Patient Preference and Adherence

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ORIGINAL RESEARCH

# Extent and reasons for nonadherence to antihypertensive, cholesterol, and diabetes medications: the association with depressive symptom burden in a sample of American veterans



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**Objective:** Persons with depressive symptoms generally have higher rates of medication nonadherence than persons without depressive symptoms. However, little is known about whether this association differs by comorbid medical condition or whether reasons for nonadherence differ by depressive symptoms or comorbid medical condition.

**Methods:** Self-reported extent of nonadherence, reasons for nonadherence, and depressive symptoms among 1,026 veterans prescribed medications for hypertension, dyslipidemia, and/or type 2 diabetes were assessed.

**Results:** In multivariable logistic regression adjusted for clinical and demographic factors, the odds of nonadherence were higher among participants with high depressive symptom burden for dyslipidemia (n=848; odds ratio [OR]: 1.42, *P*=0.03) but not hypertension (n=916; OR: 1.24, *P*=0.15), or type 2 diabetes (n=447; OR: 1.15, *P*=0.51). Among participants reporting nonadherence to antihypertensive and antilipemic medications, those with greater depressive symptom burden had greater odds of endorsing medication nonadherence reasons related to negative expectations and excessive economic burden. Neither extent of nonadherence nor reasons for nonadherence differed by depressive symptom burden among patients with diabetes.

**Conclusion:** These findings suggest that clinicians may consider tailoring interventions to improve adherence to antihypertensive and antilipemic medications to specific medication concerns of participants with depressive symptoms.

**Keywords:** adherence, compliance, chronic conditions, depression, heterogeneity

## Introduction

Pharmacotherapy for hypertension, dyslipidemia, and type 2 diabetes can reduce the risk of major cardiovascular and cerebrovascular events, but adherence is often suboptimal.[1–3] Medication nonadherence across these cardiometabolic conditions is associated with adverse events, greater inpatient and outpatient health care utilization, and higher health care costs.[4,5]

In patients with these conditions, numerous studies have shown that coexisting depressive symptoms are associated with higher rates of medication nonadherence.[6–19] However, it is unclear whether these medication nonadherence rates differ across these three comorbid conditions. Although prior condition-specific studies examining the role of depression in nonadherence have indicated different rates of nonadherence,[1,20,21] these studies have used different measures of nonadherence in different populations at different times. To our knowledge, no studies have specifically examined the association between depressive symptoms and medication nonadherence in concordant

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conditions using a consistent measure in the same population at the same time.[22]

Medication nonadherence may differ by depressive symptom burden because depressed patients tend to have a foreshortened view of the future[23–26] and may be more sensitive to physical discomfort. Medications for these three conditions differ in their regimen complexity, side effects, out-of-pocket costs, and early consequences of nonadherence. For example, nonadherence to diabetes medications may be driven by regimen complexity (particularly if insulin is required) or its considerable side effects for some patients, despite the short (primarily insulin) and early adverse effects of nonadherence. Nonadherence to antihypertensive medications may also be driven by its sometimes complex regimen or inconvenient side effects. The impact of depressive symptoms on nonadherence to lipid-lowering medications may be more modest because these medications have the least complex regimen (a single statin), the fewest side effects, and typically the lowest out-of-pocket costs.

Using a validated self-report measure that distinguishes extent of medication nonadherence from reasons for nonadherence,[27] we compared nonadherence rates and the reasons for reported nonadherence among participants with low and high depressive symptom burdens who were prescribed medication for at least one of three cardiometabolic conditions (hypertension, dyslipidemia, or diabetes). Based on prior literature, we expected that the association between depressive symptoms and extent of nonadherence would differ between patients with these different conditions for the reasons noted above. To inform what underlies the extent of nonadherence reported, we also examined the association between depressive symptoms and reasons for nonadherence among the subset of patients reporting nonadherence. These findings can serve to guide interventions to improve adherence using a framework sensitive to the unique barriers presented by different patients, medications, and disease types.

# Methods

## Study setting and population

This study was approved by the Institutional Review Board of the Durham Veterans Administration Medical Center (VAMC), Durham, NC, USA. A waiver for documentation of informed consent was approved to preserve participant anonymity. All procedures followed were in accordance with the 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 participants for being included in the study.

