Patient Preference and Adherence

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ORIGINAL RESEARCH

Development and Validation of the Patient/Caregiver Reported Hydroxyurea Evaluation of Adherence for Life (HEAL) Scale

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Introduction: Hydroxyurea reduces the incidence of vaso-occlusive episodes, stroke, and respiratory, cardiac, and renal damage in sickle cell disease by increasing fetal hemoglobin. However, because suboptimal adherence to hydroxyurea limits its effectiveness, understanding patient-specific barriers to hydroxyurea adherence could help improve adherence and health outcomes in patients with sickle cell disease. The aim of this single-site, prospective, IRB-approved study was to validate a 24-item patient- and caregiver-reported hydroxyurea treatment adherence questionnaire, the Hydroxyurea Evaluation of Adherence for Life (HEAL) scale.

Methods: A sample of 24 adults with sickle cell disease and 16 caregivers of children with sickle cell disease completed the HEAL scale, and a subset of the original sample provided a second HEAL scale for test-retest reliability. HEAL scale results were validated against global adherence ratings from participants and health-care providers, records of access to pill bottles, and laboratory values for fetal hemoglobin and absolute neutrophil count.

Results and Discussion: Results demonstrated excellent internal consistency for the HEAL Total score and eight (3-item) subscale scores (Dose, Remember, Plan, Cost, Understand, Effectiveness, Laboratory, and Pharmacy), as well as strong test-retest reliability for all HEAL scores except the Cost subscale. HEAL Total scores correlated significantly with validity measures, including global adherence ratings and lab values. The HEAL scale offers significant clinical potential for understanding adherence in individual sickle cell disease patients and significant research potential for characterizing adherence in persons with sickle cell disease who are treated with hydroxyurea.

Keywords: sickle cell disease, treatment adherence, hydroxyurea, reliability, validity, scale development

Plain Language Summary

Hydroxyurea is one of very few medicines that treats sickle cell disease. It increases the amount of fetal hemoglobin in the blood. Having more fetal hemoglobin can reduce the number of sickled red blood cells. Hydroxyurea can help prevent pain episodes, strokes, and damage to the heart, lung, and kidneys. Patients must take hydroxyurea as prescribed for it to work. If we had a better understanding of why people may not take it as prescribed, providers could work with patients to address those reasons.

We created a patient-report questionnaire that measures beliefs, barriers, and behaviors to taking hydroxyurea as prescribed (adherence): the Hydroxyurea Evaluation of Adherence for Life (HEAL) scale. In addition to a Total score, the HEAL scale has eight subscales that measure different parts of adherence: Dose, Remember, Plan, Cost, Effectiveness, Understand, Lab, and Pharmacy. Twenty-four adults with sickle cell disease and 16 caregivers of children with sickle cell disease completed the HEAL scale. Results showed that HEAL items represent the content of their subscales and give consistent results over time. We also checked to make sure the HEAL actually measures adherence by comparing HEAL results with three important measures of adherence and effectiveness:

- Patient lab results,
- How often patients opened their hydroxyurea pill bottles, and
- Patient and provider ratings of the patient's adherence to hydroxyurea.

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The HEAL Total score and several subscale scores relate to most of these important outcomes. Based on these findings, the HEAL scale is a good patient-report measure for understanding adherence to hydroxyurea.

Introduction

Sickle cell disease (SCD) is one of the most common severe monogenic disorders worldwide.[1] A multi-system disease associated with acute illness and progressive organ damage, SCD is an inherited red blood cell disorder that affects approximately 100,000 Americans.[1,2] The polymerization of sickle hemoglobin (HbS) leads to abnormally stiff, sickle-shaped red blood cells (RBCs) which causes chronic anemia, respiratory, cardiac and renal damage, acute pain (vaso-occlusive episodes [VOEs]), stroke, and splenic infarction.[3] Free hemoglobin, released during hemolysis, scavenges nitric oxide (NO) which leads to vaso-constriction, exacerbating vaso-occlusion.[4,5] Universal newborn screening (NBS) and preventative treatments have effectively eliminated early childhood mortality in the US, although people with SCD continue to experience increased morbidity and early mortality.[6,7]

