Digestive Diseases and Sciences
https://doi.org/10.1007/s10620-019-05621-7

ORIGINAL ARTICLE

Content Validity and Reliability of a Self-Report Measure of Medication Nonadherence in Hepatitis C Treatment

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Received: 19 December 2018 / Accepted: 8 April 2019

Abstract

Background Nonadherence to direct-acting agents (DAAs) for hepatitis C (HCV) decreases viral response. To measure nonadherence to DAAs, a reliable, valid, and easily implemented method is needed.

Aims The goals of this study were to refine a previously validated (in patients with hypertension) self-report measure of *extent of nonadherence* and *reasons for nonadherence* in the context of DAAs and to obtain initial evidence of content validity and reliability.

Methods Phase I involved two focus groups with patients with HCV ($n=12$) and one focus group with prescribers of HCV medications ($n=6$) to establish content validity of *reasons for nonadherence*. Subsequent cognitive interviews with patients ($n=11$) were conducted to refine items. Phase II was a prospective cohort study involving weekly administration of the refined measure by telephone to patients ($n=75$) who are prescribed DAAs to evaluate reliability and consistency with viral response.

Results In the cohort study, internal consistency ranged from acceptable ($\alpha=.69$) to very high ($\alpha=1.00$) across time points and was quite high on average ($\alpha=.91$). Across the 75 participants, there were 895 measurement occasions; of those, nonadherence was reported on only 27 occasions (3%), all of which occurred in the first 12 weeks. These 27 occasions represented 19 (26%) different individuals. At 12 weeks, 1 (1%) of patients had a detectable HCV viral load; at 12–24 weeks posttreatment, 4 (5%) had a sustained viral response. Nonadherent patients reported an average of 1.41 reasons for nonadherence.

Conclusions This multi-method study established content validity of reasons for nonadherence and reliability of extent of nonadherence. High rates of adherence and viral response were consistent with previous studies using other nonadherence measurement methods.

Keywords Adherence · Content validity · Cognitive interviews · Focus groups · Qualitative research · Psychometrics

Introduction

Chronic hepatitis C virus (HCV) infection remains a highly prevalent disease with a significant global burden. HCV affects approximately 180 million people around the world and is a leading cause of cirrhosis and liver cancer in the Western Hemisphere [1]. Although the prevalence of HCV is decreasing in the USA, the incidence of advanced liver disease associated with chronic HCV infection is predicted to increase, resulting in an estimated peak societal cost of 9.1 billion dollars in 2024 [2, 3]. HCV cure has been associated with reduced all-cause mortality [4]. Rapid and effective treatment for HCV therapy is thus an important public health imperative.

The introduction of interferon-free direct-acting antiviral (DAA) regimens has revolutionized the treatment of chronic HCV, with viral eradication rates above 90% [5]. However, suboptimal medication adherence may result in drug resistance and treatment failure [6, 7]. In order to identify patients who would benefit from adherence interventions, and to evaluate the effectiveness of such interventions, a measure is needed that can measure both extent of nonadherence and reasons for nonadherence, produce reliable and valid scores, and be implemented in routine clinical practice. Whereas various methods can be used to measure extent of nonadherence, only self-report can be used to measure reasons for nonadherence.

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Published online: 29 April 2019

In previous studies, various methods have been employed to assess extent of nonadherence, including pill count and electronic drug monitoring. These methods are impractical to implement in routine clinical practice due to cost and resources needed to collect and process the data. Self-report measures, including a visual analog scale and the AIDS Clinical Trials Group measure (ACTG), have been used in HCV patients without evidence of their reliability or validity in this patient population. The ACTG questionnaire confounds extent of and reasons for nonadherence, complicating evaluation of reliability and validity [8].

Previously, a two-domain self-report measure of medication nonadherence was developed that measures extent of nonadherence and reasons for nonadherence separately. In patients taking medications for hypertension [9, 10] or hyperlipidemia [11], extent of nonadherence items produced reliable scores (alphas ranging from 0.78 to 0.94), fit a single factor, and were correlated with concurrently assessed self-efficacy to take blood pressure medications [9, 10] and serum total cholesterol. [11] Furthermore, both baseline values and changes in extent of nonadherence predicted future cholesterol levels and changes in cholesterol over time [11]. In previous studies, patients taking medications for hypertension [9, 10, 12], hyperlipidemia [11, 12], diabetes [12], or coronary artery disease [13] endorsed various reasons for nonadherence both at a single time point and across repeated assessments. For example, in a prospective study involving repeated assessments among patients who are prescribed antihypertensive medications, nonadherent participants reported a mean of two reasons, and no single reason was endorsed by more than 40% of the sample [9]. These findings underscore the necessity of comprehensive assessment of reasons for nonadherence.

A measure that has been developed and validated in one chronic medical condition may yield different psychometric properties (e.g., reliability and relationships with other measures as evidence of validity) when applied to another population. To adapt this two-domain self-report measure for measuring nonadherence to DAAs, the first necessary steps are to ensure that *extent of nonadherence* items are suitable for these medications and to establish content validity of the *reasons for nonadherence* domain. Accordingly, in this two-phase study, focus groups and cognitive interviews were used to refine the measure to ensure its relevance for patients who are prescribed DAAs (Phase I). The refined measure was then administered to patients who are prescribed DAAs to assess the psychometric properties of the measure and to characterize both extent of nonadherence and reasons for nonadherence during treatment (Phase II).

