Published in final edited form as:
Health Psychol. 2018 November ; 37(11): 1006–1014. doi:10.1037/hea0000661.

Identifying Targets for Cardiovascular Medication Adherence Interventions through Latent Class Analysis

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Abstract

Objective.—Reasons for nonadherence to cardiovascular medications vary widely between individuals. Yet, adherence interventions are often uniformly applied, limiting their effectiveness. This study employed latent class analysis (LCA) to identify multidimensional profiles of reasons for nonadherence to cardiovascular medications.

Methods.—Participants (N = 137; M_{Age} = 58.8, SD_{Age} = 11.8) were drawn from an observational study of the impact of cardiac-induced posttraumatic stress disorder (PTSD) on cardiac medication adherence in patients presenting to the emergency department with a suspected acute coronary syndrome. Demographics and depressive symptoms were assessed at baseline. Extent of nonadherence to cardiovascular medications, reasons for nonadherence, and PTSD symptoms were assessed one month after discharge.

Results.—LCA identified three classes of reasons for medication nonadherence: *capacity* (related to routine or forgetting; approximately 45% of the sample), *capacity+motivation* (related to routine/forgetting plus informational or psychological barriers; approximately 14% of the sample), and *no clear reasons* (low probability of endorsing any items; approximately 41% of the sample). Participants reporting greater nonadherence were more likely to be in the *capacity +motivation* or *no clear reasons* classes compared to the *capacity* class. Participants endorsing higher PTSD severity were more likely to be in the *capacity+motivation* or *capacity* classes compared to the *no clear reasons* class.

Conclusions.—Three distinct classes of reasons for nonadherence were identified, suggesting opportunities for tailored interventions: *capacity*, *capacity+motivation*, and *no clear reasons*. These preliminary findings, if replicated, could aid identification of patients at risk for greater extent of medication nonadherence and inform tailored interventions to improve adherence.

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Conflicts of Interest: For the remaining authors none were declared.

Keywords

cardiovascular disease; medication adherence; latent class analysis; secondary prevention

Introduction

Nonadherence to cardiovascular medications for secondary prevention is common. In a meta-analysis of 376,162 patients who had experienced myocardial infarction (MI), only 66% were adherent to their cardiac medications as assessed by pharmacy refill data (at least 75% coverage) over a median of two years (Naderi, Bestwick, & Wald, 2012). Others have reported similar rates of nonadherence to cardiovascular medications across a range of adherence measures (~40%) (Chowdhury et al., 2013). Consequences of nonadherence to secondary prevention medications include increased risk for recurrent MI and all-cause mortality (Ho et al., 2014; Jackevicius, Li, & Tu, 2008; Wei et al., 2002), highlighting the importance of effective adherence interventions in patients with cardiovascular disease. Despite several decades of research into adherence interventions, few interventions have been sufficiently potent to impact clinical outcomes (e.g., blood pressure, cholesterol) (Ho et al., 2006). The few interventions that have improved clinical outcomes have been costly, labor-intensive, and are not being widely implemented (McDonald, Garg, & Haynes, 2002; Nieuwlaat et al., 2014).

One possible reason for the limited effectiveness of medication adherence interventions is that they tend to take a one-size-fits-all approach (e.g., provide copayment reduction or medication reminders to everyone) rather than tailoring to specific reasons for nonadherence (e.g., Volpp et al., 2017). Intervention tailoring, however, poses numerous logistical challenges. There are many combinations of reasons for medication nonadherence (Hugtenburg, Timmers, Elders, Vervloet, & van Dijk, 2013; Voils et al., 2012), and a given patient’s reasons for nonadherence may change over time. Barriers to medication adherence can relate to patients’ Capability of adhering to the medication regimen (e.g., memory problems), their Opportunity to take their regimen (e.g., drug costs, distance from pharmacy), and their Motivation to be adherent (e.g., beliefs about medications, psychological distress) (Capability, Opportunity, Motivation model of Behavior; COM-B) (Jackson, Eliasson, Barber, & Weinman, 2014; Kronish et al., 2013; Kronish & Ye, 2013; Osterberg & Blaschke, 2005; Valle & Ho, 2014). Reasons for nonadherence can occur in various combinations, requiring different strategies to improve adherence (Bosworth et al., 2011). For example, a patient who cannot afford medications will likely require a different intervention strategy than one who forgets to take medication as prescribed (e.g., reduced copays versus reminders).