Prior to 2017 there were limited treatment options to prevent the complications of SCD; hydroxyurea (HU) was the only FDA-approved treatment. A once daily oral medication, HU increases fetal hemoglobin (HbF) levels which prevents HbS polymerization, decreasing RBC sickling and hemolysis.[8–10] Laboratory evidence of HU response includes higher HbF levels and mean corpuscular volume (MCV), and lower reticulocyte, neutrophil, and platelet counts.[11,12] The observed clinical benefits of HU use include decreased frequency of painful VOEs, acute chest syndrome (ACS), and unscheduled RBC transfusions.[13–16] HU may act as a NO donor which improves blood flow.[4,5] Recent results suggest improved cognition after 1 year of HU use in a pediatric cohort[17] and a neuroprotective effect in persons with SCD 5 years and older.[18]

Despite well-documented benefits, HU is underutilized in the United States. Studies have suggested that as many as 70–75% of eligible patients are not taking HU.[19–21] Not all patients treated with HU experience an adequate clinical response, which could reflect suboptimal adherence to HU treatment, since nonadherence limits HU efficacy.[22] Reported HU medication adherence rates in non-clinical trials ranged from 39% to 67%, although adherence has been variably defined in prior studies.[22–25] Like any self-administered treatment, adherence to HU treatment requires planning, organization, and effort from patients, some of whom may struggle with those demands. Reasons for nonadherence may also involve inadequate knowledge and concerns about risk-to-benefit ratio, although the factors contributing to HU nonadherence are not well understood because of a dearth of well-defined adherence assessment instruments tailored specifically to HU.[26–30]

Measurement and monitoring of adherence involve an array of direct and indirect methods. Methods for assessing adherence, mainly in clinical trial settings, include medication event monitoring systems (MEMS; devices that record patient access to medication containers such as pill bottles), medication possession ratios (comparing prescriptions filled to medication needs), pill counts (having patients show or return unused medication, which can be compared against the amount of medication that should have been used during the time period), and patient logs (diary records kept by patients of medication usage).[23,31,32] In clinical practice, unstructured clinical interviews with patients, percentage of attended follow-up visits,[33] ratio of expected vs observed days between refills,[22] and lab values such as stable HbF and absolute neutrophil count (ANC) are more commonly used to monitor adherence.[34]

The body of existing medication adherence measures has significant limitations for assessment of HU adherence, particularly in the clinical setting. While casual/unstructured clinical interviewing and questioning by providers can be helpful, no validated HU adherence measure is systematically used in the clinical setting, despite the importance of adherence for efficacy. Furthermore, no adherence measure has been developed to assess specific HU adherence characteristics from a patient perspective. A practical, easy-to-use HU adherence scale targeting patient (or caregiver) behaviors and concerns could be feasible for implementation in the applied clinical setting and could be used to target provider-patient discussion and interventions to enhance adherence, promoting better outcomes and decreased health-care utilization. Clinically, such a scale could be helpful for understanding and addressing adherence problems in specific patients.

In order to address this need for a clinically relevant, HU-focused measure of adherence, we sought to develop a HU adherence questionnaire. Here, we report on the development and validation of a patient- and caregiver-report

Hydroxyurea Evaluation of Adherence for Life (HEAL) questionnaire to assess beliefs and barriers to adherence to HU treatment among persons with SCD.

Materials and Methods

Participants

Participants were recruited from the Indiana Hemophilia & Thrombosis Center (IHTC) and the community at large. Eligible individuals had a confirmed SCD diagnosis in the IHTC electronic medical record (EMR) and had HU prescribed for at least 6 months prior to enrollment. Exclusion criteria included: non-English speakers, pregnant women, and an older sibling taking HU (in order to select only one child from families who had multiple children taking HU).

Forty participants consented to the HEAL psychometric study and completed HEAL scales: 24 adults (ages 18 years +) who completed the HEAL scale by self-report, and 16 children (ages 1–17 years), for whom one primary caretaker completed the HEAL scale. Participant age in the entire sample ranged from 1.8 to 65.0 years, with mean age 25.6 (18.0 SD, 30.5 median). Table 1 shows demographic characteristics for the entire sample. Sixteen (8 adult self-report and 8 child caregiver-report) of the original 40 participants (40%) completed the HEAL scale a second time to evaluate test-retest reliability. The average number of days between first and second administration was 50.1 days (range 8–160, SD = 43.3) days. Demographic characteristics of the subsamples obtained for test-retest analyses were similar to those of the total sample (available from authors on request).

Recruitment and Procedures

Participants were recruited for this single-site, prospective, Ascension-St. Vincent IRB-approved study during clinic and home visits for treatment of SCD. This study complied with the Declaration of Helsinki. All adult participants signed an IRB-approved informed consent document. Parents/caregivers provided consent for minor children (ages ≥ 15 months to 17 years), who were also either consented (14–17 years) or assented (7–13 years). The individual with primary responsibility for HU adherence completed questionnaire measures of background/demographics and adherence. Laboratory testing results and other medical information were obtained from EMR review.