Methods

Phase I: Qualitative Study: Refining Measure for HCV Medications

Design and Setting

Phase I involved a three-stage, iterative, qualitative study conducted in spring of 2013. Stage I involved two focus groups with HCV patients to adapt the list of reasons for nonadherence initially developed for hypertension. Stage II involved a focus group with providers who prescribe HCV medications to determine if additional reasons for nonadherence should be added and to assess the clinical utility of using the self-report measure. Stage III involved cognitive interviews with HCV patients to evaluate comprehension and to further refine the *extent of nonadherence* and *reasons for nonadherence* items.

For all three stages, patients were recruited from the HCV clinic at Duke University Medical Center (DUMC). Providers were recruited from the Department of Medicine at DUMC. This study was approved by the DUMC institutional review board.

Recruitment (All Stages)

A list of patients meeting initial eligibility criteria was obtained from providers in the HCV clinic. Inclusion criteria were age ≥ 18 years, confirmed diagnosis of HCV, and receipt of telaprevir-based triple therapy within 1 year prior. Telaprevir-based triple therapy was the dominant therapy for HCV at the time of recruitment and comprised oral telaprevir three times daily, oral ribavirin twice daily, and interferon injection at home once weekly for 12 weeks followed by ribavirin and interferon only for an additional 12 to 36 weeks, depending on early treatment response. Because the difficulties associated with interferon are documented [14–16] and are unique, and because interferon-free regimens would soon dominate the market, our adaptation of the measure focused on the two oral medications.

Recruitment letters were mailed to patients meeting eligibility criteria. A staff member called patients 1–2 weeks after mailing recruitment letters and conducted a screening interview to further assess eligibility using the following exclusion criteria: participating in a clinical trial of HCV therapy; unable to communicate in English or by telephone; unable to take medications unaided; and presence of health problems that would make participation difficult. Interested and eligible patients were scheduled for a focus group or cognitive interview. A reminder letter was mailed a few days prior to research visits.

For provider recruitment, a list of providers who prescribe HCV antiviral therapy at DUMC was obtained, which included nine physicians and physician assistants. A recruitment letter was sent via e-mail from the senior author. Interested providers were asked to contact the study coordinator and were scheduled for a focus group.

Stage I: Patient Focus Groups to Assess Reasons for Nonadherence

Procedures

Two focus groups were convened to discuss issues related to taking telaprevir and ribavirin. Based on the study team's experience and the literature [17], this sample size was expected to provide adequate information to confirm findings from the existing literature and determine if additional reasons for nonadherence would emerge.

This study involved a directed approach to content analysis, which is appropriate when prior research exists about a phenomenon but would improve from further description [18]. Accordingly, initial questions were open-ended, followed by probes about issues present in the literature to confirm if they were relevant to participants' experiences.

Written informed consent was obtained from all individual participants prior to the focus group discussions. A social psychologist with experience in qualitative data collection and analysis moderated the discussion, with a study coordinator or gastroenterologist serving as a note taker. The focus groups were digitally audio-recorded and transcribed. At the conclusion of the discussions, a self-report demographic questionnaire was administered. Patients received a meal and $25 for their time.

The transcripts were content-analyzed by the social psychologist and gastroenterologist. The codes included initial codes based on existing knowledge about barriers to medication adherence and emergent codes to reflect additional barriers to adherence. These emergent codes were refined by a systematic process of consensus among the two coders. Transcripts were managed in ATLAS.ti (Scientific Software Development GmbH, Charlottenburg, Germany).

Results

Recruitment letters were mailed to 64 patients; all of these patients subsequently received a recruitment telephone call. Two focus groups comprising six male patients each were conducted. As shown in Table 1a, the average age was nearly 56 years, all were married, and more than half were White, were college graduates, and were employed full time.

Themes that emerged from these focus group discussions are summarized in Table 2. Patients spoke of the multiple challenges they experienced while on the triple-therapy regimen. Prominent in these discussions was the impact of medication side effects such as irritability, depression, memory lapses, rash, anal-rectal discomfort, and fatigue. Patients noted the importance of having a flexible work schedule to deal with the fatigue and to accommodate the dosing schedule.

Patients also spoke of difficulties obtaining medications due to health-system barriers such as changes in insurance policies. In some cases, patients had to obtain a few doses from their provider to tide them over until their prescription was received by mail. Patients noted that the medications were expensive and that they could not have afforded treatment without insurance or a rebate for low-income persons.

Other challenges were related to dosing instructions. Patients spoke of difficulty adhering to the fat requirement for telaprevir. In one case, the need to fulfill the fat requirement caused a participant to miss a dose. Patients also described challenges following instructions to take the medications within a 2-h window and noted that they were supposed to skip a dose if they could not take the medication within that window. Patients devised strategies to help them adhere to the schedule, such as using smartphone reminders and having family members remind them. Accommodating the dosing and food schedules was particularly difficult for patients with comorbidities such as diabetes because they had competing dosing/food schedules.

