) HRQL was similar by respondent; however, parents reported poorer disease-specific (61.4±21.1 vs 68.7 ± 18.8, $P = 0.02$) HRQL than did their youth.

Table 2 compares barriers' frequently reported by youth and parents. Six barriers were endorsed by ≥25% of parents, whereas 12 barriers were endorsed by youth. Approximately half of parents and 75% of youth reported total barriers exceeding the cutoff score of three or more barriers. Parents most frequently reported youth reliance on parent reminders to take hydroxyurea (42.9%). For youth, the majority of barriers were related to disease frustration/adolescent issues and ingestion issues. Disease frustration/adolescent issues frequently reported by youth were being tired of living with a medical condition (57.1%), not remembering to take medication (53.6%), not feeling like taking medication (39.3%), tired of taking medication (39.3%), not wanting to take medication at school (28.6%), and not wanting others to see youth taking medication (25%). Ingestion issues included having too many pills to take (39.3%), disliking the taste (35.7%), and difficulty swallowing medication (25%). Regarding knowledge and beliefs about hydroxyurea, some youth (25%) reported not understanding how hydroxyurea works; parents of girls (25%) expressed worry about the need for contraception while taking hydroxyurea and concern about the possibility of teratogenic effect on a baby born to someone taking hydroxyurea.

4.1 | Relationship between barriers and HRQL

More than one-third of youth had parent-proxy and youth-reported total generic HRQL scores (37.0% and 35.7%) that fell at or below cut-off scores indicative of being at risk for impaired HRQL. Regarding disease-specific HRQL, 44.4% of parents and 32.1% of youth reported scores of 60 or less representing impaired HRQL and 21.4% of parents and 35.7% of youth reported scores of 80 or greater representing good HRQL in youth with SCD. A greater number of total barriers were inversely associated with total generic (parent $r = -0.43$, $P = 0.03$; youth $r = -0.44$, $P < 0.001$) and disease-specific (parent $r = -0.53$, $P = 0.005$; youth $r = -0.53$, $P < 0.001$) HRQL.

5 | DISCUSSION

In our two-site sample of parent–youth dyads who were poorly adherent to hydroxyurea, a greater number of barriers to hydroxyurea were associated with poorer generic and disease-specific HRQL by both parent and youth self-report. More than 80% of parents and youth reported at least one barrier to hydroxyurea use; of those reporting barriers, the majority reported three or more barriers, exceeding PMBS and AMBS cutoff scores.[36]

Approximately one-third of parents and of youth reported generic and disease-specific quality-of-life scores indicative of impaired HRQL.

The relationship between the number of adherence barriers and HRQL in youth with chronic illness has not been widely studied. The association between greater barriers and poorer HRQL identified in our study sample is consistent with findings reported in samples of youth with other chronic conditions such as cystic fibrosis,[42] asthma,[43] and inflammatory bowel disease.[44] Among these youth, adherence barriers mediated the effect between gastrointestinal symptoms and HRQL,[44] and between family support, asthma control, and HRQL.[43] Our sample was underpowered to examine these types of relationships.

The number of barriers reported by our sample was greater than that recently reported in a sample of adolescents and young adults with SCD prescribed hydroxyurea, where most youth reported either one or no barriers.[30] These differences may be partially explained by differences in hydroxyurea adherence. In our sample, all youth were poorly adherent to hydroxyurea by HbF study entry criteria, whereas the sample surveyed by Badawy and colleagues was a clinic-based convenience sample and likely represented a range of adherence. In youth with other chronic conditions such as type 1 diabetes,[45] cystic fibrosis,[46] inflammatory bowel disease,[47] and organ transplantation,[48] multiple barriers are frequently reported with negative associations between adherence barriers and glycemic control,[45] stress and burnout,[45] and episodes of organ rejection and hospitalization.[36]

