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Co-occurring reasons for medication nonadherence within subgroups of patients with hyperlipidemia

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Abstract Medication nonadherence is a significant clinical problem among individuals taking statins. Poor adherence is often attributable to several reasons, yet most adherence interventions target a single reason. Baseline data were examined from a randomized clinical trial of 236 patients with hyperlipidemia. A latent class analysis was then performed on patients reporting any nonadherence (n = 109). A 4-class solution provided the most optimal fit and differentiation of classes. Class 1 (N = 59, 54%) included patients who reported occasionally forgetting. Class 2 (N = 16, 14%) represented patients who were concerned about side effects. Class 3 (N = 17, 16%) represented patients who reported out-of-routine life events as contributing to nonadherence. Class 4 (N = 17, 16%) represented patients who endorsed a large number reasons indiscriminately. Class membership was almost uniformly unrelated to any patient demographic factors or treatment arm. Each cluster of reasons defining these patients may be best addressed through different intervention strategies.

Keywords Medication nonadherence · Self-report · Latent class analysis · Reasons

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Introduction

Medication nonadherence is a significant clinical problem in the management of cardiovascular risk factors and disease (Ho et al., 2009). Nonadherence to cardiovascular medications, specifically including lipid-lowering medications, is associated with increased healthcare spending, hospitalization rates, morbidity, and premature mortality (Sokol et al., 2005). Epidemiologic data suggest that only approximately one-quarter of people prescribed lipid-lowering medication continue taking it longer than 6 months, and that fewer than half of patients receiving these medications achieve cholesterol management goals in line with recommended standards (van Driel et al., 2016).

Medication adherence research typically focuses on if, and to what extent, medications are not taken. Yet this conceptualization often fails to address the multidimensional nature of the behavior of medication adherence (Gellad et al., 2017). In fact, most interventions target a single reason for nonadherence (e.g., forgetting), and so fail to address other co-occurring reasons, thus reducing the intervention's effectiveness to increase adherence (Nieuwlaat et al., 2014).

Simply increasing the complexity of interventions to target multiple reasons for nonadherence is insufficient. If we are unable to identify which of these many underlying reasons for nonadherence are phenotypically displayed in different subgroups of patients presenting in clinics, then multifaceted interventions will be at best inefficient, and at worst ineffective. Person-centered approaches to categorizing individuals based on reasons for nonadherence, such as the latent class analysis presented, offer an underutilized avenue to understand these subgroups.

Adherence to statins is strongly associated with lowering low-density lipoprotein (LDL) cholesterol (Eisenberg, 1998), and has additional health benefits (e.g., lower risk of heart attacks and stroke; Liberopoulos et al., 2008). Thus, measuring and categorizing underlying reasons for statin nonadherence can inform interventions to improve treatment adherence and related health outcomes. We examine how to characterize individuals who are nonadherent to statins. Study findings will inform patient care by providing a mechanism to identify *profiles* of nonadherence behaviors within *individual patients* (rather than simply identifying nomothetic nonadherence risk factors that may or may not exist within an individual patient). These profiles of behaviors can in turn inform the tailoring of interventions and intervention components (Zhou et al., 2009).

Methods

Research study design

This cross-sectional secondary analysis involves baseline data from a recently completed randomized, controlled trial entitled, "Cardiovascular Intervention Improvement Telemedicine Study" (CITIES; clinicaltrials.gov identifier NCT01142908; Bosworth et al., 2018). CITIES tested a pharmacist-delivered chronic disease self-management intervention, administered by telephone to patients diagnosed with and taking medications for hypertension and/or hyperlipidemia for at least 1 year (to homogenize patients in the theoretical "implementation/persistence" phase of medication adherence rather than the "initiation" phase; Vrijens et al., 2012). Patients were recruited from three primary care clinics affiliated with the Durham Veterans Affairs Health Care System and were randomized to receive a multi-component, tailored, behavioral intervention or to an active educational control arm. Non-fasting serum cholesterol laboratory values were directly measured in each patient. The full method and theoretical rationale of CITIES has been described in prior publications (Melnyk et al., 2013).