In 2012, a randomly selected subset of 1,999 veterans' affairs (VA) patients from a larger claims-based cohort of 7,933 veterans in the Durham VAMC catchment area with one or more of four cardiometabolic conditions (diabetes, hypertension, dyslipidemia, and heart failure) were sent a mailed survey. Veterans were initially selected in the larger claims-based cohort from an initial cohort of 29,368 veterans identified from Durham VAMC medical records. Veterans were excluded if they had no outpatient utilization in 2008 (n=3,001), were receiving outpatient care at other VAMCs (n=11,594), died before the end of the study period (n=518), were younger than 40 years in 2008 (n=173), had a diagnosis for these conditions that could not be confirmed in VA claims data (n=5,363), were seen in outpatient primary care clinics staffed by resident physicians (n=339), had a medication for at least one of these four conditions that could not be confirmed in claims data (n=401), or were missing data for marital status or copayment status (n=46). We restricted the sample to veterans aged 40 years or older because the risk of cardiovascular disease increases markedly with each 20 mmHg increment in systolic blood pressure for adults 40 years and over[28] and the onset for the majority of type 2 diabetes patients occurs after the age of 40 years. By mailing a survey to a random 1,999 of these 7,933 patients, we were able to link the survey data for respondents back to their VAMC claims data to obtain information on demographic and clinical factors to include as covariates.

## Measures

The survey included a validated two-domain self-reported measure of medication nonadherence that assesses extent of nonadherence and reasons for nonadherence.[27] The three-item nonadherence extent measure asks respondents to complete the following statements using a 7-day recall period: "I took all doses of my [condition] medication", "I missed or skipped at least one dose of my [condition] medication", and "I was not able to take all of my [condition] medication". The five response options measured frequency: never, rarely, sometimes, often, and always.[29] Participants who reported nonadherence on the extent scale were asked to complete the 21-item measure of reasons for nonadherence in the last 7 days separately for each condition for which they were taking medications (ie, hypertension, dyslipidemia, and type 2 diabetes) using five-point scales anchored by "not at all" and "very much". Patients also completed the validated[30–35] Mental Health Inventory

(MHI)-5 scale developed by Veit and Ware[36] as a measure of depressive symptomology.

To examine and adjust for demographic differences between survey respondents across cardiometabolic conditions and levels of depressive symptom burden, we constructed covariates for age (<65 years, 65+ years), sex, race (Caucasian, non-Caucasian, and unreported), marital status (married, divorced/widowed, single/never married, and unknown), copayment status (free VA care or not), number of cardiometabolic conditions (1, 2, 3, or 4), number of other chronic conditions,[37] and number of VA prescribers (0, 1, 2, 3, or 4+) in 2012 from information VA claims data.

## Analysis

All analyses were conducted using Stata/MP (v12.1; StataCorp LP, College Station, TX, USA). We did not analyze data for the congestive heart failure patients due to the small sample size. One of the three extent of nonadherence items ("I took all of my doses of [condition] medication") was not highly correlated with the other two items ($r$=0.27 and $r$=0.20) as it had been in the initial validation study involving oral administration.[27] In this self-administration of the measure, that item, which was designed to be reverse-scored to reduce acquiescence bias, produced substantial measurement error, with many participants responding in a way that was inconsistent with the other two items. Thus, we excluded this item. The remaining two items were highly correlated ($r$=0.58) and had skewed distributions, with most respondents responding "never" (ie, perfect adherence). Accordingly, following our prior research, responses of "never" were coded as "adherent", while all other responses were coded as "nonadherent".[27] Respondents were included in the analysis for nonadherence reasons if at least one extent question was coded as nonadherent. Reasons for nonadherence examined among those reporting nonadherence on the extent scale were treated as individual items and dichotomized, with responses of "not at all" coded as "no", and all others as "yes".[27]

We calculated a weighted MHI-5 score for respondents who responded to at least four out of five items by taking the mean of all items for which responses were provided. Scores were then scaled from 0 to 100. We assigned MHI-5 scores <65 and ≥65 as "low" and "high" depressive symptom burden, respectively (based on validity testing of Rumpf et al[33] against Diagnostic and Statistical Manual of Mental Disorders [DSM] IV criteria).

We first compared survey respondents and non-respondents on demographic variables available from the VA claims data (ie, age, sex, marital status, race, copayment status, number of cardiometabolic conditions, and number of VA prescribers in 2012). For each of the three cardiometabolic conditions, we then estimated logistic regression models to compare the odds of nonadherence (ie, anything other than "never" on the extent of nonadherence scale) between respondents with high and low depressive symptom burden adjusting for the previously mentioned demographic variables. Among participants reporting nonadherence in each of the three condition cohorts, we then estimated a logistic regression for each reason for nonadherence, controlling for the same covariates to understand whether the odds of endorsing a reason for nonadherence differed by depressive symptom burden. We corrected for multiple comparisons in the 63 regressions (21 reasons × 3 cohorts) using Benjamini and Hochberg's approach to control for false discovery rate;[38,39] a post-adjusted $P$-value of <0.05 was considered significant.