Table 1 Sample Demographic and Clinical Data

	Total Sample (N=40)			Self-Report (N=24)			Care-Giver-Report (N=16)		
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
Participant Age (Years)	25.6	18	1.8–65.0	38.7	9.6	22.6–65.0	5.9	3.5	1.8–15.2
Participant Gender									
Male		16	40.0%		10			6	
Female		24	60.0%		14			10	
Participant Race									
Black/African-American		38	95.0%		23			15	
Multiracial		2	5.0%		1			1	
Participant Diagnosis									
HbSS		31	77.5%		16			15	
HbSC		4	10.0%		3			1	
HbSβ^+ thalassemia		3	7.5%		3			0	
HbSβ^0 thalassemia		2	5.0%		2			0	

To evaluate test-retest reliability, the HEAL scale was sent via US mail 2 weeks following the first administration to participants who consented to complete a second administration. A pre-stamped, addressed envelope was included for ease of return once completed. Participants not returning the HEAL scale within 2 weeks received reminder telephone calls and were considered lost to follow-up after three unreturned calls.

Measures

Hydroxyurea Evaluation of Adherence for Life Scale (HEAL)

The HEAL scale (see S1 Appendix; contact authors for permission to use or for data requests) is a 24-item questionnaire divided into 8 (three-item) subscales: Dose, Remember, Plan, Cost, Understand, Effectiveness, Laboratory, and Pharmacy. HEAL items and subscales were developed using a systematic multi step process consisting of expert consultation, focus groups, and pilot research, resulting in the final 24-item scale.

First, a research team of expert SCD care providers (physicians, advance practice providers, and nurses) and adherence researchers developed a list of 28 adherence behaviors or beliefs based on literature review of adherence questionnaires for other treatments[35] and clinical experiences with adherence and HU use. These 28 adherence behaviors/beliefs were then worded as items for presentation to two patient focus groups consisting of adults responsible for their own HU treatment and caregivers responsible for the HU treatment of their children. Focus group results suggested additional adherence issues and rewordings of items that were then presented to the research team for further refinement and organization. Based on this input, 10 domains of adherence to HU were identified (Dose, Remember, Plan, Understand, Lab, Pharmacy, Provider, Cost, Benefit, and Harm), and 4 pilot items for each adherence domain were developed. Questions were phrased to be appropriate for either caregiver- or self-report, to apply broadly to the individuals responsible for patient adherence to HU treatment.

Next, we administered the 40-item preliminary questionnaire to a pilot sample of 15 caregivers of children (0–17 years) with SCD and 11 adults with SCD for purposes of item evaluation and content development. Based on pilot results, the number of items per subscale was reduced from 4 to 3 as some items showed poor internal consistency or insufficient variability and because focus group results indicated that a shorter scale would be more feasible to implement. The Benefit and Harm subscales were combined into a single Effectiveness subscale because of high intercorrelations between items, and the Provider subscale was eliminated because of poor reliability and validity. Following slight modifications to the wording of some items based on subject and provider feedback, the final HEAL measure consisted of eight 3-item subscales (as previously described).

HEAL scale response options are presented as seven-point Likert scales ranging from “Strongly Disagree” to “Strongly Agree”, with intermediate labels of “Agree” and “Disagree” at 2-point intervals from the extreme scores; an answer of “Strongly Agree” reflects the best possible adherence for some items and the worst possible adherence for other items. Each rated item on the seven-point scale was given a numeric score, such that the response indicating the “best” adherence scored seven points and the response with the “worst” adherence scored one point. Because subscale and total scores are the average of constituent item scores, a subscale/total score maximum score of 7 would indicate strong agreement in the direction of adherence to all items, while a score of 1 would indicate strong disagreement with adherence on all items. Scores of 5 and 3 would indicate averages of “Agree” or “Disagree” with adherence, respectively.

