



5-30-2012

Predictors of Objectively Measured Medication Nonadherence in Adults With Heart Failure

Barbara Riegel

University of Pennsylvania, briegel@nursing.upenn.edu

Christopher S. Lee

Sarah J. Ratcliffe

Sabina De Geest

Sheryl Potashnik

See next page for additional authors

Follow this and additional works at: <https://repository.upenn.edu/nrs>

 Part of the [Cardiology Commons](#), and the [Cardiovascular Diseases Commons](#)

Recommended Citation

Riegel, B., Lee, C. S., Ratcliffe, S. J., De Geest, S., Potashnik, S., Patey, M., Sayers, S. L., Goldberg, L. R., & Weintraub, W. S. (2012). Predictors of Objectively Measured Medication Nonadherence in Adults With Heart Failure. *Circulation: Heart Failure*, 5 (4), 430-436. <http://dx.doi.org/10.1161/CIRCHEARTFAILURE.111.965152>

This paper is posted at ScholarlyCommons. <https://repository.upenn.edu/nrs/54>
For more information, please contact repository@pobox.upenn.edu.

Predictors of Objectively Measured Medication Nonadherence in Adults With Heart Failure

Abstract

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.

Keywords

heart failure, medication adherence, patient compliance, self-care, sleep, World Health Organization

Disciplines

Cardiology | Cardiovascular Diseases

Author(s)

Barbara Riegel, Christopher S. Lee, Sarah J. Ratcliffe, Sabina De Geest, Sheryl Potashnik, Megan Patey, Steven L. Sayers, Lee R. Goldberg, and William S. Weintraub

Published in final edited form as:

Circ Heart Fail. 2012 July 1; 5(4): 430–436. doi:10.1161/CIRCHEARTFAILURE.111.965152.

Predictors of Objectively Measured Medication Nonadherence in Adults with Heart Failure

Barbara Riegel, DNSc, RN, FAAN, FAHA [Professor],
University of Pennsylvania School of Nursing

Christopher S. Lee, PhD, RN [Assistant Professor],
Oregon Health & Science University School of Nursing

Sarah J. Ratcliffe, PhD [Associate Professor],
University of Pennsylvania School of Medicine

Sabina De Geest, PhD, RN, FAAN, FRCN [Professor],
Institute of Nursing Science, University of Basel, Switzerland

Sheryl Potashnik, PhD, MPH [Research Project Manager],
University of Pennsylvania School of Nursing

Megan Patey, BS [Research Assistant],
University of Pennsylvania School of Nursing

Steven L. Sayers, PhD [Associate Professor],
Philadelphia Veterans Affairs Medical Center

Lee R. Goldberg, MD, MPH [Associate Professor], and
University of Pennsylvania School of Medicine

William S. Weintraub, MD [Chief of Cardiology]
Christiana Care Health System, Newark, DE

Abstract

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

Methods and Results—A sample of 202 adults with HF was enrolled from the Northeastern U.S. and followed for 6 months. Specific aims were to describe the types of objectively measured medication nonadherence (e.g. taking, timing, dosing, drug holidays) and to identify contributors to nonadherence 6 months after enrollment. Latent growth mixture modeling (GMM) was used to identify distinct trajectories of adherence. Indicators of the five World Health Organization (WHO) dimensions of adherence (socioeconomic, condition, therapy, patient, and health care 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 odds ratio (OR) = 2.65, $p=0.023$), those with excessive daytime sleepiness (OR = 2.51, $p=0.037$),

and those with two or more 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.

Keywords

heart failure; medication adherence; patient compliance; self-care; sleep; World Health Organization

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

Medication adherence is defined as the extent to which the patient's medication-taking behavior corresponds with an agreed upon medication regimen from a health care 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 \pm 2 hr of the time prescribed); and 4) avoiding drug holidays (e.g. more than 48 hours between doses).

