

Predictors of Objectively Measured Medication Nonadherence in Adults With Heart Failure

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Background—Medication nonadherence rates are high. The factors predicting nonadherence in heart failure remain unclear.

Methods and Results—A sample of 202 adults with heart failure was enrolled from the northeastern United States and followed for 6 months. Specific aims were to describe the types of objectively measured medication adherence (eg, taking, timing, dosing, drug holidays) and to identify contributors to nonadherence 6 months after enrollment. Latent growth mixture modeling was used to identify distinct trajectories of adherence. Indicators of the 5 World Health Organization dimensions of adherence (socioeconomic, condition, therapy, patient, and healthcare system) were tested to identify contributors to nonadherence. Two distinct trajectories were identified and labeled persistent adherence (77.8%) and steep decline (22.3%). Three contributors to the steep decline in adherence were identified. Participants with lapses in attention (adjusted OR, 2.65; $P=0.023$), those with excessive daytime sleepiness (OR, 2.51; $P=0.037$), and those with ≥ 2 medication dosings per day (OR, 2.59; $P=0.016$) were more likely to have a steep decline in adherence over time than to have persistent adherence.

Conclusions—Two distinct patterns of adherence were identified. Three potentially modifiable contributors to nonadherence have been identified. (*Circ Heart Fail.* 2012;5:430-436.)

Key Words: heart failure ■ medication adherence ■ patient compliance ■ self-care ■ sleep
■ World Health Organization

It is estimated that 20% to 50% of chronically ill patients in general,¹ and 40% to 60% of adults with heart failure (HF) in particular,² are nonadherent with medications. Number of hospitalizations, inpatient days, emergency department visits, healthcare costs, and mortality are higher in patients with HF who do not take their medications as prescribed.³⁻⁵

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Medication adherence is defined as the extent to which the patient's medication-taking behavior corresponds with an agreed-on medication regimen from a healthcare provider.⁶ Adherence requires both behavioral execution and persistence in medication-taking.⁷ Four components are involved in the assessment of medication adherence: (1) taking adherence (taking the prescribed medicines each day); (2) dosing adherence (taking the correct number of doses each day); (3) timing adherence (taking doses within ± 2 hours of the time prescribed); and (4) avoiding drug holidays (eg, >48 hours between doses).

A wide variety of factors have been identified as contributors to medication nonadherence. The World Health Organization (WHO) groups factors influencing adherence into 5 dimensions.⁸ The socioeconomic dimension includes race and income. Condition-related factors include symptoms and depression. The therapy-related dimension includes treatment complexity. Patient-related factors are both physical (eg, cognitive impairment) and psychological/behavioral (eg, health perceptions). Finally, healthcare system-related factors include the high costs of drugs and receipt of specialty services.

Although numerous studies of medication nonadherence in adults with HF have been conducted, several gaps remain in our knowledge.^{1,2} Most studies of medication adherence in HF are cross-sectional in design and sample sizes are often small. Many different tools are used in measuring adherence, which makes it difficult to compare across studies. Self-report is the most commonly used method of adherence measurement; we located only 4 studies using electronic monitoring

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in patients with HF.^{5,9-11} Bivariate analyses testing single hypotheses have failed to provide an adequate picture of the manner in which factors interact to contribute to medication nonadherence in patients with HF.^{12,13}

We previously demonstrated that adults with HF and excessive daytime sleepiness (EDS) self-reported more problems adhering to their medication regimen than those without EDS. Lapses in attention interfered with the vigilance needed to remember their medications, leading to reports of nonadherence.¹⁴ In this study we sought to build on these results and fill some of the knowledge gaps with objective data on medication nonadherence collected over a 6-month period using electronic monitoring technology manufactured by AARDEX (www.aardex.com), the Medication Event Monitoring System (MEMS). The specific aims of this study were to identify and describe common and distinct trajectories of nonadherence (eg, taking, timing, dosing, drug holidays) during a prospective study of adults with HF and to identify contributors to medication nonadherence using the 5 WHO model dimensions of adherence.