Few studies have examined barriers to adherence from the perspective of youth–parent dyads.[42,49] Similar to our findings, barriers differed by respondent perspective. For parents in our study, the most frequently reported barrier was youth reliance on parent reminders to take hydroxyurea (regimen adaptation/cognitive issues). For youth, the most frequently reported barriers, forgetfulness about taking hydroxyurea (regimen adaptation/cognitive issues) and being tired of living with a medical condition (disease frustration/adolescent issues), are similar to those reported by adolescents across chronic health conditions.[24] Using the AMBS and PMBS, Lee and colleagues[50] measured barriers to adherence in a sample of 80 pediatric transplant recipients and their parents over an 18-month period. All but two barriers reported by parents or youth either remained stable or worsened during the timeframe. Barriers noted to be particularly resistant to change without specific intervention were those associated with disease frustration/adolescent issues and regimen adaptation/cognitive issues. This last issue may be especially relevant as neurocognitive deficits affecting verbal reasoning and executive function are not uncommon for youth with SCD both with and without identified cerebral infarct.[51–53] Collectively, these findings highlight the need to assess barriers from both perspectives as part of routine clinical care as well as develop and test interventions to reduce barriers in youth prescribed hydroxyurea and their parents.

Although not among the most frequently reported barriers, a lack of knowledge about hydroxyurea was acknowledged by one in four adolescents in this sample. Knowledge about medications is a prerequisite for but does not guarantee medication adherence.[54,55] During adolescence, youth begin to assume more self-management responsibility.[56] This developmental transition presents an opportunity during clinical visits to assess adolescent

knowledge and beliefs about their treatment regimen, address misperceptions and provide information adapted for low literacy. Provision of educational materials is a common component of transition care programs for youth with chronic health conditions.[57] All parents and youth enrolled in the HABIT feasibility study received education handouts about SCD and hydroxyurea and nearly all reported both satisfaction with and learning new things from the educational materials.[34]

In our prior multisite survey, problems with hydroxyurea ingestion were reported by 26% of parent respondents.[58] Although fewer than 15% of parents in our sample here reported youth difficulty with either the taste of or ability to swallow hydroxyurea, their youth frequently endorsed these ingestion barriers (35.7% and 25%, respectively). If recognized, ingestion barriers can be successfully overcome with a variety of interventions.[59]

These findings must be considered in light of the study's limitations. The sample size had limited statistical power. Statistical adjustment was not made for multiple comparisons, although the number of comparisons was limited. Parent and youth depressive symptoms were not measured and may affect both medication barriers and hydroxyurea adherence. The AMBS and PMBS measures were adapted with the addition of a 9-item hydroxyurea knowledge and beliefs subscale and had not been formally tested with parents and youth with SCD prior to their use in this study. Further, in our study sample, the internal consistency of the ingestion subscale of the parent barriers scale was lower than the accepted norm of 0.70. Testing of both adapted instruments in larger samples is warranted. Although youth more than one grade level below expected were excluded from study participation, formal cognitive testing was not employed. More specific cognitive issues affecting these youth, such as executive function, may have affected our results but were not identified.

Despite these limitations, the types and differences in barriers reported by parents and youth provide some insight regarding what barriers may reduce optimal utilization of hydroxyurea therapy in adolescents with SCD. To reduce barriers to hydroxyurea use in youth with SCD, perspectives of both dyad members should be addressed. The relationships between perceived barriers, hydroxyurea adherence, and HRQL are complex. Future research is needed to better understand the relationships between perceived adherence barriers, HRQL, and other correlates of interest such as healthcare utilization in youth with SCD.