We aimed to test an innovative multidimensional approach to identifying subgroups for tailored adherence interventions by examining clusters of co-occurring reasons for nonadherence using latent class analysis (LCA) (Collins & Lanza, 2010; Lanza, Collins, Lemmon, & Schafer, 2007; Lanza & Rhoades, 2013). LCA allows one to treat co-occurring reasons for nonadherence as multidimensional profiles of responding, and, in turn, create classes, or grouped patterns of item responses, that are theoretically and statistically distinct.

This approach may identify subgroups of patients who might benefit most from a particular adherence intervention (Lanza & Rhoades, 2013), thereby facilitating cost-effective tailoring of interventions, and may be particularly relevant when patients endorse multiple reasons for nonadherence.

The goal of this exploratory study was to identify distinct, multidimensional profiles of reasons for nonadherence to cardiovascular medications using LCA. Reasons were selected to span a range of common barriers to cardiovascular medication adherence. Differences in latent class membership were examined across demographics, psychological factors, and extent of nonadherence.

Method

Design

Data were drawn from the REactions to Acute Care and Hospitalization (REACH) study, an observational cohort study of the impact of cardiac event-induced posttraumatic stress disorder (PTSD) on medication adherence and cardiovascular prognosis. Patients were recruited and completed baseline assessments in the emergency department (ED) and inpatient setting after presentation with a suspected acute coronary syndrome (ACS). Follow-up assessments took place by telephone one, six, and 12 months after discharge. The cross-sectional analysis described in this paper uses data on extent of nonadherence and reasons for nonadherence collected during the one-month interview.

Participants

Participants were eligible for REACH if they presented to the emergency department of a tertiary care hospital (Columbia-New York Presbyterian Hospital, New York, NY) with symptoms of a suspected ACS (i.e., unstable angina or non-ST elevation myocardial infarction). For this secondary analysis, participants were included if they were prescribed cardiovascular medications, reported nonadherence to those medications, and answered questions about reasons for nonadherence at one month. All procedures were approved by the Institutional Review Board at Columbia University Medical Center, and participants provided informed consent before participation.

Measures

Extent of medication nonadherence.—Nonadherence to cardiovascular medications (“heart medications” or “medications for your heart”) was assessed by telephone one month after discharge using a single item, “In the past month, how often did you take your heart medications as your doctor prescribed?” Response options included, *1*, “less than half of the time (< 50%),” *2*, “about half of the time (50%),” *3*, “most of the time (75%),” *4*, “nearly all of the time (> 90%),” and *5*, “all of the time (100%)” (Gehi, Ali, Na, & Whooley, 2007; Gehi, Haas, Pipkin, & Whooley, 2005). Among patients with coronary artery disease, self-reported adherence of 75% of the time or less as assessed by this item has been associated with increased risk for adverse cardiovascular events (e.g., myocardial infarction, cardiovascular-related mortality), $HR = 2.3$ [1.3, 4.3], $p < .01$ (Gehi et al., 2007). Only patients who reported not taking their medications all of the time—i.e., those reporting less than 100% adherence (response options 1, 2, 3, or 4)—were asked about reasons for nonadherence. As patients tend to overreport their extent of medication adherence, we used any report of nonadherence as an indicator of significant nonadherence (Gallagher, Muntner, Moise, Lin, & Kronish, 2015; Stirratt et al., 2015; Voils et al., 2012).

Reasons for medication nonadherence.—Reasons for nonadherence were also assessed by telephone one month after discharge. The questionnaire was comprised of 11 common reasons for nonadherence to cardiovascular medications over the previous month. These items were selected from among a list of reasons for nonadherence to antihypertensive medications developed by adherence experts (Fernandez, Chaplin, Schoenthaler, & Ogedegbe, 2008; Voils et al., 2012). Due to time constraints of assessing reasons for nonadherence in the current study, this list of reasons was reduced by consensus of two authors—one medical doctor and one psychologist (IK, DE)—based on relevance to cardiovascular medications in this population. Items that were specific to hypertensive medications (e.g., "I did not have any symptoms of high blood pressure") were removed. Further, an item asking about cost-related nonadherence was removed due to the expectation that cost would not be a major adherence barrier, given low medication co-pays for low-income patients covered by New York State Medicaid in this study. Example items include, "You ran out of the heart medication," and "You forgot," scored from *1*, "none of the time," to *5*, "all of the time." Due to the conceptual distinction between endorsing (versus not endorsing) a reason for nonadherence, as well as the low frequencies of endorsement across response options *3, 4*, and *5*, reasons for medication nonadherence were dichotomized to indicate whether participants responded that the reason was present at least a little of the time (endorsed; response of *2* or greater) or not at all (not endorsed; response of *1*).