# Results

## Comparison of survey respondents and non-respondents

We received 1,026 returned surveys of the 1,999 originally mailed (response rate =51.3%). Respondents were more likely than non-respondents to be greater than 65 years of age, Caucasian, married, and required to pay VA copayments (Table 1). Many survey respondents completed two or all three self-reported medication adherence measures since they had two or more of the three conditions of interest: 415 (40%) completed the hypertension and cholesterol items on the survey; 24 (2%) completed the cholesterol and diabetes items; 44 (4%) completed the hypertension and diabetes items; and 358 (35%) completed items for all three conditions.

## Prevalence of nonadherence and association with depressive symptoms

The unadjusted proportion of participants reporting nonadherence was similar across the three conditions: 37% (n=338) of 917 participants taking antihypertensives, 37% (n=168) of 437 participants taking diabetes medications, and 39% (n=330) of 849 participants taking lipid-lowering medications (Table 2). The unadjusted difference between the depression symptom burden groups was only significant among participants taking lipid-lowering medications (46% vs 34%, $P$=0.001). Adjusted analyses were consistent. That is, the odds of nonadherence to medications to manage dyslipidemia were significantly greater (odds ratio [OR]: 1.42, $P$=0.025) among participants with depressive symptoms than those without (Table 3). In contrast, the adjusted odds

**Table 1** Comparison of survey responders and non-responders

| | Completed survey | | | | *P*-value |
|---|---|---|---|---|---|
| | Yes (n=1,026) | | No (n=974) | | |
| | N | % | N | % | |
| Age in years (mean, SD) | 70.0 | 9.7 | 69.0 | 10.7 | 0.036 |
| Age (n, %) | | | | | |
| >65 years | 303 | 29.5 | 341 | 35.0 | 0.010 |
| 40–64 years | 723 | 70.5 | 633 | 65.0 | |
| Sex (n, %) | | | | | |
| Male | 969 | 94.4 | 934 | 95.9 | 0.145 |
| Female | 57 | 5.56 | 40 | 4.1 | |
| Race (n, %) | | | | | |
| White | 687 | 67.0 | 569 | 58.4 | <0.001 |
| Black | 290 | 28.3 | 369 | 37.9 | |
| Other | 21 | 2.1 | 22 | 2.3 | |
| Unknown | 28 | 2.7 | 14 | 1.4 | |
| Marital status (n, %) | | | | | |
| Married | 679 | 66.2 | 570 | 58.5 | 0.001 |
| Divorced/widowed | 216 | 21.0 | 241 | 24.7 | |
| Single/never married | 95 | 9.3 | 101 | 10.4 | |
| Unknown | 36 | 3.5 | 62 | 6.4 | |
| Pays health care copay (n, %) | | | | | |
| Yes | 287 | 28.0 | 227 | 23.3 | 0.019 |
| No | 739 | 72.0 | 746 | 76.6 | |
| Missing | 0 | 0.0 | 1 | 0.1 | |
| Pays prescription copay (n, %) | | | | | |
| Yes | 711 | 69.3 | 605 | 62.1 | 0.001 |
| No | 315 | 30.7 | 368 | 37.8 | |
| Missing | 0 | 0.0 | 1 | 0.1 | |
| Gagne comorbidity score (median, IQR) | 0.3 | 1.5 | 0.0 | 1.3 | 0.012 |
| Number of conditions (mean, SD) | 6.39 | 5.0 | 6.50 | 5.0 | 0.613 |
| Number of VA prescribers (n, %) | | | | | |
| 0 | 52 | 5.1 | 63 | 6.5 | 0.025 |
| 1 | 628 | 61.2 | 540 | 55.4 | |
| 2 | 232 | 23.6 | 226 | 23.2 | |
| 3 | 70 | 6.8 | 80 | 8.2 | |
| 4 | 44 | 4.3 | 64 | 6.7 | |

**Notes:** *P*-values were estimated with two- sample *t*-test for age and number of conditions; with Wilcoxon rank sums for the Gagne Score; and with Fisher's exact test for all others.
**Abbreviations:** IQR, interquartile range; SD, standard deviation; VA, veterans' affairs.

of nonadherence did not differ by depressive symptoms for participants taking antihypertensives (OR: 1.24, *P*=0.15) or diabetes medications (OR: 1.15, *P*=0.51).