Global Adherence Rating (GAR)

The GAR is a visual analogue scale rating of global adherence to HU treatment.[35,36] The respondent indicates with a mark on a 100-millimeter (mm) line from “never” (on the left end of the line) to “always” (on the right end of the line) how much the patient takes HU as prescribed. Scores are the number of mm from the left side of the line divided by 100, such that a score of 0 = never and 1.0 = always. GAR scores were completed by the primary HEAL respondent (caregiver or self – “patient GAR”) and by an IHTC health-care provider (“provider GAR”) who was very familiar with the patient’s care (N = 36 Advanced Practice Providers/Prescribers/Physicians and 1 Nurse; 3 missing). Because of potential method bias it is important to obtain provider GAR to validate the self-report and other data. Because patient and provider GAR scores were significantly correlated ($r = 0.44$, $p < 0.01$), an additional “composite GAR” score was created

by taking the average of patient and provider GAR scores. GAR measures have been validated in past research to assess global adherence[35–37] and were used in the present study to validate the HEAL scale.

Medication Event Monitoring System (MEMS)

The MEMS consisted of a specialized bottle cap placed on a pill bottle, which recorded when the bottle was opened.[31] Nineteen participants (all adults) provided valid data using MEMS devices for a 90-day period to track adherence to HU taken in capsule form; two had less than 90 days of use because of inpatient stays that disrupted the data collection period (MEMS data for 66, 87 days respectively). Despite some limitations, MEMS devices are highly accurate and are used as a reference standard for validating other adherence measures.[31]

Laboratory Data

HbF (31 participants) and ANC (38 participants) results were extracted from the EMR for the study visit closest in time to the completion of the HEAL scale. HEAL scale administration and lab measurements occurred on average 56 (SD: 54.5, range −10 to 190 days) and 49 days (SD: 54.3, range −10 to 190 days) apart for HbF and ANC values, respectively. We utilized steady state lab values which we define as: at least 60 days after RBC transfusion and 30 days after an acute illness requiring hospitalization.

Statistical Analysis

Descriptive statistics including mean, SD, minimum, maximum, and percentiles (25th, 50th, and 75th) were calculated for all HEAL item, subscale, and total scores to evaluate distributions of scores in the entire sample. Subscale and total scores are average item scores for constituent items (eg, total of all items divided by number of items). Means and standard deviations for self-report and caregiver-report HEAL scores were reported separately and compared using *t*-tests. Subscale composition was evaluated using internal consistency reliability (Cronbach's alpha) in the entire sample. Due to the short length of the HEAL subscales, $\alpha \geq 0.8$ was considered to reflect excellent internal consistency; $0.8 > \alpha \geq 0.7$, very good; $0.7 > \alpha \geq 0.6$, good; and $0.6 > \alpha \geq 0.5$, minimally acceptable. Test-retest reliability of HEAL subscales and aggregate scores was assessed with Pearson product-moment correlations (r) and *t*-tests comparing HEAL scores at initial and retest completion times. Validity was assessed using correlational analyses (1-tailed p-values in the predicted direction of adherence) of HEAL scores with GAR, MEMS, and laboratory data. Because of limited sample sizes, self-report and caregiver-report data were combined for internal consistency, test-retest reliability, and validity analyses.

Results

HEAL Scale Descriptive Statistics

All HEAL scores (Table 2) showed a significant negative skew, indicating high self-reported adherence. All items had a median score of 5 ("Agree" in the direction of positive adherence) or higher. For 19 out of the 24 items, the median score was at least 6 (corresponding to a rating between "Agree" and "Strongly Agree" in the direction of positive adherence) and the 25th percentile was at least 5, indicating that at least 75% of the sample reported scores of 5 or higher. Items with the lowest reported adherence fell on the Remember and Plan subscales, where 25% or more of the sample reported values of less than 5 (eg, in the direction of disagreement) for all items except one. Similarly, HEAL subscale and total scores demonstrated high reported adherence across the sample, with only the Remember, Plan, and Lab median scores falling below a rating of "6" (6 corresponds to a rating between "Agree" and "Strongly Agree"). Although these values demonstrate high adherence to HU treatment across the sample, they also suggest that a significant minority – as high as 25% – report suboptimal adherence with HU treatment in specific subdomains involving organization and time management (remembering and planning treatment). *T*-tests comparing caregiver- and self-report scores indicated higher self-reported adherence compared to caregiver-rated adherence for the Pharmacy subscale and all Pharmacy items, but no other significant differences.