This scale was constructed for maximal content validity. Reasons were not expected to be highly correlated, as this scale represents causal indicator model (i.e., the reasons cause nonadherence rather than nonadherence causing reasons). Thus, traditional markers of reliability, such as internal consistency, were not appropriate. The initial validation of this scale reported test-retest intraclass correlations representing administration 2–21 days apart ranging from .07 to .64 (Voils et al., 2012).

Patient characteristics.—Demographics were assessed through patient interview upon enrollment into the study. Medical characteristics were abstracted from the electronic health record by a medically trained research coordinator. Data included gender, race, ethnicity, language, consistency of health insurance coverage, and education assessed via patient interview. Age and confirmed ACS were assessed via chart extraction. The 8-item Patient Health Questionnaire (PHQ-8) (Kroenke & Spitzer, 2002; Kroenke et al., 2009) was used to measure depressive symptoms at baseline (e.g., "Over the last 2 weeks, how often have you been bothered by: Feeling down, depressed or hopeless?"). Answers were scored from *0*, "not at all," to *3*, "nearly every day." PTSD with respect to the "heart problem, ED visit, and hospitalization" relevant to the qualifying cardiac event was assessed one month after discharge using the PTSD Checklist specific to an acute stressor (PCL-S) corresponding to DSM-IV diagnostic criteria (Weathers, Litz, Herman, Huska, & Keane, 1993). The DSM-V and corresponding PTSD assessment specific to an acute stressor (PCL-5) (Weathers et al.,

2013) were released during the course of the study. Thus, participants enrolled after the PCL-5 was released answered questions with respect to the "heart problem, ED visit, and hospitalization" on the PCL-5. Psychologists trained in PTSD research examined items and selected and matched corresponding items on the PCL-5 and PCL-S to create an overall, 17-item PTSD assessment (e.g., "Avoid thinking about or talking about the event or avoid having feelings related to it?"). Answers were scored from *1*, "not at all," to *5*, "quite a bit."

Data Analysis Strategy

LCA was conducted to identify different latent classes that encompass multidimensional patterns—or clusters—of reasons for nonadherence. This method creates different classes based on *item response probabilities*, or the likelihood that someone in a given class would endorse the items in the analysis. PROC LCA (Lanza, Dziak, Huang, Wagner, & Collins, 2015; PROC LCA & PROC LTA, 2015) software was implemented in SAS version 9.4 (SAS Institute Inc., 2012). Each model was run with 100 sets of starting values to ensure model identification (Collins & Lanza, 2010). Models were compared using multiple fit criteria: Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), Consistent AIC (CAIC), and Adjusted BIC (ABIC), as each places differing importance on parsimony (i.e., overfitting versus underfitting) (see Dziak, Coffman, Lanza, & Li, 2017, for a detailed explanation). PROC LCA is flexible in its treatment of missing data, using maximum likelihood (ML) estimation to include respondents who provided data on at least one item. To further explore class separation, or the distinguishability of the classes, posterior probabilities of class membership were examined. This entails assigning participants to the class to which they have the highest probability of belonging based on their answers to the items in the analysis, and examining the magnitude of these probabilities. The higher the probability of membership for a given individual in a given class, the lower the probability of membership in other classes, and the greater the likelihood that individual is correctly classified. In other words, when posterior probabilities are high, this means that participants' responses tend to be primarily associated with one latent class (i.e., the classes are "separated"). When probabilities are lower, there is a lack of distinction between classes.

Once we selected the final model, we examined whether demographic characteristics (age, gender, race, ethnicity, English as a first language, consistency of health insurance coverage, education, and confirmed ACS), psychological factors (depressive symptoms and cardiac event-induced PTSD), or extent of nonadherence (treated as continuous) were associated with latent class membership; extent of nonadherence (ordinal) was examined in a sensitivity analysis. This was accomplished by entering predictors of the probability of class membership into the latent class model to simultaneously estimate the probability of class membership and the latent class item response probabilities. This approach results in something similar to a multinomial logistic regression, with odds ratios of probable class membership. It has the benefit of taking into account the uncertainty of latent class membership of participants rather than definitively assigning participants to a given class (Collins & Lanza, 2010). Each class was specified as the reference group separately to incorporate all possible comparisons. An adjusted model predicting class membership was estimated including all covariates that had significant bivariate associations ($p < .05$).