## Reasons for nonadherence and association with depressive symptoms

Among the subset reporting nonadherence, the most frequent reason for not taking medications for all three conditions was "I forgot" (Table 4), but the proportion endorsing this reason was only significantly different between depressed and non-depressed for nonadherence to lipid-lowering medications (53% vs 38%, *P*=0.01). For hypertension and dyslipidemia medications, the second most frequently endorsed reason was "I ran out of medication", but this was only significantly associated with depressive symptoms in the dyslipidemia cohort. In both hypertension and dyslipidemia cohorts, there were significant differences by depressive symptoms in endorsement of "I was afraid they may affect my sexual performance", "I was worried about taking them for the rest of my life", "I was busy", "They cost a lot of money", "I had other medications to take", "I was feeling too ill to take them", "I was afraid the medication would interact with other medication I take", "I was afraid of becoming dependent on them", and "I was supposed to take them too many times a day". In the diabetes cohort, there were no significant differences by depressive symptoms for any of the 21 reasons in unadjusted or adjusted analyses.

Adjusted results were generally similar to the bivariate associations (Table 5), although more reasons remained

**Table 2** Unadjusted percent self-reported adherence and nonadherence by condition

| Covariate | Hypertension | | *P*-value | Dyslipidemia | | *P*-value | Type 2 diabetes | | *P*-value |
|---|---|---|---|---|---|---|---|---|---|
| | Adherent n=578 | Nonadherent n=338 | | Adherent n=518 | Nonadherent n=330 | | Adherent n=279 | Nonadherent n=168 | |
| Depressive symptoms | | | | | | | | | |
| MHI >65 (yes) | 59.9 | 40.1 | 0.059 | 54.1 | 45.9 | 0.001 | 58.6 | 41.4 | 0.102 |
| MHI <65 (no) | 65.2 | 34.8 | | 65.6 | 34.4 | | 64.9 | 35.1 | |
| Age (years) | | | | | | | | | |
| 40–64 | 59.2 | 40.8 | 0.034 | 54.3 | 45.7 | 0.001 | 58.2 | 41.8 | 0.092 |
| 65+ | 65.3 | 34.5 | | 65.3 | 34.7 | | 65.0 | 35.0 | |
| Sex | | | | | | | | | |
| Male | 63.8 | 36.2 | 0.068 | 61.4 | 38.6 | 0.264 | 63.9 | 36.1 | 0.009 |
| Female | 52.7 | 42.3 | | 55.6 | 44.4 | | 38.5 | 61.5 | |
| Race | | | | | | | | | |
| White | 65.1 | 34.9 | 0.139 | 66.0 | 34.0 | <0.001 | 65.8 | 34.2 | 0.145 |
| Black | 58.2 | 41.8 | | 51.2 | 48.3 | | 56.2 | 43.8 | |
| Other | 66.7 | 33.3 | | 53.1 | 46.9 | | 62.5 | 37.5 | |
| Marital | | | | | | | | | |
| Married | 63.9 | 36.1 | 0.390 | 64.5 | 35.6 | 0.013 | 64.7 | 35.3 | 0.389 |
| Divorced/widowed | 61.7 | 38.3 | | 52.5 | 47.5 | | 58.1 | 41.9 | |
| Never married | 58.8 | 41.2 | | 55.8 | 44.2 | | 56.9 | 43.1 | |
| Unknown | 100 | 0.0 | | 40.0 | 60.0 | | 100.0 | 0.0 | |
| Pays health care copay | | | | | | | | | |
| Yes | 61.3 | 38.7 | 0.797 | 67.1 | 32.9 | 0.058 | 66.4 | 33.6 | 0.528 |
| No | 63.6 | 36.4 | | 58.8 | 41.2 | | 61.3 | 38.7 | |
| Unknown | 66.7 | 36.9 | | | | | | | |
| Pays prescription copay | | | | | | | | | |
| Yes | 60.9 | 39.1 | 0.118 | 62.0 | 38.0 | 0.759 | 62.9 | 37.1 | 0.924 |
| No | 68.2 | 31.8 | | 59.0 | 41.0 | | 61.6 | 38.4 | |
| Unknown | 66.7 | 33.3 | | | | | | | |
| Number of conditions | | | | | | | | | |
| 1 | 85.7 | 14.3 | 0.458 | | | 0.792 | | | 0.879 |
| 2 | 62.2 | 37.8 | | 62.4 | 37.6 | | 65.8 | 34.2 | |
| 3 | 64.2 | 35.8 | | 60.1 | 39.9 | | 61.6 | 38.4 | |
| 4 | 55.6 | 44.4 | | 58.8 | 41.2 | | 60.7 | 39.3 | |
| Number of VA prescribers | | | | | | | | | |
| 0 | 62.6 | 37.4 | 0.278 | | | 0.433 | | | 0.157 |
| 1 | 63.7 | 36.3 | | 60.6 | 39.4 | | 65.5 | 34.5 | |
| 2 | 63.2 | 36.8 | | 57.5 | 42.5 | | 63.9 | 36.1 | |
| 3 | 53.9 | 46.2 | | 61.8 | 38.2 | | 43.6 | 56.4 | |
| 4 | 72.7 | 27.3 | | 60.4 | 39.6 | | 63.4 | 36.6 | |