Methods

Design and Sample

The methods used in this study have been described previously and are summarized here.¹⁴ This was a prospective study of adults with Stage C chronic HF who were enrolled from 3 sites in the northeastern United States. One site was a university referral center, one was a Veterans Affairs Medical Center, and one was a regional medical center. Stage C, presence of previous or current symptoms of HF in persons with an underlying structural heart problem but managed with medical treatment, was confirmed based on echocardiographic and clinical evidence. Potential subjects were screened for visual and hearing adequacy and English literacy. Otherwise eligible individuals were excluded if they lived in a setting where medication administration was not an independent activity, if they worked nights or rotating shifts, or if they had renal failure requiring dialysis, an imminently terminal illness, plans to move out of the area, or a history of serious drug or alcohol abuse within the past year. Those with a history of major depressive illness were excluded because depression is known to influence self-care.¹⁵ Although both major and minor depression are associated with poor self-care,¹⁶ we excluded only those with major depression because some of the symptoms of depression mirror those of HF. Avoiding all symptoms of depression would have severely limited enrollment. Potential participants were screened with the 9-item Patient Health Questionnaire.¹⁷ Those reporting ≥ 5 of the 9 symptoms more than half the days in the past 2 weeks were excluded if one of the symptoms was depressed mood or anhedonia.

Institutional Review Board approval was obtained from all 3 sites and all participants gave written informed consent. Data were collected at baseline and 3 and 6 months later by research assistants during home visits. These data were collected between 2007 and 2010.

In total, 280 subjects were enrolled in the study. Attrition from the study was 13.6%; 242 finished the 6-month study and were included in the analytic data set. Reasons for attrition included death ($n=6$), too ill to continue ($n=7$), withdrawal ($n=5$), and loss to follow-up ($n=20$). For the current study, taking, dosing, timing, and drug holiday components of medication nonadherence could only be described in the 202 subjects who used the MEMS device during the 6 months of the study. The 40 subjects who completed the study but did not use the MEMS device for the full 6 months were more likely to be nonwhite, to be taking a drug that needed to be taken more than once daily, to report worse health status, and to have objectively measured lapses in attention.

Measurement

Adherence to the medication regimen was assessed using MEMS. Unobtrusive microelectronic monitoring devices in the caps of medication containers document each time that the cap is removed from a medication vial. Real-time data are collected in the device and later downloaded to a personal computer and integrated with other data for analysis. Crossvalidation studies have shown that electronic monitoring using MEMS is more sensitive, reliable, and valid than other measurement techniques such as pill counts, biochemical assays, collateral reports, or clinical judgment.¹⁸

MEMS data were collected on one medication scheduled to be taken at a fixed time. Others have shown that patient adherence with medications is generally consistent among drugs in the regimen when the side effects of specific medications are accounted for; thus, one medicine was used to minimize subject burden.¹⁹ Our first choice of drugs was an angiotensin-converting enzyme inhibitor because angiotensin-converting enzyme inhibitors may be taken more often in multiple daily doses than other drugs for HF and most patients are prescribed an angiotensin-converting enzyme inhibitor. If patients were not taking a multiple-dose angiotensin-converting enzyme inhibitor, an angiotensin II receptor blocker or a β -blocker was monitored. The medicine allocated to the MEMS device was to be taken twice daily by 57.9% of participants and ≥ 3 times daily by 3% of participants; others were taking their medicines once daily. Participants were fully informed about the functioning of the MEMS device and instructed on how to use and integrate the device into their daily routine. For patients who routinely used a pill box to organize their medicines, we asked them to use the MEMS container in addition to the pill box. To facilitate this, a note was placed in the appropriate slot of the pill box to remind them to take the medicine out of the MEMS container. MEMS data were collected over the entire 6-month interval and downloaded at 3 and 6 months. Deviations in use such as accidental openings were noted in study diaries and used to correct the MEMS data before analysis. There is evidence that use of the MEMS may influence medication-taking behavior initially. That is, patients may take their medications more consistently at first because they know they are being monitored.²⁰ We took this into consideration by modeling trajectories of nonadherence as a function of MEMS data in 2 separate intervals.