Table 2 HEAL Item and Subscale Descriptive Statistics

	Mean (SD)	Min/Max Scores	Percentile			Self-Report Mean (SD)	Care-Giver Mean (SD)	Self vs Care-Giver *t*-test
			25	50	75			
Dose	***6.0 (1.2)***	***1.0/7.0***	***5.4***	***6.3***	***7.0***	***6.1 (0.9)***	***5.9 (1.6)***	***0.61***
1. Give recommended amount	6.1 (1.4)	1.0/7.0	5.3	7.0	7.0	5.9 (1.3)	6.4 (1.6)	1.09
2. Know exact amount	6.6 (1.1)	1.0/7.0	7.0	7.0	7.0	6.8 (0.6)	6.4 (1.6)	1.05
3. Give incorrect amount[a]	5.4 (1.9)	1.0/7.0	5.0	6.0	7.0	5.7 (1.8)	4.9 (2.0)	1.38
Remember	***5.1 (1.8)***	***2.0/7.0***	***3.7***	***5.7***	***6.9***	***4.7 (1.8)***	***5.7 (1.7)***	***1.77***
4. Forget to give[a]	4.9 (2.1)	1.0/7.0	3.0	5.0	7.0	4.4 (2.0)	5.7 (2.1)	1.84
5. Skip doses[a]	5.3 (1.8)	1.0/7.0	4.3	6.5	7.0	5.1 (1.8)	6.1 (1.8)	1.73
6. Miss doses[a]	4.9 (1.9)	1.0/7.0	3.0	5.0	7.0	4.6 (1.9)	5.4 (1.8)	1.25
Plan	***5.3 (1.5)***	***2.3/7.0***	***4.1***	***5.7***	***6.9***	***5.8 (1.4)***	***5.1 (1.6)***	***0.69***
7. Run out of HU[a]	5.5 (1.8)	1.0/7.0	4.0	6.0	7.0	5.5 (1.8)	5.5 (1.8)	0.01
8. Irregular dose because run out[a]	5.5 (1.6)	1.0/7.0	5.0	5.5	7.0	5.6 (1.4)	5.4 (2.0)	0.35
9. Miss dose because run out[a]	4.9 (1.9)	1.0/7.0	3.0	5.0	7.0	5.3 (1.7)	4.4 (2.2)	1.32
Cost	***6.3 (1.1)***	***2.3/7.0***	***5.1***	***7.0***	***7.0***	***6.3 (0.9)***	***6.3 (1.4)***	***0.10***
10. Too expensive to take regularly[a]	6.3 (1.3)	1.0/7.0	5.1	7.0	7.0	6.3 (1.0)	6.3 (1.7)	0.15
11. Hard to afford[a]	6.4 (1.0)	3.0/7.0	5.3	7.0	7.0	6.3 (0.9)	6.5 (1.2)	0.64
12. Cost is stressful[a]	6.2 (1.3)	1.0/7.0	5.3	7.0	7.0	6.3 (1.0)	6.1 (1.8)	0.38
Effectiveness	***6.2 (1.0)***	***3.7/7.0***	***5.3***	***7.0***	***7.0***	***6.1 (0.9)***	***6.4 (1.1)***	***1.02***
13. HU helps	6.4 (1.0)	4.0/7.0	5.3	7.0	7.0	6.2 (1.0)	6.6 (1.0)	1.13
14. HU is effective	6.2 (1.1)	3.0/7.0	5.0	7.0	7.0	6.1 (1.1)	6.4 (1.2)	0.69
15. HU is safe	6.2 (1.1)	3.0/7.0	5.0	7.0	7.0	6.0 (1.1)	6.4 (1.2)	1.02
Understand	***5.8 (1.3)***	***2.3/7.0***	***5.0***	***6.0***	***7.0***	***5.7 (1.2)***	***6.0 (1.4)***	***0.90***
16. Understand how HU works	6.0 (1.2)	3.0/7.0	5.0	7.0	7.0	5.8 (1.2)	6.3 (1.2)	1.04
17. Could explain how HU works	5.7 (1.4)	1.0/7.0	5.0	6.0	7.0	5.7 (1.3)	5.8 (1.7)	0.31
18. Know how HU works	5.7 (1.4)	3.0/7.0	5.0	6.0	7.0	5.5 (1.3)	6.1 (1.4)	1.29
Lab	***5.7 (1.2)***	***3.3/7.0***	***5.0***	***5.7***	***7.0***	***5.5 (1.2)***	***6.0 (1.1)***	***1.37***
19. Lab work is difficult[a]	5.7 (1.5)	2.0/7.0	5.0	6.0	7.0	5.4 (1.7)	6.2 (1.0)	1.69
20. Lab work is stressful[a]	5.8 (1.1)	3.0/7.0	5.0	6.0	7.0	5.8 (1.0)	5.8 (1.2)	0.06
21. Getting labs done is hard[a]	5.5 (1.6)	1.0/7.0	5.0	5.5	7.0	5.2 (1.8)	6.1 (1.2)	1.43
Pharmacy	***5.7 (1.6)***	***1.0/7.0***	***5.0***	***6.0***	***7.0***	***6.4 (0.8)***	***4.6 (2.0)***	***0.39******
22. Difficulty getting HU from pharmacy[a]	5.7 (1.7)	1.0/7.0	5.0	6.0	7.0	6.3 (0.9)	4.8 (2.1)	3.18**
23. Hard to find nearby pharmacy with HU[a]	5.5 (1.9)	1.0/7.0	5.0	6.0	7.0	6.4 (0.8)	4.2 (2.3)	4.30***
24. Working with pharmacy is stressful[a]	5.8 (1.6)	1.0/7.0	5.0	5.5	7.0	6.4 (0.8)	4.9 (2.1)	3.26**
Total	***5.8 (0.8)***	***3.8/7.0***	***5.4***	***5.9***	***6.3***	***5.8 (0.6)***	***5.8 (1.0)***	***0.06***