Table 1 Characteristics of (a) focus group patients ($n=12$), (b) cognitive interview patients ($n=11$)

Demographic variable	
(a)	
Age, mean (SD)	55.5 (4.8)
White, *n* (%)	8 (66.7)
Married, *n* (%)	12 (100.0)
Male, *n* (%)	12 (100.0)
College graduate, *n* (%)	6 (50.0)
Employed full time, *n* (%)	8 (66.7)
(b)	
Age, mean (SD)	56.6 (5.9)
White, *n* (%)	7 (63.6)
Married, *n* (%)	9 (81.8)
Male, *n* (%)	11 (100.0)
College graduate, *n* (%)	6 (54.5)
Employed full time, *n* (%)	7 (63.6)
Numeracy, mean (SD)	4.38 (0.96)
Health literacy, mean (SD)	34.36 (1.63)

Numeracy was assessed with the Subjective Numeracy Scale [23]; possible range of scores is 1–6, with greater scores indicating greater preference for words than numbers. Health literacy was assessed with the Short Test of Functional Health Literacy in Adults [22]; scores of 23–36 indicate adequate functional health literacy

Table 2 Emergent themes on medication nonadherence from patient and provider focus groups

Theme	Addressed in HTN version	Emerged in HCV discussions	
		Patient	Provider
Experiencing side effects	X	X	X
Having social support	X	X	X
Meeting dosing schedule	X	X	X
Dealing with comorbidities	X	X	
Difficulty obtaining medications	X	X	
Efficacy of medicine	X	X	
Affording medication	X	X	
Interfering with sex life	X	X	
Long-term consequences	X	X	
Making it part of your routine	X	X	
Discontinuing medication		X	X
Relationship with provider		X	X
Wanting to get cured		X	X
Fear of stigma		X	
Fearing experimentation		X	
Feeling too sick to take oral medications		X	
Getting blood test results		X	
Giving up desired drinks		X	
Hard on family		X	
Having a flexible schedule		X	
Helping others		X	
Interfering with work		X	
Meeting dietary requirements		X	
Missing doses		X	
Mode of transmission		X	
Seeking knowledge		X	
Sleeping through dose		X	
Wanting to be there for family		X	
Worrying about recurrence		X	
Believing it would not go away		X	
Knowing what they are getting into			X
Understanding dosing instructions			X
Accessing provider			X
Assessing adherence			X

HTN hypertension, *HCV* hepatitis C virus

Despite the difficulty of adhering to the regimen, patients were motivated to adhere to treatment. Primary motivations for starting and adhering to treatment included a *desire for a cure* and *to be there for family*. Blood test results indicating viral response facilitated medication adherence, whereas blood test results indicating recurrence reduced adherence. Spousal involvement also served as both a facilitator and a barrier. Some patients said that they needed their spouses to be on board and remind them to take their medications. Others said that their spouses were "too supportive" to the point of "nagging." Some patients spoke of strained relationships with their spouses, which were exacerbated by irritability due to the medications.

During both focus groups, patients spontaneously raised issues around transmission and stigma. Patients were concerned with transmitting HCV to family members and children. Patients also felt that people, including providers, were more concerned with how they got the disease than about its cure. Due to the fear of stigma, some patients stated that they did not want to disclose their diagnosis to providers other than their HCV provider. One patient did not tell his wife and had his medications mailed to his work to avoid disclosure.

Patients also discussed the importance of the relationship with their provider for motivating adherence. Empathy and familiarity with the patient were cited as important factors for motivating adherence. In contrast, "poor bedside manner" and abruptness were perceived as having an adverse effect on motivation to take medications.

Refinements to Reasons for Nonadherence Measure Based on Patient Feedback

These findings were used to improve the content validity of the scale for HCV by accommodating HCV-specific reasons (i.e., *could not meet the food requirements; the medication was not working; the medication affected my sex life; I was too late with my dose*; *treatment was hard on my family; I was feeling too ill to take it;* and *I could not get answers to my questions about the medication*). In refining the measure, we also combined similar items into a single item to reduce the total number of reasons in the scale, thus reducing response burden.

Stage II: Provider Focus Groups to Provide Feedback on the Measure and Approach

Procedures

One focus group was conducted with prescribing physicians and physician assistants at DUMC who specialize in the treatment of HCV to provide feedback on the refined measure and its potential clinical utility. Written informed consent was obtained prior to the discussion. The conversation began with an open-ended question about how providers assess patient medication adherence and how confident they are in the accuracy of their adherence assessments. Providers were then asked about their opinions of methods for assessing adherence, including self-report, electronic drug monitoring, and refills. Providers were also asked about their perceptions of barriers to and facilitators of medication adherence. At the end of the discussion, providers were asked to review our

refined *extent* and *reasons* items resulting from the HCV-patient focus groups and provide feedback. To ensure content validity of the reasons measure, providers were asked to comment on whether the *reasons* items were comprehensive in addressing the nonadherence issues encountered in clinical practice and/or research. Providers were also asked about the feasibility and likelihood of using this two-domain measure in research or clinical practice. The discussion was digitally audio-recorded and transcribed. Providers received a meal and $100 for their time. Data were analyzed using the same approach described for Stage I.

Results

The provider focus group comprised two physician assistants and four physicians. All were White, and 50% were female. Providers were not very confident in their ability to accurately assess adherence. No provider reported using a standardized method for assessing adherence; rather, all used a clinical interview. Providers reacted favorably to the idea of incorporating a brief, reliable, and valid self-report measure into clinical care to help them identify patients who miss doses and assess reasons for missing doses. Providers noted a lack of resources for following patients between biweekly visits and felt that having a standardized method for assessing adherence between visits would be valuable and allow them to follow up with patients who are having difficulties. Furthermore, they perceived a self-report measure as preferable to electronic drug monitoring (EDM) due to infeasibility of using EDM in clinical practice and concerns about validity (i.e., "just because a patient opens it does not mean that the patient takes it"). Providers felt it would be important to assess adherence soon after initiating the HCV regimen so that lack of understanding could be resolved quickly, thereby maximizing chances of treatment efficacy.

Facilitators of patient adherence perceived by providers included a good patient-provider relationship, social support, and desire to be cured. Barriers to patient adherence included side effects, lack of social support, and difficulty of the dosing schedule and side effects (Table 2).