Results

Of the 841 patients who were prescribed cardiovascular medications and had adherence assessed, 140 (16.6%) reported taking medications less than 100% of the time and were eligible to have their reasons for nonadherence assessed (i.e., this was a built-in skip pattern). Participants who completed the reasons for nonadherence questionnaire were included in this study (*N* = 137; 97.9% of those reporting nonadherence). Three participants were missing data on these questions. Demographic information is detailed in Table 1; a full list of the reasons surveyed in our sample, and endorsement of reasons for nonadherence, can be seen in Table 2. Most of these participants reported taking medications "nearly all of the time (> 90%)" (35.8%), followed by "less than half the time (< 50%)" (25.4%), followed by "most of the time (75%)" (23.9%) and "about half of the time (50%)" (14.9%).

Model Selection

Model fit continued to improve for the AIC and ABIC in the four- and five-class solutions (see Table 3). However, there was a precipitous drop in percent convergence when increasing the number of classes above 3, indicating that these models were poorly identified (Collins & Lanza, 2010) (i.e., instead of coming to the same latent class solution on each of the 100 runs, convergence to the same solution dropped to unacceptable levels of 27% and 11% with the four- and five-class solutions, respectively). Among the one-, two-, and three-class solutions, the AIC, BIC, and ABIC identified a three-class solution, whereas the CAIC identified a two-class solution as having the best fit. Because most statistics selected the three-class solution, and because the three classes were theoretically distinct and interpretable, the three-class solution was retained.

Latent Class Solution

Model results for the three-class solution are detailed in Table 4. Each class has a probability of class membership, which is an indicator of overall class size (i.e., class prevalence). The first class (approximately 45% of the sample; membership probability = .45, *se* = .06) tended to endorse items related to unintentional reasons for nonadherence or reasons related to physical and psychological process needed to engage in the critical behavior (similar to the Capability component of the COM-B model) (Jackson et al., 2014), including forgetting, leaving the medication at home, and being out of routine (*capacity* class). For example, this class was characterized by a high probability (.80) of endorsing "You forgot" as a reason for nonadherence. The second class was the smallest (approximately 14% of the sample; membership probability = .14, *se* = .04). Participants in this class not only endorsed the capacity-related reasons, but also missing doses for reasons related to automatic, emotional processes, such as not wanting to be reminded about heart problems, and reflective evaluative/motivational reasons, such as feeling the medication would not help, or lacking answers about the medication (e.g., Jackson et al., 2014; Michie, van Stralen, & West, 2011) (*capacity+motivation* class). For example, whereas both *capacity* and *capacity+motivation* were characterized by a high probability of endorsing capacity reasons for nonadherence (e.g., forgetting), *capacity+motivation* was additionally characterized by a high probability (.63) of endorsing "You were feeling down or upset" as a reason for nonadherence (versus a probability of .20 in the *capacity* class). Participants in the third class (approximately 41% of the sample; membership probability = .41, *se* = .06) did not tend to endorse any clear pattern of co-occurring reasons; in fact, this class did not have a high probability of endorsing any of the reasons assessed in this study (*no clear reasons* class) (e.g., this class was characterized by a low probability, .08, of endorsing "You had other things to deal with" as a reason for nonadherence; reasons for this are addressed further in the discussion). Posterior probabilities of class membership were quite high, indicating low classification error and good latent class separation (mean posterior probabilities: *capacity* = .87, *capacity +motivation* = .96, *no clear reasons* = .92).

Predictors of Class Membership

Demographics.—Sex was unrelated to class membership, $\Delta 2{*}LL(2) = 1.77$, $p = .41$, indicating that male and female respondents did not differ in their reasons for nonadherence. Class membership was similarly unrelated to Black race, $\Delta 2{*}LL(2) = .33$, $p = .85$, Hispanic ethnicity, $\Delta 2{*}LL(2) = .47$, $p = .79$, age, $\Delta 2{*}LL(2) = .61$, $p = .74$, native English language, $\Delta 2{*}LL(2) = .08$, $p = .96$, or presence of consistent health insurance during the past two years, $\Delta 2{*}LL(2) = .16$, $p = .92$. Class membership was different for those with college education (versus high school or less), $\Delta 2{*}LL(2) = 8.97$, $p = .011$; however, the upper bound of the odds ratio predicting membership was too large to display and the confidence interval included zero, so this difference was not interpreted. Confirmed ACS was not related to class membership, $\Delta 2{*}LL(2) = .22$, $p = .89$.