Reasons for medication nonadherence

Patients who self-reported having a cholesterol-reducing prescription during the baseline survey completed a three-item measure of extent of nonadherence on a scale ranging from 1 (none of the time) to 5 (all the time) (Voils et al., 2012). Patients reporting nonadherence to any extent item (Cronbach's alpha = 0.90) were then categorized as nonadherent and asked to report how much 21 possible reasons for nonadherence contributed to missing doses. Both extent of and reasons for adherence were assessed over the previous 7 day timeframe, which has been shown to predict functional outcomes better than other timeframes (Jerant et al., 2008). These reasons have generally been validated across several disease samples, and have shown strong test–retest reliability (Voils et al., 2012), although the reasons vary slightly depending on disease based off of qualitative interviews (e.g., Blalock et al., under review). Although these reasons for nonadherence are reported using a five-point Likert scale (1 = not at all, 5 = very much), strong positive skew in each item's endorsement, previous usage of the items as dichotomous indicators, and a need to minimize the number of estimated parameters within the current sample led us to dichotomize each reason as either endorsed (selecting any scale response from 2 to 5) or not endorsed (selecting the scale response 1) (Voils et al., 2014).

Statistical analysis

All analyses were performed in the open source analysis software R (version 3.3.3). Linear, logistic, and multinomial logistic regression models were used to examine associations of demographic variables and treatment arm with class membership. Beta coefficients presented represent the difference (either in standard deviation units, raw units, or odds ratios) in outcomes between specific sets of dummy code predictors, while controlling for any potential covariates. Dummy codes represented probabilistic class membership were used, where Class 1 was the reference group. A latent class analysis (LCA) method was used (with the R statistical package polka; Linzer & Lewis, 2011) to determine the number of classes that underlie the general classification of reasons for medication nonadherence. Models are tested iteratively, beginning with two classes and increasing. For each model, LCA uses a maximum likelihood estimation algorithm to obtain the probabilities of an individual falling within each class, as well as the conditional probability of reporting a specific reason for nonadherence given membership in a specific class. The result is individual patients separated into a discrete number of classes based on their chances of endorsing a specific pattern across all 21 reasons for nonadherence.

LCA assumes the association among observed items (reasons for nonadherence) is due to a discrete latent structure of classes. LCA allows for classification of respondents based on different responses to the same items across subgroups of respondents, whereas factor-analytic and principal component methods would only allow for classification of item groupings (e.g., clusters of reasons) across the entire sample. As opposed to standard cluster analysis, LCA is a much more flexible and robust procedure, producing lower misclassification rates even when classes have unequal variances (Magidson & Vermunt, 2002). LCA also allows for comparison of different solutions with model fit indices. There is no current gold standard criterion for determining the optimal number of classes, so all goodness of fit estimates and nested-model comparisons were conducted using both theory-driven overviews of reason probability groupings and empirical measures of fit. Beyond statistical fit indices, we used expert judgment on the number of classes that was interpretable based on knowledge of treatments for patients with hyperlipidemia.

We used the log likelihood function, Akaike's Information Criterion (AIC), and Bayesian information criterion (BIC) to assess fit between the latent class model results and the data. In addition, we used Entropy to examine the separation of classes within each solution, where higher Entropy indicates better separation of classes. Discrepant results among the indicators lead us to favor the log likelihood function and AIC estimates, since the BIC fit statistic tends to under-perform with smaller sample sizes (Yang, 2006).

The 21 reasons for nonadherence were originally constructed to reflect causal indicators of nonadherence, and thus have low inter-item covariance, which is helpful for maximizing items' ability to discriminate among classes. Finally, to avoid the problems of local maxima in the maximum likelihood estimation algorithm, two hundred iterations were performed on each of the models. Each model converged in less than one hundred iterations, suggesting little difficulty with local maxima.

Results

Sample characteristics

The baseline survey was completed by 428 participants. Of those, 243 participants reported being prescribed a medication for hyperlipidemia management. Seven participants did not respond to two or more extent of medication nonadherence items and were excluded from analyses. Thus, 236 participants reported on their extent of nonadherence with cholesterol-reducing prescriptions and make up the analytic dataset (Table 1). Respondents at baseline were on average 62 years of age (SD = 8), primarily partnered (55%, n = 130), and male (87%, n = 206).