Refinements to Reasons for Nonadherence Measure Based on Provider Feedback

Provider reactions to the draft self-report measure were overwhelmingly positive. Providers suggested revisions to the *reasons for nonadherence* items based on their clinical experience, including using *sick* instead of *ill* and adding *I was asleep*. These revisions were made to the *reasons for nonadherence* measure resulting from the patient focus groups, which was then evaluated in the cognitive interviews with patients (versions evaluated in cognitive interviews available from the first author).

Stage III: Patient Cognitive Interviews to Evaluate and Refine the Extent of and Reasons for Nonadherence Domains

Procedures

An initial round of cognitive interviews was conducted to evaluate patients' understanding of and responses to the items. After Round 1, the research team convened to discuss revision, addition, or deletion of items. The team deemed it necessary to conduct a second round of interviews to evaluate the changes. We aimed to recruit at least ten individuals based on common practice and the literature indicating that > 80% of themes are identified after eight individual interviews [19, 20].

Because the measure had been previously developed and evaluated, albeit in a different population (i.e., patients prescribed antihypertensive medications), retrospective verbal probing was used, in which patients first completed the instrument unaided and then the interviewer probed about the instructions, questions, and response scales [20]. The cognitive interviews were conducted by a social psychologist with a study coordinator or gastroenterologist taking notes. Responses were logged by the interviewer and note taker.

Patients were recruited from the same list of patients that was used to recruit for the focus groups. Patient focus group participants were eligible to participate in the cognitive interviews; these individuals provided evidence of content validity via member checks [21]. Patients provided written informed consent and then completed the items unassisted. If they reported perfect adherence on the *extent of nonadherence* items, patients were asked to consider the reasons for nonadherence hypothetically.

Three foci were investigated: clarity of items, response scales (*none of the time…every time; never…always; disagree strongly…agree strongly*), and recall period (7-day vs. longer). For the *extent of nonadherence* items, patients were probed about their understanding of the items, including specific phrases such as "*as prescribed"* and "*had a hard time*." Because participants were expected to provide consistent responses across items (i.e., because the items were designed to measure a single construct), when they did not provide the same response to each *extent of nonadherence* item, they were asked to explain their understanding of the difference in meaning of the items. Patients were also asked how difficult it was to select a response on the various response scales and how well they thought the response options matched the questions. They were also asked about the 7-day recall period and to consider alternative recall periods, such as 14 days and 1 month.

At the end of the interview, patients completed a self-report measure of demographic characteristics, health literacy, and numeracy. Health literacy was assessed with

the short Test of Functional Health Literacy in Adults (S-TOFHLA) [22]. Numeracy was assessed with the Subjective Numeracy Scale [23]. Patients received $25 for their 1-h participation.

Results

Forty-eight recruitment letters were mailed, with 42 of those mailed to patients who had received invitations for the focus groups. Two rounds of cognitive interviews were conducted with 11 males (Round 1 $n=6$; Round 2 $n=5$). As shown in Table 1b, the average age was 56.6 years, the majority were married, White, college graduates, and employed full time. All patients were classified as having adequate functional health literacy.

Cognitive interview results for both rounds are summarized in Table 3. In Round 2, the items *I missed my medicine, I skipped a dose of my medicine,* and *I did not take a dose of my medicine* were interpreted as intended and retained for the final version. All patients preferred the *none of the time* to *every time* response scale to those anchored by *never…always* and *strongly disagree… strongly agree*; therefore, it was retained for the final version. Although two patients noted that 1 month was more representative of behavior than 7 days, they suggested that anything greater than 2 weeks would be too long to allow accurate responding. All patients felt that 7 days was a reasonable time frame; it was considered long enough to reflect more general patterns, but it was not so long that they would forget. Thus, as with the first version of the scale used in patients with hypertension [10], we retained a 7-day recall period.

Reasons for Nonadherence

Patients generally agreed with the inclusion of all of the items in the *reasons for nonadherence* domain. Two additional reasons were suggested, each by one participant: not getting enough water to drink and not having medications with him/her; both were added to the scale. Patients felt that the response scale appropriately matched the items. Patients also felt that a 7-day recall period was optimal for recall of reasons for nonadherence. The resulting HCV-specific measure (Table 4) was used in the prospective longitudinal study.

Phase II: Prospective Cohort Study

Design

Our goal was to conduct a prospective cohort study among patients receiving standard-of-care treatment for HCV. This study, which was conducted from August 2014 to April 2016, involved weekly administration of the revised self-report measure throughout treatment. In accordance with the treatment algorithm, most patients received treatment for only 12 weeks, but some received treatment for 24 weeks. Viral load was assessed at weeks 4, 12, and 24 weeks (if still on treatment). Sustained virologic response (SVR), which refers to sustained eradication of detectable virus, was assessed at 12 and 24 weeks after completion of therapy.

Setting

Because many Duke HCV patients are enrolled in clinical trials, this prospective cohort study was conducted at the Durham Veterans Affairs Medical Center. Approval

Table 3 Results of cognitive interviews assessing extent of nonadherence items

Round	Extent of nonadherence item	Results
1	I missed or skipped at least one dose of my medication	No issues
1	I missed or skipped a dose of my medication	No issues
1	I did not take my medication as prescribed	"As prescribed" refers to timing and food requirements; reads as a double negative when coupled with "never"
1	I had a hard time taking my medication exactly as directed	"Hard time" does not mean that dose was missed; may refer to side effects or taking late
1	I was not able to take all of my medication	"Not able to" refers to ability and does not mean that dose was missed
2	I did not take my medication exactly as prescribed	"Exactly as prescribed" refers to timing and food requirements
2	I did not take the prescribed amount of my medication	"The prescribed amount" is difficult to understand because medication came in blister packs, so the patient either took it or did not; reads as a double negative when coupled with "none of the time"
2	I did not take my medication as prescribed	"As prescribed" refers to timing and food requirements
2	I skipped a dose of my medication	No issues
2	I did not take a dose of my medication	May be interpreted as intentional missing
2	I missed my medication.	No issues

Table 4 Final two-domain measure of extent of, and reasons for, nonadherence to oral therapy for HCV

In order for hepatitis C medication to work, people have to take it as prescribed. For one reason or another, many people can't or don't always take all of their medication as prescribed. We want to know how often you have missed your hepatitis C medication. When responding, please think about your pills only (not interferon).