A wide variety of factors have been identified as contributors to medication nonadherence. The WHO groups factors influencing adherence into five 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 (e.g. cognitive impairment) and psychological/behavioral (e.g. health perceptions). Finally, health care system-related factors include the high costs of drugs and 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 in HF patients.^{5, 9–11} And, 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 HF patients.^{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 (e.g. taking, timing, dosing, drug holidays) during a prospective study of adults with HF and to identify contributors to medication nonadherence using the five 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 three sites in the Northeastern U.S. 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 (PHQ-9).¹⁷ Those reporting 5 or more 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 three sites and all participants gave written informed consent. Data were collected at baseline, 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 dataset. 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 non-white, 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. Cross validation 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 (ACE-I) because ACE-I may be taken more often in multiple daily doses than other drugs for HF and most patients are prescribed an ACE-I. If patients were not taking a multiple-dose ACE-I, an angiotensin II receptor blocker (ARB) 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 three times or more 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 pillbox. To facilitate this, a note was placed in the appropriate slot of the pillbox 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 two separate intervals.

The World Health Organization (WHO) dimensions were measured as follows (Table 1). Social and economic characteristics of race, household income, education, and practical self-care support were measured by self-report. Formal education is thought to be an inconsistent indicator of knowledge in the U.S. so education was measured indirectly using oral reading scores on the revised American National Adult Reading Test (ANART-R).²¹ Scores range from 0–50 reflecting the number of irregular words (e.g. 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 (e.g., 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 (PHQ-2).¹⁷ This short version of the PHQ-9 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 (NYHA) functional class. Symptoms, physical limitations, social limitations, and quality of life were assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ), 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.

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 gender, health perceptions, knowledge of HF, and cognitive impairment. 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 (PVT) were used as the measure of cognition; > 4.69 (transformed) lapses was judged as an abnormally high level of inattention.²⁶

Health care 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 (GMM) was used to identify distinct trajectories of nonadherence. GMM 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, GMM employs 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 GMM 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 v6.0 (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 (BIC),²⁹ convergence (entropy near 1.0), the proportion of sample in each trajectory (not less than 5%), and posterior probabilities (average posterior probability of belonging in "most likely" trajectory near 1.0) were used to compare alternative models (e.g. k vs. $k-1$ trajectories) and quantify model uncertainty.^{30, 31} Changes in adherence by trajectory were quantified using pairwise t tests, repeated-measures ANOVA, or McNemar's 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). Odds ratios (OR) and 95% confidence intervals (CI)s were calculated for each model factor, and model fit was quantified using χ^2 , McFadden's 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 1 individual was uninsured. Overall, there were significant—yet heterogeneous increases in taking nonadherence ($81.3\% \pm 25.8\%$ vs. $87.2\% \pm 19.4\%$; $t = 4.51$; $p < 0.001$), dosing nonadherence ($73.2\% \pm 30.1\%$ vs. $79.7\% \pm 23.8\%$; $t = 4.89$; $p < 0.001$), and timing nonadherence ($59.0\% \pm 32.8\%$ vs. $65.5\% \pm 29.6\%$; $t = 4.99$; $p < 0.001$) over time (i.e. 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% vs. 47.5% ; $p = 0.177$).

Using GMM, we identified two 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 vs. 1 trajectories, model entropy was 0.975, and sample-size adjusted BIC 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 Figure 1, 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 two 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 increased slightly for patients in the persistent adherence subgroup (38.9% to 43.9%; $p=0.172$), and increased moderately in the steep decline subgroup (77.8% to 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, three contributors to a steep decline in adherence were identified. Specifically, participants with lapses in attention, those with excessive daytime sleepiness, and those with two or more 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 two 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, excessive daytime sleepiness, and dosing frequency. These factors represent three of the five WHO dimensions as predictors of nonadherence. No one dimension was over-represented suggesting the usefulness of the WHO model is 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 thrice daily^{2,32,34} and once versus four daily doses.³⁴ Some have suggested that taking a medication two or three times daily is still better in promoting adherence than four 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 Dinges argue that the ability to sustain attention is the fundamental process underlying cognitive processing.³⁶ If sustained attention is needed for memory, some HF patients 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 40–60% in patients with HF. In our study, taking adherence averaged 81%–87%, dosing adherence averaged 73%–80%, and timing adherence averaged 59%–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 to 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.