Non-fasting serum total cholesterol was positively correlated with endorsement of nonadherence after controlling for gender, age, race, and treatment arm as covariates ($\beta = 0.31$, Standard Error (se) = .06, $p < .001$). Forty-six percent of patients (n = 109) reported any nonadherence. Of these, 28.4% reported nonadherence on average less than or up to "rarely," 43.1% reported nonadherence on average more than "rarely" up to "sometimes," 16.5% reported nonadherence on average more than "sometimes" up to "often," and 11.9% reported nonadherence on average more than "often" up to "always." These patients reporting any nonadherence (average total cholesterol = 211.40 mg/dL) had significantly higher total cholesterol than patients reporting adherence (average total cholesterol = 188.69 mg/dL; $t = 3.97$, $p < .001$). Moreover, patients reporting any nonadherence (average LDL = 134.25) had significantly higher LDL cholesterol than patients reporting adherence (average LDL = 111.11; t = 5.01, $p < .001$). This represents 12% higher total cholesterol and 21% higher LDL cholesterol in patients reporting any nonadherence to statins. HDL cholesterol was not significantly different between adherence groups.

Reasons for medication nonadherence

Across the 109 patients who reported nonadherence, the most commonly endorsed reasons for nonadherence were forgetting (58%, n = 63), worried about taking medications for the rest of one's life (30%, n = 33), busy (26%, n = 28), side effects (25%, n = 27), coming home late (25%, n = 27), and traveling (23%, n = 25). The two least commonly reported reasons, which may be expected given the relative short-term stability of cholesterol levels and low cost in the Veterans Affairs Healthcare system, were: cholesterol being too low (5%, n = 5) and costing a lot of money (7%, n = 8). Additional reasons are reported in Table 2. On average, patients endorsed 4.10 reasons for nonadherence (ranging from 1 reason to 20 reasons of the 21 possible).

Latent classes of participants based on reasons for nonadherence

In the sample of 109 patients who reported nonadherence, fit criteria and probability estimates were compared for 2-class, 3-class, and 4-class models (presented in Table 3). Degrees of freedom available to reliably estimate param-

Table 1 Demographic characteristics of participants at baseline. n = 236

	Total (n = 236)	Adherers (n = 127)	Nonadherers (n = 109)
Age at baseline, mean(SD)	61.57 (8.03)	62.02 (8.66)	61.04 (7.22)
Male, n(%)	206 (87.29%)	111 (87.40%)	95 (87.15%)
Race			
White	112 (47.46)	67 (52.76)	45 (41.28)
Black	114 (48.31)	55 (43.31)	59 (54.13)
Other minority race	10 (4.23)	5 (3.94)	5 (4.6)
Education*			
Grade school/junior high	4 (1.69)	4 (3.15)	0 (0.00)
Some high school	4 (1.69)	1 (0.79)	3 (2.75)
High school equivalent or graduate	63 (26.69)	29 (22.83)	34 (31.19)
Some college or technical school	110 (46.61)	56 (44.09)	54 (49.54)
College graduate	55 (23.31)	37 (29.13)	16 (14.68)
Marital status			
Married or living with partner	130 (55.08)	78 (61.42)	52 (47.71)
Single, never married	12 (5.08)	5 (3.94)	7 (6.42)
Separated or divorced	85 (36.02)	41 (32.28)	44 (40.37)
Widowed	9 (3.81)	3 (2.36)	6 (5.50)
Employment status			
Employed full or part time	62 (26.27)	30 (23.62)	32 (29.36)
Disabled and unable to work	90 (38.14)	46 (36.22)	44 (40.37)
Retired and not working	84 (35.59)	51 (40.16)	33 (30.28)
Cholesterol information			
Total cholesterol levels (mg/dL)*	199.25 (45.46)	188.69 (46.17)	211.40 (41.61)
LDL cholesterol levels (mg/dL)*	121.57 (36.85)	111.11 (34.63)	134.25 (35.38)
HDL cholesterol levels (mg/dL)	44.98 (14.80)	45.97 (16.41)	43.67 (12.50)
Yes, doctor said you have high cholesterol	225 (95.34)	119 (93.70)	106 (97.25)
Yes, blood relative has high cholesterol	125 (52.97)	70 (55.12)	55 (50.46)
How many years ago you learned you had high cholesterol, mean(SD)	10.54 (8.99)	11.32 (9.47)	9.61 (8.34)
Not counting costs paid by insurance or VA, how much do you prescription medications cost you and your family each month?			
$0–50 per month	186 (78.39)	93 (73.23)	93 (85.32)
$51–100 per month	38 (16.10)	26 (20.47)	12 (11.01)
More than $100 per month	13 (5.51)	9 (7.09)	4 (3.67)
If needed, is there someone who could help you with tasks such as taking you to the doctor, fixing lunch, or home repairs?*			
Yes	210 (89.36)	119 (93.70)	91 (83.49)
No	25 (10.64)	8 (6.30)	17 (15.60)