Over the past 7 days…	**None of the time**	**A little of the time**	**Some of the time**	**Most of the time**	**Every time**
I missed my medicine.	○	○	○	○	○
I skipped a dose of my medicine.	○	○	○	○	○
I did not take a dose of my medicine.	○	○	○	○	○

People miss doses for various reasons. Please tell us which reasons contributed to you missing a dose of your hepatitis C pills. When responding, please think about your pills only (not interferon).

Over the past 7 days…

I missed my dose because…	Not at all				Very much
I was out of my routine	○	○	○	○	○
I missed my dose because…	Not at all				Very much
I forgot	○	○	○	○	○
I missed my dose because…	Not at all				Very much
the medication caused side effects	○	○	○	○	○
I missed my dose because…	Not at all				Very much
I could not meet the food requirements	○	○	○	○	○
I missed my dose because…	Not at all				Very much
I did not have my medicines with me	○	○	○	○	○

Table 4 (continued)

I missed my dose because…	Not at all				Very much
I could not afford the medication	○	○	○	○	○
I missed my dose because…	Not at all				Very much
the medication was not working	○	○	○	○	○
I missed my dose because…	Not at all				Very much
I did not want others to see my medications	○	○	○	○	○
I missed my dose because…	Not at all				Very much
the medication affected my sex life	○	○	○	○	○
I missed my dose because…	Not at all				Very much
I was too late with my dose	○	○	○	○	○
I missed my dose because…	Not at all				Very much
I was asleep	○	○	○	○	○
I missed my dose because…	Not at all				Very much
there was no one to help me	○	○	○	○	○
I missed my dose because…	Not at all				Very much
treatment was hard on my family	○	○	○	○	○
I missed my dose because…	Not at all				Very much
I had other medications to take	○	○	○	○	○
I missed my dose because…	Not at all				Very much
I ran out of medication	○	○	○	○	○
I missed my dose because…	Not at all				Very much
I was afraid the medication would interact with other medication I take	○	○	○	○	○
I missed my dose because…	Not at all				Very much
I was feeling too sick to take it	○	○	○	○	○
I missed my dose because…	Not at all				Very much
I could not get answers to my questions about the medication	○	○	○	○	○

Cognitive interview results showed that it is necessary to include "I missed my dose because…" at the beginning of each reason for nonadherence to ensure patients report reasons for nonadherence rather than general experiences with the medication

was obtained from the VA Institutional Review Board and Research and Development Committee.

Participants and Recruitment

Patients were eligible if they had a diagnosis of HCV *recorded in the electronic medical record* and were planning to initiate DAA therapy in the next 6 months. Study staff mailed patients a recruitment letter and placed a recruitment call approximately 1 week later to describe the study, assess eligibility, and obtain verbal consent. Patients were excluded if they had already started their medications; were unable to communicate by telephone or were not going to have a telephone for the duration of treatment; were a resident in a nursing home or receiving home health care; were enrolled in the VA telehealth HCV adherence intervention that is offered as part of standard of care; had active substance abuse; or had at least one error on a validated six-item screener for cognitive impairment [24].

Procedures

After obtaining verbal informed consent, the research assistant obtained demographic information and administered two measures for the purpose of evaluating construct validity via correlations with *extent of nonadherence*: the Beliefs about Medication Questionnaire [25] (BMQ) and the short Medication Adherence Self-Efficacy Scale (MASES-R) [26]. After administering these measures, the RA obtained information about the days and times of day that participants would be available to participate in follow-up study phone calls. To reduce expectancy effects, participants were told that they would be called weekly throughout their treatment but were not told which day or time of day they would be called.

Adherence telephone calls occurred every week during treatment (up to 24 weeks), within a 5-day window to assist with scheduling (i.e., 5–9 days after the previous measurement). Each week, participants were administered the three-item *extent of nonadherence* measure. If participants indicated nonadherence, operationalized as a response other than *none of the time* to at least one item, then they received the 18-item *reasons for nonadherence* measure (Table 4). These data were not shared with the treating provider.

Per usual care, patients completed a blood draw at weeks 4, 12, and 24 (if still on treatment) so that viral load could be evaluated during treatment; viral load was characterized as detectable or undetectable. Viral load was also checked at 12 and 24 weeks after completion of therapy to detect whether patients achieved SVR; SVR was characterized as present or absent. A chart review was conducted after participants completed follow-up to ascertain viral load and SVR.

Analyses

Descriptive statistics (means and standard deviations for continuous variables and frequencies and percentages for categorical variables) were calculated for all demographic items. Internal consistency was calculated as a measure of reliability of the *extent of nonadherence* domain at each time point. Given that few patients reported nonadherence and the distribution of *extent of nonadherence* scores was skewed, a binary variable was created at each time point categorizing patients as adherent (*none of the time* to all three items) or nonadherent (any response other than *none of the time* to any item); Ns and percentages were calculated at each time point. Ns and percentages of participants having detectable viral load at weeks 4 and 12 and SVR are presented. SVR status was determined based on viral load at 24 weeks after treatment completion with the exception of patients who had missing values; in those cases, viral load at 12 weeks was utilized. Associations between *extent of nonadherence* and detectable viral load and SVR were examined using the Chi-square exact test to evaluate predictive validity. Because there was so little variability in extent of nonadherence, correlations with the BMQ and MASES-S were not calculated.