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 DiMatteo³⁹ 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 dosing 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 HF patients. If corroborated the two 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 pillbox; perhaps using both a pillbox 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 odds ratio 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.

Acknowledgments

This work was funded by the National Heart, Lung & Blood Institute (RO1 HL084394-01A1) and by the Philadelphia Veterans Affairs Medical Center, VISN 4 Mental Illness Research, Education, and Clinical Center (MIREC).

The authors gratefully acknowledge Thomas A. Gillespie, MD, FACC for scoring the New York Heart Association (NYHA) interviews and Jia-Rong Wu, PhD, RN for her review of a prior version of this manuscript.

References

1. Blegen MA. The winding road from research to practice through theory. *Nursing Research*. 2011; 60:367. [PubMed: 22067593]
2. Wu JR, Moser DK, Lennie TA, Burkhart PV. Medication adherence in patients who have heart failure: A review of the literature. *Nurs Clin North Am*. 2008; 43:133–153. vii–viii. [PubMed: 18249229]
3. Esposito D, Bagchi AD, Verdier JM, Bencio DS, Kim MS. Medicaid beneficiaries with congestive heart failure: Association of medication adherence with healthcare use and costs. *The American journal of managed care*. 2009; 15:437–445. [PubMed: 19589011]
4. Fitzgerald AA, Powers JD, Ho PM, Maddox TM, Peterson PN, Allen LA, Masoudi FA, Magid DJ, Havranek EP. Impact of medication nonadherence on hospitalizations and mortality in heart failure. *Journal of Cardiac Failure*. 2011; 17:664–669. [PubMed: 21807328]
5. Wu JR, Moser DK, Chung ML, Lennie TA. Objectively measured, but not self-reported, medication adherence independently predicts event-free survival in patients with heart failure. *J Card Fail*. 2008; 14:203–210. [PubMed: 18381183]
6. De Geest S, Sabate E. Adherence to long-term therapies: Evidence for action. *European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology*. 2003; 2:323. [PubMed: 14667488]
7. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: Longitudinal study of electronically compiled dosing histories. *Bmj*. 2008; 336:1114–1117. [PubMed: 18480115]
8. World Health Organisation. Overview: Medication adherence—where are we today?; 2006. p. 7-16.
9. Murray MD, Young JM, Morrow DG, Weiner M, Tu W, Hoke SC, Clark DO, Stroupe KT, Wu J, Deer MM, Bruner-England TE, Sowinski KM, Smith FE, Oldridge NB, Gradus-Pizlo I, Murray LL, Brater DC, Weinberger M. Methodology of an ongoing, randomized, controlled trial to improve drug use for elderly patients with chronic heart failure. *The American journal of geriatric pharmacotherapy*. 2004; 2:53–65. [PubMed: 15555479]
10. Dahri K, Shalansky SJ, Jang L, Jung L, Ignaszewski AP, Clark C. Accuracy of a provincial prescription database for assessing medication adherence in heart failure patients. *The Annals of pharmacotherapy*. 2008; 42:361–367. [PubMed: 18303147]
11. Gwadyr-Sridhar F, Guyatt G, O'Brien B, Arnold JM, Walter S, Vingilis E, MacKeigan L. Teach: Trial of education and compliance in heart dysfunction chronic disease and heart failure (hf) as an increasing problem. *Contemporary clinical trials*. 2008; 29:905–918. [PubMed: 18703166]