*Significant differences at $p < .05$ between adherers and nonadherers from Chi square tests. Due to rounding some totals exceed 100%. The following values were missing: doctor told you high cholesterol (n = 3), blood relative high cholesterol (n = 88), years since learned high cholesterol (n = 14), someone could help you (n = 1)

eters were insufficient to examine models with 5-classes or more, yet fit statistics are included in Table 3 to illustrate potential model fit. The 4-class model yielded the best fit compared to the 2-class and 3-class models on two out of three fit criteria, including the lowest maximum likelihood residual estimate (− 2LL = − 734.5436), and the lowest AIC (1643.087). While the BIC was higher for the 4-class model (1871.460), it is likely an uninformative estimate due to the lower sample size. Finally, the 4-class solution obtained the highest Entropy value (.60), demonstrating the best separation of classes.

Figure 1 illustrates the weighted endorsement probabilities of each reason for nonadherence by class for the 4-class solution. Exact probabilities for each reason for nonadherence by each latent class can be found in the supplemental material. Class 1 (occasionally forgetful nonadherers; N = 59, 54%) had an almost 50/50 chance of endorsing forgetting (47%), and occasionally endorsed running out (16%), but were highly unlikely to endorse any

Table 2 Reasons for medication nonadherence reported by nonadherers (n = 109)

Reason for nonadherence	n (%) endorsed
I *forgot*	63 (57.8)
I *worried* about taking them for the rest of my life	33 (30.3)
I was afraid they may affect my *liver*	30 (27.5)
I was *busy*	28 (25.7)
The medication caused some *side effects*	27 (24.8)
I came *home late*	27 (24.8)
I was *traveling*	25 (22.9)
I *ran out* of medication	25 (22.9)
I was with *friends or family members*	21 (19.3)
I had *other medications* to take	21 (19.3)
I felt I did *not need* them	20 (18.4)
The time to take them was *between my meals*	18 (16.5)
I was afraid of becoming *dependent* on them	15 (13.8)
I was afraid the medication would *interact with other medication* I take	15 (12.8)
I was afraid they would cause *muscle pain*	14 (12.8)
I was in a *public place*	13 (11.9)
I *did not have any symptoms* of high cholesterol	13 (11.9)
I was feeling *too ill* to take them	12 (11.0)
I was supposed to take them *too many times* a day	11 (10.1)
They *cost* a lot of money	8 (7.3)
My *cholesterol was too low*	5 (4.6)

Table 2 is among a subset of patients who reported nonadherence on the extent of nonadherence items (109 nonadherent patients out of 236 patients who completed the extent of nonadherence items). Patients who endorsed reasons at any time (i.e., a little, somewhat, much, or very much) are included in the endorsed column. Italicized portions represent key terms of each item used for variable naming in Fig. 1 below

Table 3 Comparison of latent class models by fit statistics

# of Classes	− 2LL	Residual df	AIC	BIC	Entropy
2	− 807.6077	59	1701.215	1814.089	.57
3	− 766.2949	37	1662.590	1833.213	.55
4[a]	**− 734.5436**	**15**	**1643.087**	**1871.460**	**.60**