**Note:** Percentages and *P*-values estimated using Fisher's exact test.
**Abbreviations:** MHI, Mental Health Inventory; VA, veterans' affairs.

statistically significant between groups with hypertensive medications than dyslipidemia (six reasons vs two reasons). The group differences by depression symptom burden disappeared for the most frequently reported nonadherence reasons.

## Discussion

This study represents the first comparison, to our knowledge, of the association between depressive symptoms and self-reported medication nonadherence and reasons for nonadherence across three concordant cardiometabolic conditions. We expected that the association between depressive symptoms and nonadherence and reasons for nonadherence might differ by condition because the individual medication regimens differ among these conditions in terms of regimen complexity, side effects, out-of-pocket costs, and consequences of nonadherence.

Our rates of extent of nonadherence are similar to nonadherence rates from prior condition-specific analyses based on medication refill data,[1,20] but lower than nonadherence rates reported in studies using other self-report measures.[12,40] In our study, depressive symptom burden was significantly

**Table 3** Adjusted self-reported nonadherence by condition

| Condition | Hypertension n=917 | | Dyslipidemia n=849 | | Type 2 diabetes n=437 | |
|---|---|---|---|---|---|---|
| **Covariate** | **OR** | ***P*-value** | **OR** | ***P*-value** | **OR** | ***P*-value** |
| High depressive symptom burden | 1.24 | 0.149 | 1.42 | 0.025 | 1.15 | 0.512 |
| Age ≥65 years | 0.77 | 0.087 | 0.74 | 0.058 | 0.84 | 0.450 |
| Female | 1.55 | 0.139 | 0.88 | 0.706 | 2.55 | 0.041 |
| Race | | | | | | |
| Black | 1.38 | 0.045 | 1.59 | 0.005 | 1.39 | 0.139 |
| Other | 0.87 | 0.727 | 1.65 | 0.196 | 0.83 | 0.75 |
| Marital status | | | | | | |
| Divorced/widowed | 1.03 | 0.875 | 1.55 | 0.016 | 1.23 | 0.401 |
| Single/never married | 1.03 | 0.265 | 1.21 | 0.325 | 1.01 | 0.969 |
| Pays health care copay | 1.19 | 0.347 | 0.94 | 0.723 | 0.98 | 0.938 |
| Pays prescription copay | 1.45 | 0.038 | 1.17 | 0.381 | 1.09 | 0.72 |
| Number of conditions | | | | | | |
| 3 | 0.90 | 0.464 | 0.99 | 0.944 | 1.04 | 0.877 |
| 4 | 1.51 | 0.254 | 1.11 | 0.792 | 1.25 | 0.633 |
| Number of VA prescribers | | | | | | |
| 1 | 0.88 | 0.523 | 1.34 | 0.199 | 0.82 | 0.496 |
| 2 | 0.87 | 0.562 | 1.40 | 0.187 | 0.73 | 0.355 |
| 3 | 1.33 | 0.341 | 1.05 | 0.338 | 1.81 | 0.162 |
| 4 | 0.63 | 0.199 | 1.16 | 0.683 | 0.83 | 0.674 |

**Abbreviations:** OR, odds ratio; VA, veterans' affairs.



associated with extent of nonadherence to lipid-lowering medications but not to nonadherence to antihypertensive or diabetes medications. The finding of no association for antihypertensive or diabetes medications is at odds with other condition-specific studies, which have used different adherence and depression measures (antihypertensive, diabetes).[40,41–44] The lack of an observed difference in our study may be the result of measurement sensitivity (MPR and various self-report), or, in the case of diabetes, small sample size (168 diabetes vs 578 for hypertension and 518 for dyslipidemia). Future research in larger samples should examine the extent of and reasons for nonadherence separately for individuals taking oral agents and those taking insulin. We suspect there are important differences between oral and injectable diabetes medications, but our measure did not address these medication modes independently.