12. Hope CJ, Wu J, Tu W, Young J, Murray MD. Association of medication adherence, knowledge, and skills with emergency department visits by adults 50 years or older with congestive heart failure. *Am J Health Syst Pharm*. 2004; 61:2043–2049. [PubMed: 15509127]
13. Patterson ME, Blalock SJ, Smith AJ, Murray MD. Associations between prescription copayment levels and beta-blocker medication adherence in commercially insured heart failure patients 50 years and older. *Clinical therapeutics*. 2011; 33:608–616. [PubMed: 21665045]
14. Riegel B, Moelter ST, Ratcliffe SJ, Pressler SJ, De Geest S, Potashnik S, Fleck D, Sha D, Sayers SL, Weintraub WS, Weaver TE, Goldberg LR. Excessive daytime sleepiness is associated with poor medication adherence in adults with heart failure. *J Card Fail*. 2011; 17:340–348. [PubMed: 21440873]
15. Gonzalez JS, Safren SA, Delahanty LM, Cagliero E, Wexler DJ, Meigs JB, Grant RW. Symptoms of depression prospectively predict poorer self-care in patients with type 2 diabetes. *Diabetic medicine : a journal of the British Diabetic Association*. 2008; 25:1102–1107. [PubMed: 19183315]
16. Egede LE, Ellis C, Grubaugh AL. The effect of depression on self-care behaviors and quality of care in a national sample of adults with diabetes. *General hospital psychiatry*. 2009; 31:422–427. [PubMed: 19703635]
17. Kroenke K, Spitzer RL, Williams JB. The phq-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine*. 2001; 16:606–613. [PubMed: 11556941]
18. Knafl GJ, Fennie KP, Bova C, Dieckhaus K, Williams AB. Electronic monitoring device event modelling on an individual-subject basis using adaptive poisson regression. *Stat Med*. 2004; 23:783–801. [PubMed: 14981675]
19. Viswanathan H, Anderson R, Thomas J 3rd. Evaluation of an antiretroviral medication attitude scale and relationships between medication attitudes and medication nonadherence. *AIDS Patient Care STDS*. 2005; 19:306–316. [PubMed: 15916493]
20. Deschamps AE, Van Wijngaerden E, Denhaerynck K, De Geest S, Vandamme AM. Use of electronic monitoring induces a 40-day intervention effect in hiv patients. *J Acquir Immune Defic Syndr*. 2006; 43:247–248. [PubMed: 17003672]
21. Gladsjo JA, Heaton RK, Palmer BW, Taylor MJ, Jeste DV. Use of oral reading to estimate premorbid intellectual and neuropsychological functioning. *Journal of the International Neuropsychological Society : JINS*. 1999; 5:247–254. [PubMed: 10217924]
22. Johns MW. Reliability and factor analysis of the epworth sleepiness scale. *Sleep*. 1992; 15:376–381. [PubMed: 1519015]
23. Kubo S, Schulman S, Starling R, Jessup M, Wentworth D, Burkhoff D. Development and validation of a patient questionnaire to determine new york heart association classification. *J Card Fail*. 2004; 10:228–235. [PubMed: 15190533]
24. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the kansas city cardiomyopathy questionnaire: A new health status measure for heart failure. *Journal of the American College of Cardiology*. 2000; 35:1245–1255. [PubMed: 10758967]
25. van der Wal MH, Jaarsma T, Moser DK, van Veldhuisen DJ. Development and testing of the dutch heart failure knowledge scale. *Eur J Cardiovasc Nurs*. 2005; 4:273–277. [PubMed: 16126459]
26. Dinges DF, Pack F, Williams K, Gillen KA, Powell JW, Ott GE, Aptowicz C, Pack AI. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep*. 1997; 20:267–277. [PubMed: 9231952]
27. Lo Y, Mendell NR, Rubin DB. Testing the number of components in a normal mixture. *Biometrika*. 2001; 88:767–778.
28. Ram N, Grimm KJ. Methods and measures: Growth mixture modeling: A method for identifying differences in longitudinal change among unobserved groups. *International Journal of Behavioral Development*. 2009; 33:565–576.
29. Schwarz GE. Estimating the dimension of a model. *Annals of Statistics*. 1978; 6:461–464.
30. Jung T, Wickrama KA. An introduction to latent class growth analysis and growth mixture modeling. *Social and Personality Compass*. 2008; 2:302–317.