Psychological factors.—Cardiac event-induced PTSD symptoms were related to class membership, $\Delta 2{*}LL(2) = 9.23$, $p = .010$. For each unit increase in PTSD symptoms, participants were more likely to be in the *capacity+motivation* class, *OR* = 1.07 [1.03, 1.11], or the *capacity* class, *OR* = 1.06 [1.01, 1.10], as opposed to the *no clear reasons* class. When PTSD symptoms were dichotomized to indicate probable PTSD (score $\geq$ 30), PTSD was associated with a greater likelihood of membership in the *capacity+motivation* class, *OR* = 5.52 [1.64, 18.59], or the *capacity* class, *OR* = 2.65 [.93, 7.59]. Depressive symptoms were not related to class membership, $\Delta 2{*}LL(2) = .18$, $p = .92$.

Extent of nonadherence.—Extent of nonadherence was related to class membership, $\Delta 2{*}LL(2) = 10.94$, $p = .004$. Participants who were more adherent had a lesser probability of membership in either the *capacity+motivation* class, *OR* = .45 [.26, .77], or the *no clear reasons* class, *OR* = .60 [.39, .92], as compared to the *capacity* class. Stated otherwise, people who endorsed greater extent of nonadherence were more likely to be in the *capacity +motivation* or *no clear reasons* class.

Although extent of nonadherence was treated as continuous, sensitivity analysis explored results when this was treated as an ordinal variable. Findings mirrored the primary analysis: compared to patients who reported taking medications < 50% of the time, those taking them 50%, 75%, and > 90% of the time were less likely to be in the *capacity+motivation* class (*OR*s = .08, .10, and .02, respectively) or the *no clear reasons* class (*OR*s = .05, .06, and .07, respectively).

Adjusted model.—In a final model including all significant correlates of class membership from bivariate testing, both PTSD and extent of nonadherence remained significant, *p*s = .026 and .025, respectively. In the adjusted model, PTSD symptoms continued to predict a greater probability of falling into the *capacity+motivation* or *capacity* class, *OR* = 1.04 [1.01, 1.08], and *OR* = 1.04 [1.01, 1.07], respectively, and better adherence continued to be associated with a reduced probability of membership in the *capacity +motivation* class, *OR* = .57 [.38, .85], or the *no clear reasons* class, *OR* = .71 [.52, .98].

Discussion

Using LCA, this study took a multidimensional approach to investigate reasons for nonadherence to cardiovascular medications among patients initially presenting to the emergency department with a suspected ACS who reported less than 100% adherence to cardiovascular medications one month later. Though preliminary, results suggested three distinct clusters of reasons for nonadherence. The first, the *capacity* class, was exclusively comprised reasons for nonadherence related to forgetting or routine barriers to adherence. Building on the first class, the second (the *capacity+motivation* class) included people who also tended to endorse psychological and informational reasons for nonadherence (e.g., not wanting to be reminded of a heart problem). The third, the *no clear reasons* class, did not tend to endorse any of the possible reasons for nonadherence assessed in this study. The first two of these classes—*capacity* and *capacity+motivation*—are similar to theoretical distinctions in literature on medication nonadherence that have been made previously (e.g., nonintentional and intentional) (Hugtenburg et al., 2013; Valle & Ho, 2014) (capability and motivation) (Jackson et al., 2014) (or logistical and psychological reasons, among others) (Cook, 2008), suggesting the validity of our solution. These two groups have also been identified as potentially responsive to different interventions, such as reminder devices or text message reminders for the *capacity* (nonintentional) group, and reminders supplemented by more intensive psychological and informational intervention for the *capacity+motivation* (intentional) group (Hugtenburg et al., 2013). The presence of a third cluster that did not tend to endorse any clear pattern of reasons for nonadherence assessed in this study suggests a need for future research to assess additional reasons for nonadherence, for example, systemic barriers (e.g., cost, distance to pharmacy) and reasons related to self-efficacy (i.e., confidence in ability to take medications as prescribed). It is also possible that patients in the *no reasons* class did not have insights into reasons for nonadherence, or that they had implicit biases against taking medications that cannot be captured by standard reasons for nonadherence questions.

Although demographics were unrelated to latent class membership, class membership differed by psychological factors and extent of nonadherence (which ranged from less than half the time to nearly all of the time). Specifically, the *no clear reasons* and *capacity +motivation* classes were associated with greater extent of nonadherence, and the *capacity* and *capacity+motivation* classes were associated with cardiac event-induced PTSD symptoms. Cardiovascular medications may serve as aversive reminders for patients who develop PTSD symptoms related to the trauma of the acute cardiovascular event, which may facilitate development of emotional reasons for nonadherence (Edmondson, 2014;

Edmondson, Horowitz, Goldfinger, Fei, & Kronish, 2013; Husain, Edmondson, Kautz, Umland, & Kronish, 2018).