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Abbreviations:

AMBS	Adolescent Medication Barriers scale
CHW	community health worker
HABIT	Hydroxyurea Adherence for Personal Best in Sickle Cell Disease
HRQL	health-related quality of life

PMBS	Parent Medication Barriers scale
SCD	sickle cell disease

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TABLE 1

Parent and youth barriers and HRQL

	Parent (*N* = 28)		Youth (*N* = 28)	
Total scores and subscales	**Cronbach alpha[a]**	**Mean ± SD**	**Cronbach alpha**	**Mean ± SD**
Barriers (total score)[b]	0.88	3.5 ± 3.2	0.91	5.0 ± 3.9
Adolescent frustration	0.78	0.9 ± 1.3	0.80	2.5 ± 2.1
Regimen adaptation/cognitive	0.60	0.8 ± 1.0	0.66	0.6 ± 1.0
Ingestion issues	0.25	0.5 ± 0.6	0.69	1.1 ± 1.2
Parent reminder[c]	–	0.4 ± 0.5	–	–
Hydroxyurea knowledge/beliefs	0.74	0.9 ± 1.0	0.83	0.8 ± 1.2
Generic HRQL (total score)	0.94	70.5 ± 20.8	0.92	76.8 ± 17.0
Disease-specific HRQL (total score)	0.97	61.4 ± 21.1	0.95	68.7 ± 18.8

[a] An alpha score ≥0.70 is considered as adequate reliability.[41]

[b] A score of ≥3 barriers was considered high based on established cutoff scores.[36]

[c] One item parent subscale.

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TABLE 2

Barriers to hydroxyurea frequently endorsed by at least 25% of parents and/or youth

	Parent (*N* = 28)		Youth (*N* = 28)	
	N	**%**	***N***	**%**
Reporting one or more barriers	23	82.1	24	85.7
Reporting three or more barriers (of those reporting barriers)	13	56.5	18	75.0
Subscale: Disease frustration/adolescent issues (7 items [parent]; 8 items [adolescent])				
My child (I) does (do) not want other people to notice him/her (me) taking medication.	4	14.3	7	**25.0**
Parent: My child sometimes feels sick and can't take medication.	1	3.6	11	**39.3**
Youth: I sometimes just don't feel like taking medication.				
My child (I) is (am) tired of taking medication.	6	21.4	11	**39.3**
My child (I) is (am) tired of living with a medical condition.	10	**35.7**	16	**57.1**
I don't want to take medication at school.[a]	–	–	8	**28.6**
Subscale: Regimen adaptation/cognitive (5 items)				
I am forgetful and don't remember to take medication every time.[b]	3	10.7	15	**53.6**
I am not very organized about when and how my child (I) takes medication.	5	17.9	8	**28.6**
My child (I) finds (find) it hard to stick to a fixed medication schedule.	8	**28.6**	6	21.4
Subscale: Ingestion issues (3 items [parent]; 4 items [adolescent])				
Parent: My child has a hard time swallowing hydroxyurea.	4	14.3	7	**25.0**
Youth: I believe that hydroxyurea is hard to swallow.				
My child (I believe that I) has too many pills to take.	5	17.9	11	**39.3**
My child (I) does (do) not like how hydroxyurea tastes.	4	14.3	10	**35.7**
Subscale: Parent reminder (1 item; parent only)				
My child relies on me to remind him/her when to take his/her hydroxyurea.[c]	12	**42.9**	–	–
Subscale: Hydroxyurea knowledge/beliefs (9 items)				
I do not understand how my child's (my) medication works.	3	10.7	7	**25.0**
I am worried that the medication could cause cancer.	5	17.9	2	7.1
I am concerned about possible effects of hydroxyurea on either getting pregnant or getting someone pregnant in the future.	7	**25.0**	4	14.3
I am concerned about the possibility of health problems to a baby born to someone taking hydroxyurea.[d]	3	**25.0**	3	**25.0**
I am worried about my child's need to take birth control when taking hydroxyurea.[d]	3	**25.0**	2	16.7

[a] Youth item only.

[b] Item included in the regimen adaptation subscale for parent but adolescent frustration subscale for youth.

[c] Parent item only.

[d] Parents of females or female youth only; barriers reported by ≥25% of the sample are bolded.