31. Nylund KL, Asparouhov T, Muthen B. Deciding on the number of classes in latent class analysis and growth mixture modeling: A monte carlo simulation study. *Struct Equ Modeling*. 2007; 14:535–569.
32. Andrejak M, Genes N, Vaur L, Poncelet P, Cleron P, Carre A. Electronic pill-boxes in the evaluation of antihypertensive treatment compliance: Comparison of once daily versus twice daily regimen. *American journal of hypertension*. 2000; 13:184–190. [PubMed: 10701819]
33. Kardas P. Comparison of patient compliance with once-daily and twice-daily antibiotic regimens in respiratory tract infections: Results of a randomized trial. *J Antimicrob Chemother*. 2007; 59:531–536. [PubMed: 17289766]
34. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 2001; 23:1296–1310. [PubMed: 11558866]
35. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *JAMA : the journal of the American Medical Association*. 1989; 261:3273–3277. [PubMed: 2716163]
36. Lim J, Dinges DF. Sleep deprivation and vigilant attention. *Ann N Y Acad Sci*. 2008; 1129:305–322. [PubMed: 18591490]
37. Cheyne JA, Carriere JS, Smilek D. Absent-mindedness: Lapses of conscious awareness and everyday cognitive failures. *Conscious Cogn*. 2006; 15:578–592. [PubMed: 16427318]
38. Riegel B, Glaser D, Richards K, Sayers SL, Marzolf A, Weintraub WS, Goldberg LR. Modifiable factors associated with sleep dysfunction in adults with heart failure. *European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology*. 2011 Feb 23. [Epub ahead of print].
39. DiMatteo MR. Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. *Med Care*. 2004; 42:200–209. [PubMed: 15076819]
40. Rockwell JM, Riegel B. Predictors of self-care in persons with heart failure. *Heart Lung*. 2001; 30:18–25. [PubMed: 11174364]
41. Jackson JE, Doescher MP, Saver BG, Fishman P. Prescription drug coverage, health, and medication acquisition among seniors with one or more chronic conditions. *Medical Care*. 2004; 42:1056–1065. [PubMed: 15586832]

Commentary

As many as 60% of heart failure (HF) patients are nonadherent in taking their medications. Hospitalizations, costs, and death are higher in HF patients who do not take their medications as prescribed. In this study we followed 202 adults with HF for 6 months, measuring their daily medication adherence electronically. Latent growth mixture modeling was used to identify patterns of adherence. The World Health Organization (WHO) dimensions of adherence (socioeconomic, condition, therapy, patient, and health care system) were tested to identify contributors to nonadherence. We identified two 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 two or more 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.