These findings suggest the importance of a tailored approach to adherence support and further emphasize the reasons that less complex interventions may not be as effective as desired (Choudhry et al., 2017; Hugtenburg et al., 2013). If items with high discrimination between classes identified in this exploratory analysis (i.e., items that are highly likely to be endorsed by one class but not others) are confirmed in future studies and subsequently administered via questionnaire, then responses might be used to reliably identify the likelihood that patients will fall into a class that would benefit from a particular type of intervention. For example, patients who say they forget medications when they are out of their routine or have other things to deal with, but do *not* endorse needing information or feeling down (i.e., *capacity* class), could be given tools to help them remember or build medications into their routine. If patients also endorse feeling down or needing information (*capacity+motivation* class), then they could be targeted for more intensive interventions addressing motivation because reminders may be insufficient to improve adherence. Intervention effectiveness across different classes could also be empirically examined.

It is also worth noting the complexity in the associations between extent of nonadherence and PTSD with class membership, given that these two factors were differentially associated with class membership. Specifically, results suggested that the *capacity+motivation* class may be at the highest risk for poor health and psychological outcomes given its association with both greater extent of nonadherence and greater cardiac event-induced PTSD symptoms. On the other hand, the *capacity* class was associated greater PTSD symptoms but with less severe nonadherence. Different PTSD symptom clusters may motivate different behaviors. For example, PTSD symptoms of hyperarousal or intrusions may motivate medication taking, whereas symptoms of avoidance may have the opposite effect. Future studies with a larger sample size should replicate these results and parse potential differences in class membership related to distinct PTSD symptom clusters.

It is perhaps surprising that depressive symptoms were not associated with class membership, given that depression is often associated with poor adherence (DiMatteo, Lepper, & Croghan, 2000; Gehi et al., 2005; Kronish et al., 2006), and that depressive symptoms were associated with specific reasons for nonadherence in hypertensive patients (e.g., worry about taking medications for the rest of one's life, cost) (Weidenbacker, Beadles, Maciejewski, Reeve, & Voils, 2015). This difference could be explained by the fact that the present study examined clustered patterns of reasons for nonadherence instead of individual reasons. Further, researchers have only recently begun to assess PTSD in cardiovascular patients, and many of the studies that have examined both depression and PTSD have found PTSD to be more strongly associated with nonadherence (Edmondson et al., 2013; Kronish, Cohen, Lin, Voils, & Edmondson, 2014; Kronish, Edmondson, Goldfinger, Fei, & Horowitz, 2013; Kronish, Edmondson, Li, & Cohen, 2012). If PTSD is uniquely associated with the psychological cluster of reasons for nonadherence, or with greater concerns about medication (Edmondson et al., 2013), it may suggest a tailored intervention for this population at particularly high risk for adverse cardiovascular prognosis.

To our knowledge, this is among the first studies to use LCA to classify patients into groups that share common reasons for nonadherence. Yet, the utility of LCA and other group-based modeling techniques as applied to nonadherence is clear. For example, Jaeger et al. (2012) applied LCA to understand different aspects of adherence in a group of patients with schizophrenia and uncovered meaningfully different classes of adherence (e.g., “good compliers” versus “critical discontinuers”) that were associated with clinical endpoints (e.g., rehospitalization), and Trivedi et al. (2010) found distinct classes representing hypertensive patients who tended to be more (or less) adherent to an array of prescribed health behaviors, including medication adherence. Group-based trajectories have been used to uncover distinct patterns in adherence to medications in patients with coronary heart disease, with implications for treatment and timing of intervention (e.g., early discontinuation and recovery versus rapid decline in adherence) (Librero, Sanfélix-Gimeno, & Peiró, 2016). In another study, Benner et al. (2010) applied LCA to parse different reasons people reported discontinuing medication for overactive bladder syndrome, and identified two classes. One class, encompassing the vast majority of respondents (~89%), did not have a greater than 50% probability of endorsing any reasons. The other class, in contrast, reported a general aversion to taking medications or to taking them for too long, with implications for tailoring treatment (e.g., alternative approaches to disease management). The fact that reasons for nonadherence to medications for secondary cardiovascular prevention also manifest in distinct response patterns emphasizes the need for a tailored, person-centered approach to intervention development (Lanza & Rhoades, 2013). The benefits of a tailored approach to intervention across latent classes have also been demonstrated in other fields. For example, latent classes in regards to patterns of alcohol use predict the effectiveness of peer- and family-based interventions to reduce drinking (Cleveland, Collins, Lanza, Greenberg, & Feinberg, 2010).