[a]Best-fitting model, whose classes are subsequently described in-text and in Fig. 1

other reason (< 15% chance for any other reason). Class 2 (side effect nonadherers; N = 16, 14%) were very likely to report side effects as reasons, such as being worried about side effects in general (100%), being afraid of liver damage (61%), or being afraid of muscle pain (41%). In this class, the only reason endorsed with any frequency not directly related to side effects was forgetting (14%). Class 3 (out-of-routine nonadherers; N = 17, 16%) were very likely to endorse forgetting (100%) in addition to other reasons indicative of random life events that may have thrown off their routine, such as coming home late (80%), traveling (75%), being with friends or family (61%), or because they ran out (50%). Class 4 (ubiquitous nonadherers; N = 17, 16%) were very likely (above 70%) to endorse five seemingly unrelated reasons, were more likely than not (above 50%) to endorse 15 out of the 21 reasons, and still endorsed their least likely reason (being too ill) at 19%.

Associations of latent classes and demographic characteristics

We examined the associations between the probability of falling into one of these four latent classes and key demographic features of patients, including age, race, gender, education, and income. Because Class 1 (occasionally forgetful nonadherers) represented the largest proportion of our sample, all dummy-coded regressions used Class 1 as the reference group. Each demographic variable was tested in a separate regression with no covariates to maximize the chances of finding differences. No classes differed from Class 1 on demographic factors

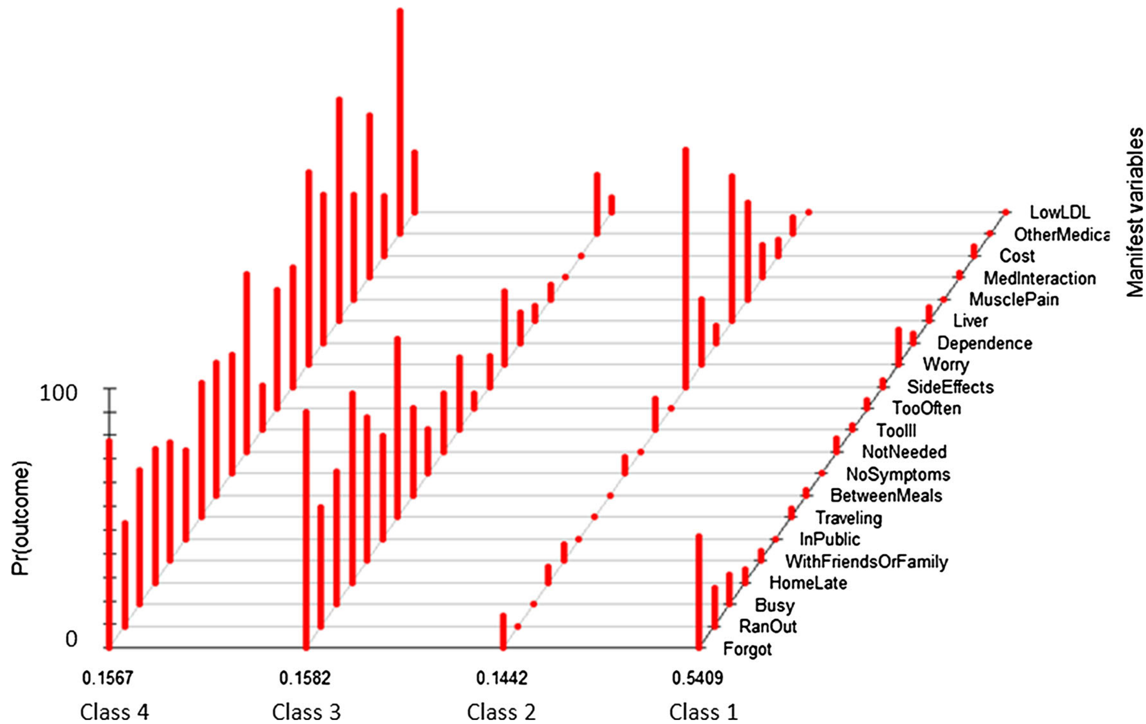

Fig. 1 Weighted endorsement probabilities of reasons for nonadherence by latent class. Note: variable names represent key portions of items as underlined in Table 2. Actual conditional probability values can be found in the supplementary materials table. Classes are ordered from right to left for ease in horizontal tracking to variable name and ease in estimating of conditional probabilities by the comparison bar in the left foreground