Notes: Subscale and total scores are in bold, italicized font (subscale and total scores are average item scores for constituent items [eg, total of all items divided by number of items]). Items are indicated by number under subscales. Item descriptions are summaries of item content; for exact item wordings, please contact the authors. [a]Reverse scored item. **p < 0.01; ***p < 0.001; *df* for *t*-tests=38.

Abbreviation: HU, hydroxyurea.

Reliability

All subscales showed very good to excellent internal consistency, and the total score had excellent internal consistency (Table 3). Test-retest reliability was also strong (r ≥0.60) for all subscales except Cost. Total score test-retest reliability

Table 3 HEAL Subscale and Total Score Reliability

Subscale	Internal Consistency (Alpha)	Test-Retest Reliability		Validity Correlations					
		r	t (df=15)	GAR			MEMS	Lab Values	
				Participant	Provider	Composite		HbF	ANC
Dose	0.70	0.94***	1.78	0.34*	0.05	0.17	0.18	0.22	−0.14
Remember	0.90	0.75***	1.13	0.47***	0.18	0.31*	0.33	0.53**	−0.24
Plan	0.78	0.60*	0.93	0.07	0.18	0.16	−0.04	0.11	0.26
Cost	0.88	0.06	0.05	0.14	0.42**	0.39*	−0.22	0.23	−0.06
Effectiveness	0.91	0.65**	0.40	0.30*	0.48**	0.49**	0.01	0.13	−0.15
Understand	0.95	0.80***	0.86	0.23	0.28*	0.31*	−0.23	0.15	−0.34*
Lab	0.77	0.62**	0.99	0.25	0.24	0.30*	−0.34	0.19	0.04
Pharmacy	0.93	0.83***	0.22	0.00	0.01	0.01	−0.15	0.03	−0.04
Total	0.88	0.82***	0.20	0.38*	0.35*	0.42*	−0.06	0.37*	−0.14

Note: *p < 0.05; **p < 0.01; ***p < 0.001.
Abbreviations: GAR, global adherence rating; MEMS, medication event monitoring systems; HbF, fetal hemoglobin; ANC, absolute neutrophil count.

was excellent (r = 0.82). *T*-tests comparing initial and retest scores for HEAL subtests and total scores were not statistically significant (all p > 0.10), indicating stability over a short period of time.

Validity

HEAL scores were validated using GAR measures, MEMS values, and lab values (Table 3). Results demonstrated statistically significant (1-tailed p < 0.05) correlations between HEAL Total scores and patient, provider, and composite GAR scores. Patient GAR scores were significantly associated with HEAL Dose, Remember, and Effectiveness subscales, whereas provider GAR scores were significantly correlated with Cost, Effectiveness, and Understand subscales. The composite GAR score was significantly associated with HEAL Cost, Effectiveness, Understand, and Total scores. Although patient GAR and MEMS were highly related (r = 0.78, p < 0.001), MEMS score failed to correlate significantly with any HEAL score, possibly because of the small sample size (N = 19) for MEMS results. HbF values were significantly correlated with HEAL Total and Remember scores, whereas ANC values were significantly negatively correlated only with HEAL Understand scores.

Discussion

This manuscript provides data supporting the reliability and validity of the first multidimensional patient-report measure to specifically address HU adherence in individuals with SCD. Our Hydroxyurea Evaluation of Adherence for Life (HEAL) scale data show that subscale and total scores have strong internal consistency, test reliability, and validity, supporting the use of the HEAL scale to measure HU adherence in people with SCD. Additionally, data obtained using the HEAL scale provides a first look into self-reported adherence rates and challenges in a sample of children and adults with SCD treated with HU.