The WHO dimensions were measured as follows (Table 1). Social and economic characteristics of race, household income, education, and practical support for self care were measured by self-report. Formal education is thought to be an inconsistent indicator of knowledge in the United States so education was measured indirectly using oral reading scores on the revised American National Adult Reading Test.²¹ Scores range from 0 to 50 reflecting the number of irregular words (eg, bouquet, capon) pronounced correctly. Practical support for self-care was measured with a 7-item true/false survey measuring specific ways in which family and friends assist with the treatment regimen (eg, they remind me of things I need to do, they drive me places like the doctor's office, they help me interpret my symptoms).

Condition-related influences included comorbid illnesses, depression, EDS, functional class, physical limitations, symptoms, social limitations, and quality of life. The number of comorbid illnesses was abstracted at enrollment from the medical record by registered nurses using the Charlson Index. The total score was used in analysis. Depression was assessed using the 2-item Patient Health Questionnaire.¹⁷ This short version of the 9-item Patient Health Questionnaire was used to avoid items assessing fatigue and sleepiness, which were measured in other ways. Dichotomized scores on the Epworth Sleepiness Scale was used to measure EDS.²² To assess functional class, research assistants interviewed patients about activities causing symptoms using a structured interview.²³ Interview results were used by a single board-certified cardiologist to score New York Heart Association functional class. Symptoms, physical limitations, social limitations, and quality of life were assessed using the Kansas City Cardiomyopathy Questionnaire, a 23-item disease-specific questionnaire.²⁴ Responses are scored on a Likert scale, summed, and standardized to a scale of 100 with higher scores indicating better health status.

Table 1. Factors Tested as Potential Contributors to Medication Nonadherence

1. Social and economic dimension
Race
Household income
Education
Practical support for self-care
2. Condition-related dimension
Comorbid illnesses
Depression
Excessive daytime sleepiness
NYHA functional class
KCCQ Physical limitations
KCCQ symptom frequency, burden, stability
KCCQ social limitations
KCCQ quality of life
3. Therapy-related dimension
No. of medications taken per day
Dosing frequency of medicine used in the MEMS device
4. Patient-related dimension
Sex
Perceived overall health
Knowledge of heart failure
Cognition and attentiveness
5. Healthcare system dimension
Cost of medications
Receipt of heart failure specialty services

NYHA indicates New York Heart Association; KCCQ, Kansas City Cardiomyopathy Questionnaire; MEMS, medication electronic monitoring system.

The therapy-related dimensions specific to medication adherence included the total number of prescription medications taken daily and the prescribed dosing frequency for the medication used in the MEMS device. To capture the number of routine medications, research assistants gathered information on every medicine taken during face-to-face visits, usually by direct review of medication containers.

Patient-related characteristics included sex, health perceptions, knowledge of HF, and cognition. Perceived overall health was measured with a single item: How would you rate your health? (fair, poor, good/very good). To assess HF knowledge, subjects completed the Dutch HF Knowledge Scale, a 15-item survey with a possible score range of 0 to 15. The scale measures HF knowledge in general, knowledge of HF treatments, and HF symptom recognition.²⁵ Higher scores indicate more knowledge. We previously demonstrated that lapses in attention were the primary cognitive contributor to self-reported medication nonadherence.¹⁴ So, dichotomized scores on the Psychomotor Vigilance Task were used as the measure of cognition; >4.69 (transformed) lapses was judged as an abnormally high level of inattention.²⁶

Healthcare system factors assessed were the participants' perception that the cost of medications was a factor impairing medication adherence (yes or no) and the receipt of HF specialty care (yes or no). Both of these factors were assessed by self-report.