In addition to being novel by assessing medication nonadherence in concordant conditions using a consistent measure in the same population at the same time, this study is also novel because we examined whether the impact of depressive symptoms on reasons for nonadherence differed between these three conditions. We found that some reasons offered for nonadherence varied between participants reporting higher and lower depression symptom burden. Although the overall top reason for nonadherent behavior in all conditions was forgetting, this reason was not significantly different between depressed and non-depressed respondents in any condition. Participants with greater depressive symptom burden taking antihypertensive medications expressed more concerns about the medication, although participants with a higher depressive symptom burden taking dyslipidemia medications were more likely to actually be nonadherent. Cost was also a concern for individuals with a higher depressive symptom burden taking hypertension and dyslipidemia medications, even though it was not one of the most commonly endorsed reasons for any condition. Although many veterans obtain VA medications at no cost or for a relatively low copayment (US$9 per 30-day supply), participants with a higher depressive burden with these conditions were somewhat more likely to be responsible for copays.

These adjusted results suggest that extent of nonadherence to lipid-lowering medications may have the greatest room for improvement for patients with comorbid depression. Providers may want to assess whether patients who are nonadherent to lipid-lowering medications are concerned about having to take them for their entire lives or out-of-pocket costs because these two reasons were more likely to be endorsed by participants with depressive symptoms. Participants were also concerned about the impact of antihypertensives on their sexual performance[45] and complexity of their regimen, so these issues should be considered when counseling patients about increasing their adherence. Similar to Laba et al[46] we assume that medication nonadherence

**Table 4** Frequency and percent of reported reasons for nonadherence by depressive symptom burden and condition

| Condition | | Hypertension | | | | | Dyslipidemia | | | | | Type 2 diabetes | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No | Item | Low (n=192) | | High (n=146) | | FDR-p | Low (n=175) | | High (n=155) | | FDR-p | Low (n=87) | | High (n=80) | | FDR-p |
| | | Freq | % | Freq | % | | Freq | % | Freq | % | | Freq | % | Freq | % | |
| | **Negative expectations or worry** | | | | | | | | | | | | | | | |
| 4 | I worried about taking them for the rest of my life | 22 | 12.64 | 38 | 29.92 | <0.001 | 15 | 9.87 | 36 | 26.47 | <0.001 | 7 | 8.97 | 18 | 26.87 | 0.070 |
| 10 | I was afraid of becoming dependent on them | 10 | 5.88 | 15 | 15.20 | 0.018 | 14 | 9.21 | 24 | 17.52 | 0.012 | 5 | 6.49 | 6 | 9.09 | 0.692 |