The HEAL scale is brief and encompasses a range of relevant content domains. Analyses demonstrated very good to excellent internal consistency reliability of all subscales and the total score, demonstrating that items on the same subscales measured the same constructs. Test-retest reliability correlations for all subscales except Cost were strong, and *t*-tests during the test-retest period showed no change in subscale scores during the test-retest period, indicating that HEAL ratings of adherence are stable over a short-period of time averaging approximately 7 weeks. The low test-retest reliability for the Cost subscale was not anticipated and should be addressed with future research. The Cost subscale had

the highest adherence score and the second lowest variability of all HEAL subscales (Table 2), likely because of clinic and government programs ensuring access to HU for the population served in this study. It is likely that in a setting with less consistent cost coverage, Cost scores would show greater variability and stronger psychometrics.

Validity results showed significant correlations between global self-report HU adherence ratings on a visual analogue scale (GAR) and HEAL Total scores, as well as some specific HEAL subscale scores. These findings support the validity of the total HEAL scale score as reflecting participants' general impressions of their own adherence. Findings with HEAL subscales indicate that participants base their general impressions of HU adherence on the amount and timing of taking HU, as well as their impressions of HU effectiveness. Specifically, participant conceptualization of adherence to HU treatment is driven largely by providing the correct dose (Dose subscale) at the correct time (Remember subscale), resulting in effective treatment. Other adherence domains, such as planning, cost, understanding the medication, lab issues, and pharmacy issues, may be important for adherence in individual cases but are not as central to ratings of overall patient adherence to HU treatment, across the entire sample.

The validity of the HEAL scale was further supported by significant correlations with provider-rated adherence on the GAR. In addition to correlating significantly with total HEAL scores, provider GAR was significantly associated with HEAL Cost, Effectiveness, and Understand scores. These latter findings suggest that, in contrast to patient global HU adherence ratings, provider global HU adherence ratings may be driven more by feasibility and effectiveness of treatment in the form of patient experience of access, understanding, and efficacy.

Importantly, provider and patient GAR were significantly correlated ($r = 0.44$, $p < 0.01$), supporting the validity of the GAR measures and indicating that patients and providers show moderate agreement on HU adherence. A composite GAR based on the average of patient and provider GAR scores was significantly correlated with total HEAL scores, supporting the validity of the HEAL scale as a HU adherence measure. The Remember, Cost, Effectiveness, Understand, and Lab subscales of the HEAL scale were significantly correlated with patient-provider GAR composite, further supporting the validity of those subscales as reflective of HU adherence.

The total HEAL and Remember scores were significantly (positively) correlated with HbF and the Understand subscale was negatively correlated with ANC values. These findings support the validity of the HEAL scale through direct measures of HU's mechanism of action. Given the importance of lab values for documenting outcomes of HU treatment, these findings indicate the clinical usefulness of the HEAL scale to assess adherence.

MEMS values were not significantly correlated with HEAL Total or subscale scores, despite MEMS data being highly correlated with participants' global self-report of HU adherence on the GAR ($r=-0.78$, $p < 0.001$), but not with provider GAR scores ($r = 0.36$, $p = 0.17$). Thus, MEMS data support the validity of the patient GAR ratings, which in turn were significantly correlated with HEAL scores though did not support HEAL subscale or total score validity. MEMS data were acquired on a small number of participants, which may have provided insufficient power and variability. Additionally, patients willing to use the MEMS system may have differed in some unknown systematic way from those who did not, potentially limiting the range of adherence behaviors in that sample. The MEMS system measures one index of adherence (opening pill bottles) but is not a comprehensive or fail-safe measure of the complex set of adherence behaviors; it may be that most HEAL adherence domains show limited overlap with opening/closing pill bottles. Research with larger samples is recommended and some correlation of MEMS and HEAL scores is expected.