Statistical Analysis

Latent growth mixture modeling was used to identify distinct trajectories of nonadherence. Growth mixture modeling identifies trajectories that vary around different means and have unique estimates

of variances, separate covariate influence, and homogenous within-trajectory growth. Unlike deterministic methods of clustering that involve minimizing within-group and maximizing between-group variance, growth mixture modeling uses a model-based naturalistic approach wherein probabilities of trajectory membership are calculated. Cases are then assigned to a "most likely" trajectory and uncertainty in trajectory membership is quantified. Our growth mixture modeling included taking (%), timing (%), and dosing adherence (%) and drug holidays (yes or no) recorded from the MEMS during the first 3 months and the second 3 months of the study. We compared fit among models with 2 to 5 trajectories using Mplus Version 6.0 (Los Angeles, CA). The Lo-Mendell-Rubin adjusted likelihood ratio test ($P<0.05$),²⁷ parametric bootstrapped likelihood ratio test ($P<0.05$),²⁸ Bayesian Information Criterion,²⁹ convergence (entropy near 1.0), the proportion of sample in each trajectory (not <5%), and posterior probabilities (average posterior probability of belonging in "most likely" trajectory near 1.0) were used to compare alternative models (eg, k versus $k-1$ trajectories) and quantify model uncertainty.^{30,31} Changes in adherence by trajectory were quantified using pairwise t tests, repeated-measures analysis of variance, or McNemar tests where appropriate. Out of concern for the potential effects of model saturation, predictors of unfavorable trajectories of medication adherence were quantified using backward stepwise logistic regression modeling (P set to 0.20) in StataMP 11 (College Station, TX). ORs and 95% CIs were calculated for each model factor, and model fit was quantified using χ^2 , McFadden pseudo R^2 , and Hosmer-Lemeshow goodness-of-fit tests.

Results

The characteristics of these 202 subjects at study enrollment are shown in Table 2. The average subject was 63 years old, male (65.4%), white (68.3%), and had 2.8 comorbid conditions. Most (54.9%) had government health insurance; only one individual was uninsured. Overall, there were significant yet heterogeneous increases in medication-taking nonadherence (81.3%±25.8% versus 87.2%±19.4%; $t=4.51$; $P<0.001$), dosing nonadherence (73.2%±30.1% versus 79.7%±23.8%; $t=4.89$; $P<0.001$), and timing nonadherence (59.0%±32.8% versus 65.5%±29.6%; $t=4.99$; $P<0.001$) over time (ie, comparing data from the second 3 months with data from the first 3 months of the study). Comparable proportions of patients took drug holidays during the second 3 months compared with the first 3 months of the study (47.0% versus 47.5%; $P=0.177$).

Using growth mixture modeling, we identified 2 distinct trajectories of nonadherence. Both the Lo-Mendell-Rubin test (781.8; $P=0.0007$) and parametric bootstrapped likelihood ratio test (811.23; $P<0.001$) supported 2 versus one trajectory, model entropy was 0.975, and sample size-adjusted Bayesian Information Criterion was 10719.3. Based on observed characteristics, we labeled the first and largest trajectory ($n=157$ [77.8%]) as a "persistent adherence" subgroup; average posterior probability for membership in this trajectory was 98.3%. We labeled the second trajectory ($n=45$ [22.3%]) as a "steep decline" subgroup; average posterior probability for membership in this trajectory was 99.6%.

As displayed in the Figure, those in the persistent adherence subgroup had minimal changes in taking adherence during the study, whereas those in the steep decline subgroup had considerable declines in taking adherence during the study ($F=80.33$; $P<0.001$). Similar patterns existed among the 2 groups with respect to changes in dosing adherence ($F=72.9$; $P<0.001$) and timing adherence ($F=58.62$; $P<0.001$). In addition, the frequency of drug holidays