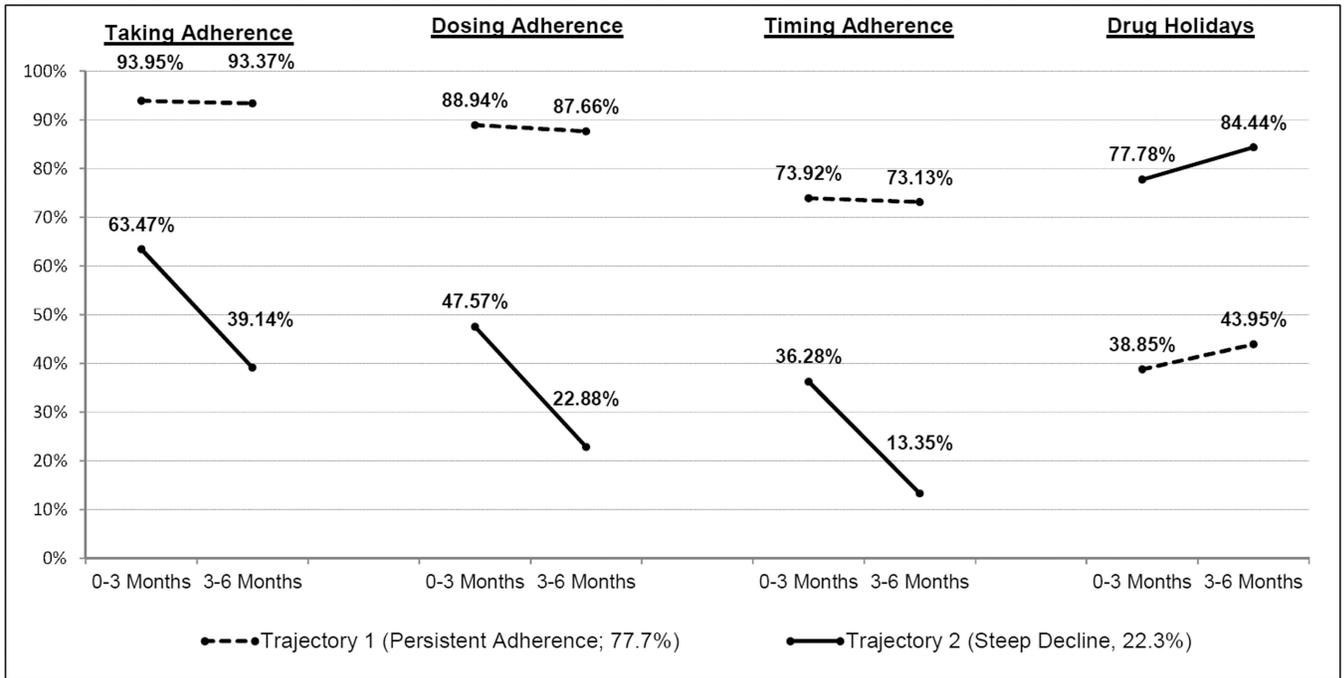


Figure 1.
Three Trajectories of Medication Adherence

Table 1

Factors tested as potential contributors to medication nonadherence.

1. Social and Economic Dimension	3. Therapy-Related Dimension
Education	Number of medications taken per day
Race	Dosing frequency of medicine used in the MEMS device
Household income	4. Patient-Related Dimension
Practical support for self-care	Gender
2. Condition-Related Dimension	Perceived Overall Health
Comorbid illnesses	Knowledge of heart failure
Depression	Cognition and attentiveness
Excessive daytime sleepiness	5. Health Care System Dimension
NYHA functional class	Cost of medications
KCCQ Physical limitations	Receipt of heart failure specialty services
KCCQ symptom frequency, burden, stability	
KCCQ social limitations	
KCCQ quality of life	

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

Table 2

Characteristics of the sample. Mean \pm standard deviation or column n (%) are reported.

	(n=202)
Age (years)	63.1 \pm 11.8
Male	132 (65.4)
Race/Ethnicity	
• White	138 (68.3)
• Non-White	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 \pm 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 number of comorbid conditions on Charlson Index	2.8 \pm 1.8
NYHA functional class	
• Class I & II	49 (24.3)
• Class III	119 (58.9)
• Class IV	34 (16.8)
Daily Dosing with MEMS	
1; once daily	79 (39.1)
2; twice daily	117 (57.9)
3; thrice or more daily	6 (3.0)
# of daily medications	9.9 \pm 3.8
High lapses on the PVT	71 (35.9)
Excessive Daytime Sleepiness (6)	112 (55.5)
Patient Health Questionnaire (PHQ2)	0.8 \pm 1.0
Self-Care Support Score	1.5 \pm 1.5
Medication costs impair adherence	20 (10.3)
KCCQ Physical Limit Score	71.6 \pm 22.0
KCCQ Symptom Score	76.3 \pm 19.4
KCCQ Social Limitations Score	68.4 \pm 25.3
KCCQ Quality of Life Score	66.7 \pm 23.3
Dutch Knowledge Scale Score	11.7 \pm 1.7

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

Table 3

Logistic regression model predicting steep declines in adherence using MEMS data.

Steep Declines in Adherence	
Variable Grouped by Dimension	OR (95% CI), p-value
<i>Social & economic dimension</i>	
Caucasian (vs. Non-Caucasian)	0.55 (0.23–1.28), 0.162
<i>Condition-related dimension</i>	
Depression	0.73 (0.48–1.12), 0.151
Excessive daytime sleepiness	2.51 (1.06–5.95), 0.037
<i>Therapy-related dimension</i>	
2+ medication dosings per day	2.59 (1.19–5.64), 0.016
<i>Patient-related dimension</i>	
Lapses in attention on PVT	2.65 (1.14–6.16), 0.023
<i>Health care system dimension</i>	
Heart failure specialty services	1.77 (0.78–4.02), 0.173

Note: Adjusted odds risk ratios are displayed with persistent adherence as the referent subgroup. CI = Confidence Interval; HF = Heart failure; MEMS= Medication Event Monitoring System; OR = odds ratio; PVT = psychomotor vigilance task.