| 11 | I was afraid they may affect my sexual performance | 22 | 12.64 | 39 | 29.77 | <0.001 | 19 | 12.18 | 33 | 23.24 | <0.001 | 10 | 12.82 | 16 | 25.53 | 0.070 |
| 19 | I was afraid the medication would interact with other medication I take | 17 | 9.94 | 21 | 17.21 | 0.038 | 10 | 6.58 | 21 | 15.11 | 0.030 | 5 | 6.49 | 9 | 13.85 | 0.070 |
| | **Poor memory** | | | | | | | | | | | | | | | |
| 2 | I forgot | 78 | 43.33 | 70 | 51.85 | 0.095 | 59 | 37.82 | 76 | 52.78 | 0.011 | 41 | 5.62 | 31 | 41.89 | 0.787 |
| 18 | I ran out of medication | 44 | 25.73 | 41 | 31.78 | 0.117 | 31 | 20.0 | 39 | 27.66 | 0.044 | 22 | 28.21 | 16 | 24.24 | 0.436 |
| | **Complex medication regimen** | | | | | | | | | | | | | | | |
| 15 | I was supposed to take them too many times a day | 4 | 2.35 | 14 | 11.38 | 0.013 | 7 | 4.64 | 16 | 11.68 | 0.012 | 4 | 5.19 | 8 | 12.12 | 0.070 |
| 16 | I had other medications to take | 17 | 10.06 | 30 | 24.39 | 0.015 | 15 | 9.87 | 24 | 17.65 | 0.013 | 8 | 10.39 | 7 | 10.94 | 0.692 |
| | **Concerns about drug effects** | | | | | | | | | | | | | | | |
| 3 | The medication caused some side effects | 23 | 13.07 | 25 | 19.84 | 0.046 | 22 | 14.47 | 33 | 24.09 | 0.012 | 10 | 12.82 | 19 | 27.94 | 0.070 |
| 17 | They make me need to urinate too often | 30 | 17.34 | 35 | 28.23 | <0.001 | 20 | 13.16 | 28 | 20.44 | 0.012 | 12 | 15.38 | 13 | 19.70 | 0.184 |
| 20 | My (lab measure) was too low | 32 | 18.29 | 19 | 15.57 | 0.623 | 13 | 8.44 | 13 | 9.42 | 0.716 | 20 | 25.64 | 22 | 33.33 | 0.428 |
| 21 | I was feeling too ill to take them | 18 | 1.47 | 22 | 18.18 | 0.044 | 11 | 7.19 | 24 | 17.78 | 0.012 | 10 | 12.82 | 9 | 13.85 | 0.353 |
| | **Does not take condition seriously** | | | | | | | | | | | | | | | |
| 13 | I felt I did not need them | 24 | 14.20 | 20 | 16.53 | 0.407 | 18 | 11.92 | 23 | 16.55 | 0.081 | 10 | 12.99 | 13 | 19.70 | 0.184 |
| 7 | I did not have any symptoms of (condition) | 33 | 19.19 | 27 | 22.50 | 0.033 | 21 | 13.82 | 24 | 18.05 | 0.081 | 18 | 22.78 | 17 | 25.37 | 0.977 |
| | **Financial burden** | | | | | | | | | | | | | | | |
| 5 | They cost a lot of money | 27 | 15.61 | 32 | 25.20 | <0.001 | 14 | 9.40 | 25 | 18.25 | <0.001 | 10 | 12.82 | 11 | 16.18 | 0.153 |
| | **Interferes with lifestyle** | | | | | | | | | | | | | | | |
| 1 | I was busy | 26 | 14.86 | 33 | 25.78 | 0.015 | 21 | 13.82 | 26 | 18.71 | 0.025 | 14 | 18.18 | 13 | 19.12 | 0.692 |
| 6 | I came home late | 32 | 18.5 | 28 | 23.14 | 0.414 | 28 | 18.79 | 25 | 18.25 | 0.559 | 19 | 25.33 | 16 | 23.19 | 0.738 |
| 8 | I was with friends or family members | 31 | 17.92 | 26 | 21.49 | 0.117 | 20 | 13.25 | 24 | 17.52 | 0.116 | 13 | 16.88 | 9 | 13.24 | 0.911 |
| 9 | I was in a public place | 20 | 11.83 | 18 | 14.88 | 0.300 | 16 | 10.67 | 16 | 11.85 | 0.523 | 11 | 14.29 | 6 | 8.96 | 0.869 |
| 12 | The time to take them was between my meals | 18 | 10.47 | 18 | 14.52 | 0.06 | 17 | 11.04 | 18 | 12.86 | 0.287 | 7 | 8.97 | 15 | 22.39 | 0.070 |
| 14 | I was traveling | 40 | 22.99 | 26 | 2.63 | 0.843 | 32 | 21.05 | 23 | 16.91 | 0.716 | 27 | 34.62 | 13 | 19.40 | 0.911 |