Table 2. Characteristics of the Sample

	(n=202)
Age, y	63.1±11.8
Male	132 (65.4)
Race/ethnicity	
White	138 (68.3)
Nonwhite	64 (31.7)
Education	
Less than high school	17 (8.4)
High school	68 (33.7)
Some college	117 (57.9)
ANART-R score	30.9±11.2
Household income	
More than enough	78 (38.6)
Enough	92 (45.5)
Not enough	32 (15.8)
Perceived overall health	
Good, very good	103 (51.0)
Fair	78 (38.6)
Poor	21 (10.0)
Total no. of comorbid conditions on Charlson Index	2.8±1.8
NYHA functional class	
Classes I and II	49 (24.3)
Class III	119 (58.9)
Class IV	34 (16.8)
Daily dosing with MEMS	
Once daily	79 (39.1)
Twice daily	117 (57.9)
Three times or more daily	6 (3.0)
No. of daily medications	9.9±3.8
High lapses on the PVT	71 (35.9)
Excessive daytime sleepiness (≥6)	112 (55.5)
Patient Health Questionnaire (PHQ2)	0.8±1.0
Self-care support score	1.5±1.5
Medication costs impair adherence	20 (10.3)
KCCQ Physical Limit Score	71.6±22.0
KCCQ Symptom Score	76.3±19.4
KCCQ Social Limitations Score	68.4±25.3
KCCQ Quality of Life Score	66.7±23.3
Dutch Knowledge Scale Score	11.7±1.7

Mean±SD or column no. (%) are reported.

ANART-R indicates revised American National Adult Reading Test; NYHA, New York Heart Association; MEMS, Medication Event Monitoring System; PVT, psychomotor vigilance task; KCCQ, Kansas City Cardiomyopathy Questionnaire; PHQ2, 2-item Patient Health Questionnaire.

increased slightly for patients in the persistent adherence subgroup (38.9%–43.9%; $P=0.172$) and increased moderately in the steep decline subgroup (77.8%–84.4%; $P<0.001$).

Determinants of steep declines in adherence are presented in Table 3 (model $\chi^2=24.7$, $P=0.0005$, pseudo $R^2=13.5\%$; Hosmer-Lemeshow=65.32, $P=0.636$). Based on the WHO model, 3 contributors to a steep decline in adherence were

identified. Specifically, participants with lapses in attention, those with EDS, and those with ≥ 2 medication dosings per day were more likely to have a steep decline in adherence over time than to have persistent adherence.

Discussion

To the best of our knowledge, this is the first study to explore patterns of objectively measured medication adherence using a naturalistic rather than a deterministic approach in adults with HF. In this study we identified 2 distinct trajectories: persistent adherence and a steep decline in medication adherence. Taking, dosing, and timing adherence decreased significantly over time in the steep decline subgroup and drug holidays were more common. Three likely contributors to a steep decline in adherence were identified: lapses in attention, EDS, and dosing frequency. These factors represent 3 of the 5 WHO dimensions as predictors of nonadherence. No one dimension was overrepresented suggesting the usefulness of the WHO model in the analysis of this important issue.

The only therapy-related dimension we identified as important in medication nonadherence was dosing frequency, which has been identified repeatedly as an important factor influencing medication adherence in chronically ill populations.¹ Others have demonstrated that adherence is better with medications prescribed once versus twice daily.^{32,33} A similar relationship exists for once versus 3 times daily^{2,32,34} and once versus 4 daily doses.³⁴ Some have suggested that taking a medication 2 or 3 times daily is still better in promoting adherence than 4 times daily.³⁵ Timing adherence also improves when the dosing regimen declines.^{1,19} These results should serve to remind clinicians of the importance of streamlining the dosing schedule whenever possible.

Excessive daytime sleepiness contributed to a steep decline in medication adherence over time, confirming our prior results obtained by self-report in this same sample.¹⁴ In that study, subjects with EDS and cognitive decline were 2.5 times as likely to report being nonadherent compared with subjects without EDS or cognitive decline. The component of cognition most associated with nonadherence was lapses in attention, which also confirms these results.