HEAL results also provide new insights into HU adherence based on the current sample. Adherence to HU is good to excellent in 75% of patients and fewer than 25% of patients have mild or worse problems with non-adherence. Scores also indicate that the domains of greatest risk for nonadherence involve organization and time management – planning and remembering HU. In those domains, 25% of the sample reported non-agreement with adherence behaviors, identifying the importance of addressing organization and time management of dosing (remembering and planning doses) when prescribing HU. Conversely, greatest adherence domains were cost, providing the correct dose of HU, and believing that HU is effective; in these domains, reinforcing knowledge and beliefs may be sufficient, since adherence is already likely to be strong. Prior research has confirmed that caregiver HU knowledge varies by clinic/institution, suggesting that our findings may vary by study sample.[21] Resources and support for IHTC patients and caregivers includes care coordination for patients across the lifespan, beginning when an infant is identified on the newborn screen and continuing throughout adulthood. Caregivers and patients receiving care coordination may be more knowledgeable

about HU and the importance of adherence. HEAL scales may help institutions and care providers identify patients who have HU-related knowledge gaps; identifying these gaps may drive increased HU adherence.

The HEAL scale is based on patient/caregiver self-report and provides scores for multiple potential dimensions of adherence. The HEAL scale is brief, easy to complete and score, thus, could be used to track adherence in multiple domains over time, revealing different challenges or improvements with situational change or systematic intervention. Furthermore, the HEAL scale yields important data from the patient/caregiver's perspective. The HEAL scale has potential limitations (discussed below); even so, patient/caregiver-report is a critical and immensely valuable domain of medical evaluation.[38] Additionally, patient/caregiver beliefs and behaviors are important underlying contributors to adherence, and adherence interventions require addressing patient beliefs and behaviors. Self-report scales are inexpensive, can be obtained at a distance (eg, by phone or online), and are quick and easy to score, making them quite practical.

The HEAL scale also provides scores for multiple dimensions of adherence, in contrast to single-value, global adherence measures (including global self-rated adherence and "objective" measures based on cap openings or medication pill counts). Adherence measures that provide only a single value or score are valuable for identifying adherence problems, but they do not allow for an understanding of the factors contributing to adherence or nonadherence. In contrast, the multidimensional HEAL subscales allow for a more detailed understanding of factors involved in adherence, potentially facilitating better communication about adherence and more targeted interventions. For example, the most difficult domains of adherence to HU treatment, on average, appear to be remembering and planning. Reports of evaluating impact of reminders show improved adherence and laboratory values.[25,39] In certain cases, however, the changes did not persist after the reminders ended, suggesting a need for continued monitoring of adherence to tailor interventions specific to each patient's needs.[25] Therefore, we believe that the HEAL scale offers significant clinical potential for understanding adherence in individuals with SCD and significant research potential for understanding successes in and threats to HU adherence in SCD patient populations.

Notably, our data come from a regional center in a high-income and resource-rich nation. The HEAL scale may show different barriers to adherence in resource-poor settings. Items related to Cost, Laboratory, and Pharmacy may be more important to patients in those settings. Lack of knowledge and cost were the greatest barriers identified in Nigeria.[40] In Ireland, "recall barriers" were cited as the most difficult aspect of adherence for adolescents; this finding is similar to our data and relates to our Remember subscale.[41] We suspect that while cost may not be a barrier in all settings, patient and caregiver knowledge and remembering to take hydroxyurea are likely universally important factors of adherence in patients with SCD.

Limitations

In addition to limitations associated with self-report, several other characteristics of the present study should be considered when interpreting results. First, one of the primary validating measures for the HEAL scale (patient GAR) was also based on self-report, which could bias the results. On the other hand, the provider GAR provided strong validating support for the HEAL scale. MEMS scores were provided by only about half of the sample, limiting the variability and power of the MEMS as a validation tool. The sample size was small and required combination of caregiver- and self-report HEAL scale results across a wide age range. The HEAL scale should be used in the context of a broader assessment of adherence with appropriate understanding of the advantages and limitations of self-report. Additional research validating the HEAL scale with other measures of adherence in much larger samples of caregivers and patients is recommended now that initial reliability and validity have been evaluated. Research with larger samples is especially important because HEAL scale results indicate skewed (high) self-reports of adherence and limited variability at the low end of adherence (fewer than 25% of the sample showing mild or greater nonadherence), reflecting positive bias in self-report or an inherently high level of adherence to HU in this sample. Research with larger samples could interrogate potential sex or age-based differences as well. Finally, studies at diverse sites are recommended to investigate site-specific effects as prior research indicates site-specific variation.[21]

Conclusions

We developed and validated a novel, multidimensional self-report measure of HU adherence, which is brief and easy to complete, score, and interpret. Results showed high HU adherence rates in most domains, although organization and time

management were most challenging. The HEAL scale has potential as a clinical and research measure of HU adherence in the context of a broad adherence assessment. Additional psychometric and clinical research with the HEAL scale in larger, more diverse populations is recommended.

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