**Abbreviation:** FDR-p, false discovery rate *P*-value; Freq, response frequency.

is a multifactorial outcome influenced not only by the patient's affective status, but also by symptom severity, complexity of the medication regimen, number and nuisance value of the medication side effects, short- and medium-term consequences of not taking the medication, and the affordability of the drug to the patient. It is of particular interest that adherence was worst for dyslipidemia, which arguably has the least complex regimen and fewest side effects. Several reasons may explain this result: Elevated cholesterol is relatively asymptomatic; cholesterol levels do not vary significantly over short periods of time; and cholesterol levels cannot be self-monitored. In contrast, elevated blood pressure and blood glucose cause symptoms; values can vary significantly over short periods of time; and patients can self-monitor their blood pressure and blood glucose levels.

**Table 5** Adjusted odds of self-reported reasons for nonadherence among participants with high depressive symptom burden

| Condition | | Hypertension (n=338) | | Dyslipidemia (n=330) | | Type 2 diabetes (n=167) | |
|---|---|---|---|---|---|---|---|
| **No** | **Item** | **OR** | **FDR-p** | **OR** | **FDR-p** | **OR** | **FDR-p** |
| | **Negative expectations/worry** | | | | | | |
| 4 | I worried about taking them for the rest of my life | 3.09 | 0.011 | 3.63 | 0.021 | 4.96 | 0.105 |
| 10 | I was afraid of becoming dependent on them | 2.38 | 0.152 | 2.13 | 0.119 | 1.44 | 0.818 |
| 11 | I was afraid they may affect my sexual performance | 3.09 | 0.011 | 2.34 | 0.084 | 3.41 | 0.205 |
| 19 | I was afraid the medication would interact with other medications I take | 2.27 | 0.108 | 2.64 | 0.105 | 2.79 | 0.391 |
| | **Poor memory** | | | | | | |
| 2 | I forgot | 1.44 | 0.263 | 1.71 | 0.116 | 0.70 | 0.53 |
| 18 | I ran out of medication | 1.54 | 0.252 | 1.61 | 0.206 | 0.94 | 0.979 |
| | Complex medication regimen | | | | | | |
| 15 | I was supposed to take them too many times a day | 6.52 | 0.017 | 2.40 | 0.185 | 3.38 | 0.348 |
| 16 | I had other medications to take | 3.11 | 0.011 | 1.70 | 0.282 | 0.98 | 0.979 |
| | **Concerns about drug effects** | | | | | | |
| 3 | The medication caused some side effects | 1.42 | 0.479 | 2.03 | 0.116 | 2.88 | 0.205 |
| 17 | They make me need to urinate too often | 2.33 | 0.028 | 2.04 | 0.116 | 3.10 | 0.252 |
| 20 | My (lab measure) was too low | 1.07 | 0.854 | 1.36 | 0.573 | 1.57 | 0.488 |
| 21 | I was feeling too ill to take them | 1.57 | 0.386 | 2.76 | 0.084 | 1.16 | 0.922 |
| | **Does not take condition seriously** | | | | | | |
| 13 | I felt I did not need them | 1.62 | 0.252 | 1.45 | 0.452 | 1.78 | 0.445 |
| 7 | I did not have any symptoms of (condition) | 1.26 | 0.613 | 1.38 | 0.503 | 2.54 | 0.348 |
| | **Financial burden** | | | | | | |
| 5 | They cost a lot of money | 2.86 | 0.011 | 3.17 | 0.042 | 1.96 | 0.445 |
| | **Interferes with lifestyle** | | | | | | |
| 1 | I was busy | 1.90 | 0.126 | 1.50 | 0.402 | 0.86 | 0.922 |
| 6 | I came home late | 1.22 | 0.613 | 0.91 | 0.85 | 0.53 | 0.445 |
| 8 | I was with friends or family members | 1.20 | 0.621 | 1.40 | 0.483 | 1.02 | 0.979 |
| 9 | I was in a public place | 1.31 | 0.613 | 1.00 | 0.999 | 0.64 | 0.652 |
| 12 | The time to take them was between my meals | 1.31 | 0.613 | 1.05 | 0.951 | 3.81 | 0.205 |

**Abbreviations:** FDR-p, false discovery rate *P*-value; OR, odds ratio.



There are several limitations to this study. First, these associations between reasons for nonadherence and depressive symptom burden are cross-sectional, and they should not be considered causal relationships. We adjusted for a number of demographic and clinical variables in our analysis, but unobserved covariates (eg, severity of conditions, income, daily pill burden) may have influenced our findings. Second, it is possible that individuals with high vs low depressive burden have different reporting tendencies, such that self-reported information may be more accurate among one group than the other (eg, Tang et al[17]; but also see Wang et al[7] Gonzalez et al[47]). Third, we do not have information about what class(es) of medications our participants were taking for their conditions, which could influence extent of nonadherence and specific reasons for nonadherence. Fourth, we did not have access to medication possession ratios from claims data contemporaneous to this survey, which would have allowed us to compare how the association of depressive symptom burden varies between self-reported medication adherence and refill measures of adherence. Last, the estimated association between depressive symptoms and self-reported medication nonadherence may be subject to survey response bias, since survey responders were more likely to be older, white, and married than non-responders.

## Conclusion

This research provides initial evidence demonstrating heterogeneity in both the extent of medication nonadherence and specific reasons for nonadherence among individuals with and without depressive symptoms in three concordant cardiometabolic conditions. Survey respondents with depressive symptoms generally expressed more concerns about medication side effects/interactions and the duration and frequency of taking their medications than participants without depressive symptoms. Our results suggest that clinicians may be able to identify specific medication concerns of participants with depressive symptoms that can serve as intervention targets for achieving improved adherence.

Future research should systematically reckon with the variety of regimens, side effects, and costs of different medications within chronic conditions to observe which factors are medication-specific, which are associated with depressive symptom burden, and how these factors interact. With a framework to structure short- and medium-term costs and rewards for adherence, the heterogeneity in reasons for medication nonadherence across chronic conditions, medication classes, and patient characteristics may begin to form more predictable categories. Similarly, longitudinal studies of variability in reasons for nonadherence and how these reasons fluctuate with the point of pharmaceutical intervention (ie, initiation vs maintenance) and changing depressive symptom burden over time are also needed.[29] Together, these areas of research will inform development of more effective interventions to improve medication adherence in at-risk patient populations.

## Disclosure

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