Analyses of *reasons for nonadherence* were conducted among the subset of participants who were nonadherent. Because there were so few instances of nonadherence and the distributions of *reasons* scores were skewed, a binary variable was calculated at each time point for each reason representing endorsement (anything other than *not at all*) or non-endorsement (*not at all*); Ns and percentages were calculated.

The primary goals of this study were to obtain descriptive data on self-reported nonadherence and to evaluate reliability of the measure across repeated assessments. Accordingly, no power analysis was performed. Our a priori goal was to enroll 75 patients, which we thought would be sufficient to achieve these goals.

Results

Recruitment letters were mailed to 125 patients, of whom 102 were assessed for eligibility by telephone (Fig. 1). Of the 82 who were eligible and provided verbal consent, 75 provided at least one assessment and were thus included in the analytic dataset. Demographic data were available for 74 participants, who were 60 years old on average and 93% male (Table 5). Just over one-third identified as White, and 60% as Black. Treatment regimens varied based on clinical decision making in the clinic. Approximately 85% of participants underwent treatment for 12 weeks, and all but one patient had all-oral therapy.

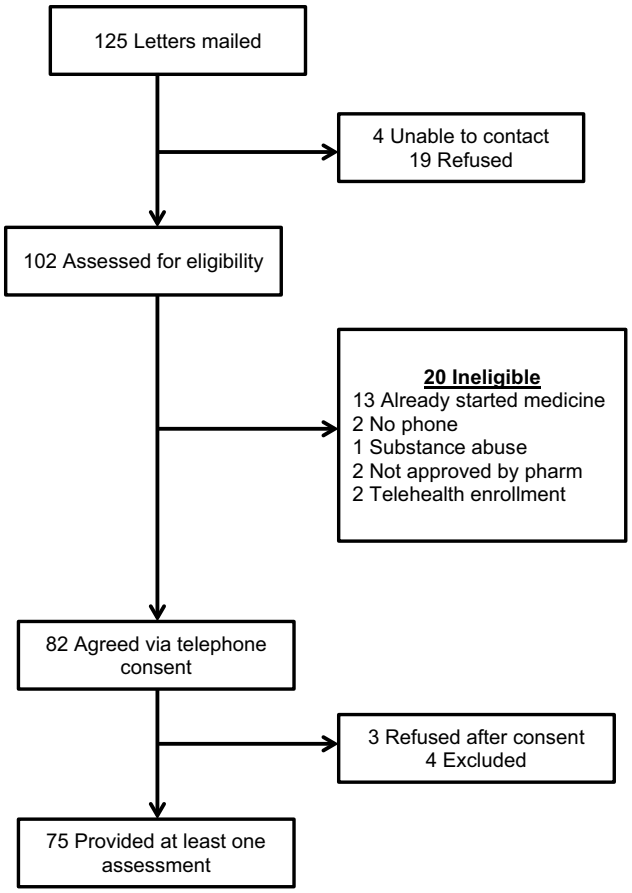

Fig. 1 Flow diagram for recruitment process

Extent of Nonadherence

Across the 75 participants, there were 895 measurement occasions; of those, nonadherence was reported on only 27 occasions (3%), all of which occurred in the first 12 weeks. These 27 occasions represented 19 (26%) different individuals; of those, 14 participants reported nonadherence in one call, three participants reported nonadherence in two calls, one participant reported nonadherence in three calls, and one participant reported nonadherence in four calls. Internal consistency ranged from acceptable ($\alpha = .69$) to very high ($\alpha = 1.00$) across time points and was quite high on average ($\alpha = .91$).

At 4 weeks, 34% of participants ($n = 26$) had detectable viral load; at 12 weeks, 1% ($n = 1$) did. Five percent ($n = 4$) had a detectable viral load at 12- or 24-week posttreatment follow-up (i.e., 95% had SVR). Due to the small number of participants with nonadherence occasions and with detectable viral load at all time points, bivariate associations between nonadherence and viral load were nonsignificant at all time points ($\chi^2 = 0.02$, $p = .882$ at week 4; $\chi^2 = 0.28$, $p = .595$ at week 12; $\chi^2 = 1.42$, $p = .23$ at posttreatment

Table 5 Baseline characteristics of participants in prospective cohort study ($n = 75$)

Characteristic	
Age in years, mean (SD)	60.49 (5.76)
Male, *n* (%)	68 (93.2)
Race, *n* (%)	
White	27 (37.0)
Black	44 (60.3)
Other	1 (1.4)
Latino/a ethnicity, *n* (%)	3 (4.1)
Marital status, *n* (%)	
Married or living in marriage-like relationship	30 (41.1)
Divorced/separated	29 (39.7)
Widowed	7 (9.6)
Single, never married	6 (8.2)
Education, *n* (%)	
High school or less	26 (35.7)
Some college or vocational school	38 (52.1)
Bachelor's degree	4 (5.5)
Postgraduate work	4 (5.5)
Employment status[a], *n* (%)	
Disabled	34 (46.6)
Full time	4 (5.5)
Part time	6 (8.2)
Retired	23 (31.5)
Searching for work	7 (9.6)
Not searching for work	6 (8.2)
Student	2 (2.7)
Income, *n* (%)	
< 10,000	9 (12.3)
10,000–19,999	25 (34.2)
20,000–29,999	13 (17.8)
30,000–39,999	9 (12.3)
≥ 40,000	14 (19.2)
Insurance[a], *n* (%)	
VA	67 (91.8)
Medicare	27 (37.0)
Medicaid	12 (16.4)
Tricare	5 (6.8)
Employer	6 (8.2)
Private insurance	3 (4.1)
Other	1 (1.4)
Duration of treatment, *n* (%)	
2 weeks	1 (1.4)
8 weeks	2 (2.7)
12 weeks	63 (85.1)
16 weeks	3 (4.1)
24 weeks	5 (6.8)
Previous treatment	19 (25.7)
Cirrhosis	31 (41.9)
Prior liver transplant	3 (4.1)
HCV genotype	