including age (all *p*'s $>$ .70), race (all *p*'s $>$ .90), education (all *p*'s $>$ .85), and income (all *p*'s $>$ .95). Regarding sex, however, males were much more likely to belong to Class 2 (side effect nonadherers; $b = 15.6$, $t = 16.26$, $p < .001$) than Class 1. Sex was not significantly different between Class 3 (out-of-routine nonadherers; $b = -0.68$, $t = -0.16$, $p = .87$) and Class 1, or Class 4 (ubiquitous nonadherers; $b = 0.46$, $t = 0.04$, $p = .97$) and Class 1. Finally, treatment arm did not significantly differ across classes (all *s*'s $>$ .90).

Discussion

To our knowledge, this study represents the first attempt to classify individuals with hyperlipidemia based on reasons for nonadherence to their statin medications. First, a group of individuals who reported any nonadherence to their statin medications (47%) was identified, which is commensurate with other nonadherence estimates in the literature (Osterberg & Blaschke, 2005). This group of nonadherers had, on average, 12% higher cholesterol than the group of adherers. Moreover, this 12% increase placed the average nonadherer with a total cholesterol value above 200 mg/dL, compared to the average perfect adherer being below 200 mg/dL. Total cholesterol levels above 200 mg/dL represent a commonly referenced initial cutoff whereby patients begin incurring some health risks (see: Stone et al., 2014). Thus, this higher risk group of 109 patients was worth investigating for subgroups to determine if different processes led to the same behavior placing them in a higher risk group.

Four distinct classes of nonadherers were found. Fifty-four percent of the sample reported nonadherence due primarily to forgetting only, with some endorsement of running out, which arguably could be categorized as a form of forgetting. Despite being the largest class, this solution illustrates that only half of nonadherers endorsed a single (or close to it) reason for nonadherence. The remaining three classes, representing 46% of the sample, endorsed more complex constellations of reasons, including numerous side effects (14%), life events pushing them out of a normal routine (16%), and a group endorsing most or at least many of the varied reasons (16%). Demographic factors of patients were almost unrelated to latent classes, with the exception that males were more prominent in the side effect nonadherers class than the occasionally forgetful nonadherers class. Although education was significantly different and some descriptive trends are present, it is also interesting that demographic factors were largely unable to explain differences between adherers and nonadheres as well (Table 1). While associations with more externally prevalent factors such as demographic information may be easier to assess, it may be that patterns of nonadherence relate more to internal factors such as motivation, self-efficacy, and self-regulatory capacity.

Examining each class within the broader literature of medication nonadherence supports their validity and generalizability. Similar to other estimates in the literature, forgetfulness seemed to be the reason that categorized the largest percentage of the sample of nonadherers (Gadkari & McHorney, 2012). In addition, the World Health Organization's (WHO) broader categorization of five domains related to nonadherence (patient-related factors, therapy-related factors, condition-related factors, health system factors, and social/economic factors; Sabaté, 2003) offer interesting parallels and deviations. The occasionally forgetful nonadherers (Class 1) and out-of-routine lifestyle nonadherers (Class 3) could be classified more broadly as nonadherence due to "patient-related" factors, whereas the side effect nonadherers (Class 2) could be classified more broadly as nonadherence due to "therapy-related" factors. Ubiquitous nonadherers (Class 4), however, present more of a challenge, and in doing so shows some important limitations of typical categorizations that is remedied with the current person-centered approach.

Using the WHO's categorizations does not fully capture the behavior of medication nonadherence as it is expressed in the real world (AlGhurair et al., 2012). For example, the current sample's ubiquitous nonadherers (Class 4) would span at least four of the five WHO categories. Moreover, these categories provide broad organization, whereas class membership in the current sample is distinguished by specific and actionable reasons that might translate more easily into multi-component interventions. Developing interventions based on broader organizations of reasons for nonadherence may provide a useful framework, but will likely miss the complexity of reasons that can be present in any individual patient (Kardas et al., 2013). The limitations of these traditional categorizations are also underscored by the fact that almost no demographic information of patients was useful in distinguishing these classes. Utility in developing effective, tailored interventions should be the key metric for determining the value of these classifications.