Limitations

These results should be considered in light of a number of limitations. Foremost, this study was exploratory, and results should be replicated. Extent of nonadherence was self-reported, and may be subject to social desirability or recall biases. This measure was also a single item, which may be less reliable and valid than a multi-item measure, and may be better conceptualized as ordinal rather than continuous. However, due to sparsity in the data and extremely wide confidence intervals, this measure was treated as continuous. Future studies should consider behavioral measures of medication adherence, such as electronic medication monitoring (Dunbar-Jacob & Mortimer-Stephens, 2001; Osterberg & Blaschke, 2005) or newer technologies (e.g., sensors that detect pill ingestion, wrist-worn monitors) that more precisely measure daily adherence behaviors. Nonadherence as assessed by this single item has, however, been associated with clinical endpoints (e.g., myocardial infarction, death due to coronary heart disease) (Gehi et al., 2007). Practitioners and interventionists are frequently interested in understanding how patients will behave in the future; however, our cross-sectional data precluded us from using latent classes to predict future nonadherence.

Only participants who endorsed missing medications at least some of the time were asked about reasons for nonadherence, which could limit generalizability of study results. Another point for consideration is that patients were asked to report on reasons for nonadherence to heart medications as a whole, rather than individually, whereas reasons for nonadherence may vary for different medications within one individual. On one hand, this could have introduced variability into the list of reasons for nonadherence, and may have contributed to the emergence of the *no reasons* class. On the other, however, this method of measurement may increase generalizability of the latent classes across a range of cardiovascular medications, and it would be challenging to operationalize separate latent classes of reasons for nonadherence for each class of cardiovascular medication in patients on complex cardiovascular medication regimens.

The measure of reasons for nonadherence was limited in that systemic and environmental reasons (e.g., cost, distance to the pharmacy) were not included. Furthermore, reasons related to self-efficacy/behavioral control—a potent predictor of health behaviors (Armitage & Conner, 2001; Barclay et al., 2007)—were not assessed. We selected a brief set of reasons due to relevance and to reduce participant burden. This limitation may have contributed to the emergence of a class that did not tend to endorse any reasons for nonadherence, limiting the utility of the classification approach, and precluding clinically significant inference regarding optimal interventions for this group. Future studies would benefit from assessing a broader range of reasons. If a *no clear reasons* class continues to emerge when additional reasons for nonadherence are included, follow-up interviews for participants likely to fall into this class would be beneficial.

The small sample size also limited the ability to explore differences in the magnitude of reasons for medication nonadherence. That is, it was necessary to dichotomize reasons as endorsed or not endorsed due to sparseness and model underidentification had the range of possible response options been included. This could have masked nuanced differentiations between classes; results should be replicated in a larger sample and using the full range of response options. Additional classes may emerge in larger studies with enough power to reliably detect a greater number of classes (Dziak, Lanza, & Tan, 2014). The small sample size with repeated assessments at later points in the study also precluded an examination of stability in class membership over time (Lanza et al., 2007; Lanza et al., 2015). Future studies examining the stability in class membership, with concurrent or prospective changes in medication-taking behavior, are needed. In addition, findings from a cross-sectional analysis may reflect personality characteristics (e.g., conscientiousness) that impact patient reports of both reasons for, and extent of, nonadherence.

Conclusion

These results suggest distinct patterns of reasons for nonadherence. If confirmed in future studies, these classes could help healthcare providers identify patients at the greatest risk for nonadherence and select appropriately tailored interventions that are both efficient and cost-effective. Benefits could be even greater if future research can identify additional reasons for nonadherence that characterize the *no clear reasons* class from this study.

Acknowledgments

Source of Funding: This work was supported by National Heart, Lung, and Blood Institute (NHLBI) grants to Dr. Edmondson [grant numbers R01HL117832, R01HL128310] and Dr. Kronish [R01HL123368]. The content is solely the responsibility of the authors and does not necessarily represent the official view of the National Institutes of Health. The funding body had no role in the design of the study, collection and interpretation of data, or in writing this manuscript. Effort on this manuscript was also made possible by a Research Career Scientist award from the Health Services Research & Development service of the Department of Veterans Affairs (VA) [grant number RCS 14–443]. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the VA or the United States Government.

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Table 1.

Demographic information for participants. Continuous variables are reported as Mean (SD); categorical variables are reported as percentages.