Table 5 (continued)

Characteristic	
1	60 (81.0)
2	11 (14.9)
3	3 (4.1)
Treatment regimen	
Ledipasvir/sofosbuvir	16 (21.6)
Ledipasvir/sofosbuvir/ribavirin	2 (2.7)
Simepravir/sofosbuvir	9 (12.2)
Simepravir/sofosbuvir/ribavirin	11 (14.9)
Sofosbuvir/pegylated interferon/ribavirin	1 (1.4)
Sofosbuvir/ribavirin	13 (17.6)
Dasabuvir/ombitasvir/paritaprevir/ritonavir	9 (12.2)
Dasabuvir/ombitasvir/paritaprevir/ritonavir/ribavirin	13 (17.6)
Beliefs about Medication Questionnaire	
Specific necessity	3.66 (0.75)
Specific concerns	2.10 (.070)
General overuse	2.04 (0.54)
General harm	2.82 (0.81)
Medication Adherence Self-Efficacy Scale	3.90 (0.27)

Demographic data were available for 74 of 75 participants. Among the 74 who provided data, data were missing for marital status ($n=1$), education ($n=1$), income ($n=3$), age ($n=1$), race ($n=1$), ethnicity ($n=2$), beliefs about medications ($n=2$), and medication self-efficacy ($n=1$)

[a]Participants could check all that apply, so numbers will not sum to 100%

follow-up). Associations did not differ by number of nonadherence occasions.

Reasons for Nonadherence

Across the 27 occasions of nonadherence, a range of 0–4 and mean of 1.41 reasons for nonadherence were endorsed. Endorsed reasons for nonadherence are reported in Table 6. The three most commonly endorsed reasons were *I forgot* ($n=7$); *the medication caused side effects* ($n=6$); and *I was out of my routine* ($n=6$). Two individuals provided reasons that were not on the measure, including being unable to swallow the medication and being hospitalized.

Discussion

Measures often are validated in a single disease and then implemented broadly without attention to adapting them for new health conditions. Our two-domain measure was designed with the intent that the three *extent of nonadherence* items could be administered across patient populations and would provide reliable and valid scores. In contrast, the *reasons for nonadherence* designed to be tailored to treatment regimens to ensure content validity [8, 10].

Table 6 Reasons for medication nonadherence endorsement

Reason endorsed	Number of times endorsed
"I forgot"	7
"The medication caused side effects"	6
"I was out of my routine"	6
"I ran out of medication"	5
"I was too late with my dose"	4
"I did not have my medicines with me"	4
"I was feeling too sick to take it"	2
"I was asleep"	2
"I had other medications to take"	1
"I was afraid the medication would interact with other medication I take"	1
"I was unable to swallow the medication"[a]	1
"I was hospitalized"[a]	1

[a]Reasons provided that were not on the measure

This multi-method study evaluated the performance of the *extent of nonadherence* items, initially validated for nonadherence to antihypertensive medications, for assessing nonadherence to DAAs for treatment of HCV. Making slight wording changes (e.g., removing "as prescribed") was necessary because phrases in the original version were interpreted differently in the context of HCV medications owing to specifics of the treatment regimen. For example, whereas "as prescribed" might mean once daily to a patient with hypertension, "as prescribed" meant with 20 g of fat and every 8 h (with a 2-h window around each dose) to a patient taking telaprevir-based triple therapy. The items were modified so that they would measure missed doses as well for patients with complex dosing instructions as they would for patients with simpler regimens. The updated items should produce reliable and valid scores across other treatment regimens as well, although this will need to be verified with future research.

In the prospective cohort study, few participants endorsed nonadherence, which was consistent with viral load results indicating high treatment response. Our finding of high adherence rates was consistent with several recent studies that were conducted in various populations and in which adherence was assessed with a variety of measurement approaches (electronic drug monitoring, pill count, and/or self-report) [27–29]. The high rates of adherence and viral response are unsurprising given the resources and multidisciplinary professional effort devoted to managing this group of patients at the VA medical center.

In addition to optimizing measurement of *extent of nonadherence*, this study evaluated how much the *reasons for*

nonadherence domain needed to be modified to capture relevant reasons for HCV medications. Although some reasons were consistent for blood pressure medications, statins, and DAAs, such as forgetting, other reasons were regimen specific, such as needing to meet food requirements. The result is a list of generalizable reasons that can be administered to other patient populations and disease-specific reasons that can be administered to patients taking DAAs.