Finding that lapses in attention contribute to objectively measured nonadherence contributes to our growing understanding of medication nonadherence. Lim and Dinges³⁶ state that sustaining attention is fundamental to successful cognitive processing. If sustained attention is needed for memory, some patients with HF may not be able to sustain the attention needed to establish a consistent pattern of execution and persistence in medication-taking. Wu et al² noted in their systematic review that forgetfulness was associated with nonadherence in all of the studies in which forgetfulness was examined. Together these results suggest that poor sleep may contribute to inattention, which together pose a significant risk for nonadherence. Factors other than sleep deprivation known to impair the ability to be attentive include anxiety, boredom, and distraction.³⁷ In this sample, the most likely contributor to inattention was poor sleep. In a prior analysis we demonstrated that 21.8% of this sample had significant sleep dysfunction.³⁸

Most authors have found medication nonadherence rates between 40% and 60% in patients with HF. In our study, taking

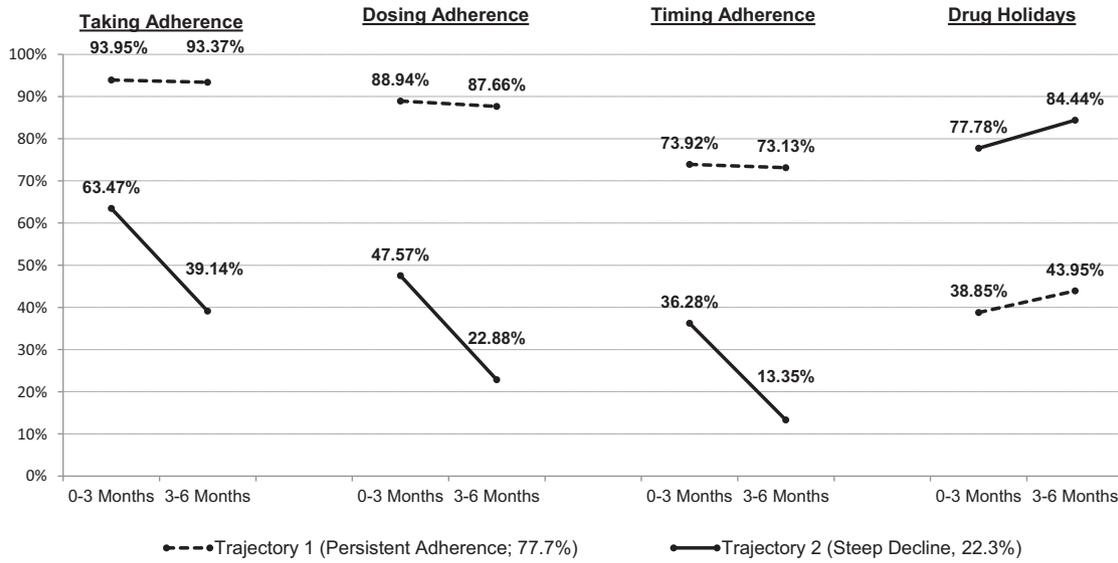


Figure. Two trajectories of adherence were identified for each of the 4 types of medication-taking behavior. In each type of adherence examined (taking, dosing, time adherence, and drug holidays), most participants were fairly adherent. In each of these types, however, a subgroup of participants was identified who demonstrated a steep decline in medication-taking behavior.

adherence averaged 81% to 87%, dosing adherence averaged 73% to 80%, and timing adherence averaged 59% to 66% with considerable heterogeneity. Ours is a very different perspective on adherence, however, and it is important to recognize that we are not reporting an overall adherence rate. Instead, it is the proportion of patients who were categorized as being persistently adherent. The persistent adherers had rates approximately 94% for taking adherence, approximately 89% for dosing adherence, and approximately 74% for timing adherence. As such, we cannot compare this number with other average and direct calculations of overall adherence. What we can say is that 70.8% of patients fit the persistent adherence profile, which is not the same as saying the medication nonadherence rate was approximately 29%. We believe that this approach represents a significant advance in how nonadherence is measured and examined.

Table 3. Logistic Regression Model Predicting Steep Declines in Adherence Using MEMS Data

Variable Grouped by Dimension	Steep Declines in Adherence OR (95% CI), P Value
Social and economic dimension	
White (versus nonwhite)	0.55 (0.23–1.28), 0.162
Condition-related dimension	
Depression	0.73 (0.48–1.12), 0.151
Excessive daytime sleepiness	2.51 (1.06–5.95), 0.037
Therapy-related dimension	
2+ medication dosings per day	2.59 (1.19–5.64), 0.016
Patient-related dimension	
Lapses in attention on PVT	2.65 (1.14–6.16), 0.023
Healthcare system dimension	
Heart failure specialty services	1.77 (0.78–4.02), 0.173

Adjusted odds risk ratios are displayed with persistent adherence as the referent subgroup.