Close to half of the present sample is classified by multiple reasons for nonadherence. This complexity underscores the aforementioned problem of medication adherence interventions as often focusing on a single reason for nonadherence. This tendency to focus on one reason for medication nonadherence is exemplified in recent intervention trials. In one study of 53,000 nonadherers, for example, there was no significant difference in the odds of optimal adherence between any of the treatment arms using devices to target forgetting and the control arm (Choudhry et al., 2017). Addressing forgetfulness alone (characteristic of Class 1 in the current study) will likely not improve adherence by people who miss medications due to other reasons such as side effects (characteristic of Class 2) or life event constraints (characteristic of Class 3). This focus on one or a small number of reasons for nonadherence may explain why small or null effects are so often found, even in well-powered trials Nieuwlaat et al., 2014). The study findings suggest the ideal intervention may be multi-modal, addressing several prevalent reasons for nonadherence, so that the intervention can be tailored based on which subgroup (or class) the individual may likely be in based on their characteristics.

One type of simple and easily scalable intervention strategy that may benefit multiple classes of nonadherers, such as the "occasionally forgetful nonadherers" and "out-of-routine nonadherers" is habit formation (Bosworth et al., in press). Turning a health behavior into a personal habit can reduce the degree to which internal processes like memory and motivation play a factor. Forming implementation intentions (known as if–then statements or "instant habits") is one method of habit formation, and has been shown to increase medication adherence in other diseases (e.g., Brown et al., 2009). Still, more complex interventions may be necessary when patients endorse more internal and cognitive reasons for nonadherence, such as worries about side effects. In these cases, multimodal interventions that involve patient education and collaborative planning, in addition to monitoring and reminders, may be more necessary even if difficult to implement on a broader scale (e.g., Ho et al., 2014).

Despite the potential utility for intervention development, the current analysis has three primary limitations. First, the sample size is modest, as can be seen by the limited utility of the BIC and overall lower entropy values. Despite this, however, the high degree of discrimination among items and low relationships among them help clarify and increase confidence in a class structure supported by the literature that could otherwise be difficult to interpret with a modest sample size. Second, given the current wording of reasons, our Class 2 (side-effect nonadherers) cannot be distinguished between patients that were directed by their physician to stop taking the medication because of side effects. This class likely represents patient-initiated nonadherence due to side effects, as expected side effects are minimal and unlikely to lead physicians to recommend abrupt stoppage, and worries or beliefs about potential side effects are also a cause for nonadherence. Nevertheless, future studies should parse out these different sources. Third, although most latent class analyses are conducted with single timepoint items, there is increasing evidence that nonadherence to medications may be a time-varying phenomenon (Vrijens et al., 2012). Previous validation work has demonstrated good test–retest reliability for these reasons of nonadherence (Voils et al., 2012); however, future studies should examine latent growth mixture models to determine the stability of these classes over time, or identification of new classes due to variation in reasons for nonadherence.

In the current study, we present evidence for four distinct classes of medication nonadherers based on patient endorsement of a previously validated list of reasons for nonadherence. As with most initial findings, the stability of these classes, and utility for tailored interventions, will only be shown through further research aimed at these specific questions. Still, the current results suggest multiple subgroups based on reasons that vary widely, from simply forgetting, to more intentional nonadherence due to beliefs about potential side effects. These varied subgroups illustrate that, to be effective, interventions aimed at improving medication adherence must meet individual patients where they are at by targeting mechanisms of action (reasons for nonadherence) that are specific to the individual patient. Given that the vast majority of medication adherence behaviors occur outside of the supervision of clinical settings, understanding and subsequently intervening on the specific individual will be a necessary step to improving adherence rates.

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Compliance with ethical standards

Conflict of interest Dan V. Blalock, Hayden B. Bosworth, Bryce B. Reeve and Corrine I. Voils declare that they have no conflict of interest.

Human and animal rights and Informed consent All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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