The reasons for nonadherence to oral DAAs elicited during focus groups were similar to those reported in recent qualitative and quantitative studies with HCV-treated patients or providers. Barriers to adherence reported in the literature include changes to the daily routine, actual or feared side effects, family and work responsibilities, strained family relationships, pill burden, homelessness, substance use, a poor patient-provider relationship, lack of symptoms, and sleeping through doses [16, 28, 30, 31]. Prior studies have also highlighted fear of stigmatization among HCV patients as a barrier to medication adherence [32, 33]. Although hiding one's diagnosis and medications may be protective against social rejection, it reduces opportunities for social support, which is important for reducing medication nonadherence [31]. Facilitators to adherence reported in the literature include a positive patient-provider relationship, social support from family and friends, desire to clear the virus, viral response, and adherence to previous HCV regimens. Assessment of reasons for nonadherence is necessary to inform the content of behavioral interventions to increase adherence. For example, to reduce the impact of forgetting on nonadherence or to avoid sleeping through a dose, smartphone calendar reminders—a strategy used by some focus group participants—may prove useful.

The two-domain measure resulting from this study can be used in clinical and research settings to measure the implementation of the medication regimen. The three *extent of nonadherence* items should be administered to all patients to screen for nonadherence. Among patients endorsing nonadherence, a list of relevant reasons can be administered to identify patient-specific barriers to guide appropriate intervention. A two-step method involving a short screener followed by more detailed assessment is used in other clinical contexts, such as screening for depression in primary care [34]. Investigators seeking to apply the revised measure to other populations, or for newer DAAs, are advised to conduct formative research to determine whether additional, medication- or disease-specific reasons need to be added or, conversely, whether some reasons can be removed. As future studies are conducted to establish the content validity of the reasons for nonadherence measure with additional diseases, saturation will be achieved, such that few new reasons will emerge. A collection of reasons can be created from these efforts, from which clinicians and researchers could select a menu of reasons for nonadherence that are appropriate for the target disease or treatment. Repeated assessments of *extent of nonadherence* and *reasons for nonadherence* should be obtained to provide more precision about medication-taking behavior [35]. As noted by the providers in our focus group and by the results of our prospective cohort study, it may be particularly important to conduct repeated assessments of adherence early in HCV treatment to detect nonadherence and enable appropriate intervention to avoid development of drug resistance. As noted by patients, viral load results may positively or negatively affect subsequent medication adherence, so providers should keep this in mind when reviewing test results and adherence data with patients.

Although our findings of high adherence and treatment response in the prospective cohort study are desired clinically, they served as a limitation in the context of a research study. First, findings of high HCV medication adherence may not generalize to settings that lack a strong multidisciplinary clinical approach to HCV management. Second, reports of nonadherence may have been reduced due to the Hawthorne effect. Third, HCV treatment is undergoing rapid change. As the qualitative study was being completed, the standard of care changed from telaprevir-based triple therapy to treatment with all-oral, DAA therapy. Although the regimens used in the prospective cohort study are still being used in current clinical practice, new regimens are emerging [37]. Reasons for nonadherence may need to be updated as new therapies emerge.

There are other limitations to the studies reported herein. For one, the focus groups and cognitive interviews involved only married men, which may have precluded us from learning about experiences unique to unmarried individuals, who may have a different (or no) support system, and females. Relatedly, our cognitive interview participants had high health literacy and numeracy. Thus, we may not have identified issues with comprehension or response tendencies that would emerge in participants with other characteristics or with a larger sample size. Additionally, most participants in the prospective cohort study were male, potentially limiting generalizability; however, the population was reflective of patients with HCV within the VA health care system, which has the largest population of HCV in the USA [36]. Another limitation is that the measure was administered orally; future research will need to evaluate reliability and validity with self-administration of written surveys as this format may be more readily implemented in clinical practice. Finally, the measure was designed to assess implementation of the medication adherence regimen and, as such, does not measure initiation or discontinuation of medications. To measure these other behaviors, one could use a self-report measure designed to measure them or other nonadherence assessment methods (e.g., pharmacy refill).

Conclusions

In summary, this paper describes a qualitative process for adapting a self-report measure of nonadherence that was initially validated for antihypertensive medications to oral medications for chronic HCV. This process can provide a template for investigators who wish to expand the generalizability of validated self-report measures of patient medication nonadherence. The result of this process—a refined measure—could greatly improve the collection of clinically meaningful nonadherence data for clinical practice in HCV and, hopefully, other diseases. The measure may also allow more comprehensive collection of nonadherence data in clinical trials, where reasons for nonadherence are critically important in interpreting trial data. Finally, given that content validity has been established in the context of HCV regimens, research can move to understanding barriers and facilitators to implementation of this measure in clinical practice and testing the effectiveness of interventions tailored to reasons for nonadherence.

Acknowledgments The authors would like to extend special thanks to Andrew Muir, MD MHS, and Christine Hunt, MD, for their clinical input and Jamiyla Bolton, Jahdai Dawes, Leslie Gaillard, Tina Lucas, Elizabeth Strawbridge, and Cherisa Williams for their assistance with recruitment and data collection. The views represented in this article represent those of the authors and not those of the VA or the United States Government.

Funding Phase I of this study was supported by an investigator-initiated grant from Vertex Pharmaceuticals to Dr. Voils. Phase II of this study was funded by the Department of Medicine at Duke University Medical Center. Effort on this paper was supported by resources and facilities at the Veterans Affairs Medical Centers in Madison and Durham and by a Research Career Scientist award to Dr. Voils from the Health Services Research and Development (HSR&D) service of the Department of Veterans Affairs (VA; RCS 14-443) and a VA HSR&D Career Development Award to Dr. Gellad (CDA 14-158).

Compliance with ethical standards

Conflict of interest Dr. Gellad is cofounder and holds equity in Higgs Boson Inc. No other author declares a conflict of interest.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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