MEMS indicates Medication Event Monitoring System; PVT, psychomotor vigilance task.

Several of the factors anticipated to predict medication adherence were not significant predictors. Practical support for self-care was not significant in any of the models, although in the meta-analysis by DiMatteo,³⁹ the odds of adherence were 3.6 times higher among those who received practical support than among those who did not. Neither income nor the cost of medications was a significant predictor of adherence, contrary to what others have found.^{40,41} Minor depression also was not a significant predictor of adherence, although we cannot say anything about major depression because those individuals were excluded from enrollment. The most likely reason for the difference between our results and those of others is the method of measurement; most prior studies measured adherence using self-report.

Further research is needed to determine if these results hold in larger samples of patients with HF. If corroborated, the 2 identified groups would likely benefit from very different interventions. Those with persistent adherence probably need regular encouragement but no additional intervention resources. The patients with a steep decline in adherence over time may be particularly amenable to an intervention focused more on persistence than execution such as alarms and reminders when medications are due. Screening for patients with lapses in attention and daytime sleepiness can help identify those patients at risk for declining adherence. These patients also need a simplified medication dosing regimen. Providers are strongly encouraged to focus their efforts on simplifying the medication dosing regimen whenever possible.

Strengths and Limitations

A major strength of this study was the analysis approach, which allowed us to move beyond mean trends to examine heterogeneity and identify subgroups to explain the heterogeneity. The major limitation was that a small portion of the final sample failed to use the MEMS device for the full 6 months, which limited the sample size available to analyze

the specific types of medication nonadherence. Some of these participants may have been those using a pill box; perhaps using both a pill box and the MEMS device was too arduous for them. However, no data from these subjects were used in the analysis, so this was not judged to be a major limitation. Sensitivity analyses suggest that these findings might have been even more robust had all participants used the device because those without 6 months of MEMS data were subjects with lapses in attention and multiple-dosing regimens. Moreover, our mean estimates and precision of ORs must be interpreted with an appreciation of the small subgroup and overall sample sizes. Although we were successful in identifying unique subgroups of nonadherence and significant predictors thereof, additional testing in a larger sample would increase the precision of the OR estimates and further limit the risk of errors of the first and second kind.

In summary, in this study of adults with HF, we demonstrated the complexity of medication adherence and the factors contributing to nonadherence. Clearly, nonadherence is a complex and multifaceted issue that defies a simple solution. These results, however, illustrate some potentially modifiable contributors to nonadherence that could be addressed in future intervention trials.

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Disclosures

None.

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CLINICAL PERSPECTIVE

As many as 60% of patients with heart failure are nonadherent in taking their medications. Hospitalizations, costs, and death are higher in patients with heart failure who do not take their medications as prescribed. In this study we followed 202 adults with heart failure for 6 months, measuring their daily medication adherence electronically. Latent growth mixture modeling was used to identify patterns of adherence. The World Health Organization dimensions of adherence (socioeconomic, condition, therapy, patient, and healthcare system) were tested to identify contributors to nonadherence. We identified 2 distinct groups of patients: those (77.8%) who were persistently adherent in their medicines as prescribed and a subset (22.3%) who had a steep decline over time in adherence. Three contributors to the steep decline in adherence were identified: lapses in attention, excessive daytime sleepiness, and those taking a medication ≥ 2 times per day. Medications that need to be taken in multiple daily doses are known to be associated with poor adherence, but this study confirms the importance of prescribing once-a-day medicines whenever possible. Excessive daytime sleepiness and lapses in attention are likely correlated in that patients who do not sleep well are more sleepy during the day and may have trouble being sufficiently vigilant or attentive to remember to take their medicines. Thus, promoting sleep may be a modifiable factor that could improve medication adherence.

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