Variable		***M (SD)* or %**
Age		58.8 (11.8)
Sex	*Female*	52.8%
Race	*Black*	39.6%
	White	16.4%
	Other	44.0%
Ethnicity	*Hispanic*	49.6%
Education	*High School or Less*	50.4%
	Trade School/Some College	20.4%
	College Degree	18.3%
	Graduate Degree	11.0%
Health Insurance	*Yes*	85.4%
English as a First Language	*Yes*	67.2%
Confirmed ACS	*Yes*	22.6%
PTSD Symptoms		27.9 (12.8)
Depression		7.7 (6.5)
Number of Cardiovascular Medications		2.5 (1.8)

Table 2.

Frequency of endorsement of different reasons for nonadherence to cardiovascular medications.

Reason	N	% Endorsing[a]	% Response[b]				
			1	2	3	4	5
You forgot.	134	61.19	38.81	26.12	14.93	8.21	11.94
You were out of your routine.	136	50.74	49.26	16.16	17.65	9.56	7.35
You did not have the heart medication with you.	135	41.48	58.52	17.04	11.85	7.41	5.19
You had other things to deal with.	134	39.55	60.45	12.69	14.18	7.46	5.22
You ran out of the heart medication.	136	25.00	75.00	9.56	6.62	6.62	2.21
The heart medication caused side-effects.	136	21.32	78.68	5.88	6.62	3.68	5.15
You were feeling down or upset.	137	18.25	81.75	10.22	3.65	2.92	1.46
There was no-one to help you.	135	11.11	88.89	5.19	2.96	1.48	1.48
You did not think the heart medication would help you live a longer life.	135	10.37	89.63	1.48	3.70	3.70	1.48
You did not want to be reminded about your heart problem.	136	10.29	89.71	5.88	1.47	2.21	0.74
You could not get answers to your questions about why you needed to take the heart medication.	136	10.29	89.71	4.41	2.21	2.94	0.74

[a]For the latent class analysis, items were dichotomized to indicate endorsed (2–5) or not endorsed (1).

[b]*1* = "none of the time," *2* = "a little of the time," *3* = "some of the time," *4* = "most of the time," *5* = "all of the time"

Table 3.

Fit statistics and model selection. The selected model is in bold.

NClass	*DF*	G^2	*AIC*	*BIC*	*CAIC*	*ABIC*	*Entropy*	*Percent Solution*
1	2036	477.74	499.74	531.86	542.86	497.07	1.00	100
2	2024	357.43	403.43	470.59	493.59	397.82	.70	100
3	**2012**	**292.03**	**362.03**	**464.23**	**499.23**	**353.50**	**.78**	**100**
4	2000	267.95	361.95	499.19	546.19	350.50	.83	27
5	1988	241.31	359.31	531.59	590.59	344.94	.85	11

Table 4.

Item response probabilities and class membership probabilities for the three-class solution. Response probabilities indicate the likelihood that a patient who is a member of this latent class would endorse a particular reason for nonadherence (e.g., for the reason "You were out of your routine," it is highly probable that patients in the *capacity+motivation* and *capacity* class would endorse this item, but that patients in the *no clear reasons* class would not). Standard errors are reported in parentheses; response probabilities greater than .50 are in bold.

Reason	**Item Response Probabilities**		
	Capacity	**Capacity+ Motivation**	**No Clear Reasons**
Class Membership Probabilities	**.45 (.06)**	**.14 (.04)**	**.41 (.06)**
You forgot.	**.82 (.06)**	**.77 (.10)**	.32 (.08)
You were out of your routine.	**.76 (.07)**	**.65 (.12)**	.19 (.07)
You had other things to deal with.	**.60 (.08)**	**.66 (.12)**	.08 (.04)
You did not have the heart medication with you.	**.64 (.07)**	**.53 (.12)**	.12 (.07)
You were feeling down or upset.	.20 (.06)	**.63 (.12)**	.00 (.01)
You could not get answers to your questions about why you needed to take the heart medication.	.01 (.02)	**.63 (.13)**	.01 (.02)
You did not think the heart medication would help you live a longer life.	.00 (.01)	**.61 (.14)**	.03 (.03)
You did not want to be reminded about your heart problem.	.03 (.03)	**.58 (.13)**	.02 (.02)
The heart medication caused side-effects.	.09 (.05)	.49 (.12)	.25 (.06)
You ran out of the heart medication.	.37 (.07)	.39 (.12)	.07 (.05)
There was no-one to help you.	.12 (.05)	.39 (.12)	.00 (.01)