Drug Side Effect Symptoms and Adherence to Antihypertensive Medication

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BACKGROUND

Non-adherence to antihypertensive medication increases the risk of uncontrolled hypertension. Antihypertensive drug-related symptoms (side effects) are frequently cited as a main cause of non-adherence, but with little support from prospective studies. We evaluated the association between drug side effects and prospective adherence to treatment.

METHODS

We collected data on the number and dose of antihypertensive drugs at enrollment and at 3, 6, 9, and 12 months of follow-up in a cohort of 175 hypertensive patients starting or restarting antihypertensive treatment (mean age: 50 years; 58% women). During the follow-up visits, we gathered data on 24 side effects during the last month and the pill count adherence ratio (PCAR = pills taken out of number prescribed $\times$ 100) since the previous visit. The association between side effects at a visit and adherence through the next visit was estimated using mixed effect models.

RESULTS

Eighty-five percent of the participants experienced side effects, and 34.5% became non-adherent (PCAR <80%). After adjusting

for confounders, PCAR was 6.0 percentage points lower ($P = 0.04$) among individuals with number of side effects above the median value (4 symptoms). Also, in individuals with genitourinary side effects, PCAR was 7.1 percentage points lower ($P = 0.02$) than in those without such side effects. Specifically, PCAR was 6.5 ($P = 0.06$) and 7.6 ($P = 0.01$) percentage points lower among individuals with excessive urination and decrease in sexual drive, respectively.

CONCLUSION

Antihypertensive drug side effects was associated with drug adherence but only excessive urination and decrease in sexual drive significantly predicted lower adherence. These symptoms could be used as markers to screen out patients at high risk of non-adherence.

Keywords: blood pressure; cohort study; drug side effects; hypertension; medication adherence.

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Hypertension affects almost 43 million adults (≥ 18 years old) in the United States.¹ Fifty-two percent of them receive pharmacologic treatment, but only 24% have their blood pressure (BP) controlled (systolic BP <140 and diastolic BP <90 mm Hg).¹ Medication non-adherence (taking <80% of the number of prescribed pills)² occurs in about 50% of newly treated hypertensive patients within the first year of treatment,^{3–5} and has been identified as a main cause of uncontrolled hypertension.⁶ Non-adherence increases the risk of uncontrolled hypertension about 5 times,⁶ as well as overall mortality, hospitalization rate, and cost of care.^{7,8} The impact of non-adherence is likely mediated through uncontrolled hypertension, which is known to increase the risk of heart failure,⁹ stroke,¹⁰ and cardiovascular mortality.¹¹

It is estimated that about 20–97% of patients who take antihypertensive medications experience drug side effects^{12,13} (unintended effects that occur at regular doses and are related to the properties of the drug).¹⁴ Some studies suggest that side effects are a main determinant of low adherence

to antihypertensive drugs.^{6,12,15,16} Unfortunately, these were cross-sectional studies and, therefore, were prone to reverse causality bias, except one.¹⁵ In addition, information errors, particularly correlated errors, were a likely source of bias in all of them because both the exposure (symptoms) and the outcome (adherence) were measured by self-report during the same interview.^{17,18} Finally, none of these studies accounted for the frequency and severity of side effects.

In light of the limitations of previous studies we investigated the association between antihypertensive drug side effects and adherence to treatment in a cohort of hypertensive patients starting antihypertensive treatment for the first time or after ≥ 2 months without treatment.

METHODS

We analyzed data from a longitudinal study of the role of symptoms of depression and anxiety on adherence to antihypertensive medication among individuals starting or restarting treatment.³ This study was approved by the

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Institutional Review Board of the University of Wisconsin (UW)-Madison.

Individuals were eligible if they had essential hypertension (systolic/diastolic BP $\geq 140/90$ mm Hg, based on the mean of 2 or more measurements) and started antihypertensive treatment for the first time (within 1 week before enrollment into the study) or restarted treatment after stopping for ≥ 2 months. Pregnant women and individuals with secondary hypertension, self-reported history of chronic kidney disease, hepatitis, cancer, diabetes, rheumatoid arthritis, psychiatric disease requiring drug treatment, coronary heart disease, congestive heart failure, taking mood-modifying medications, and <20 or ≥ 70 years old were not eligible. Participants were recruited from clinics at the Department of Family Medicine, UW-Madison and the Wisconsin Research and Education Network. Follow-up visits were conducted at 3 (baseline for the present study), 6 (follow-up visit 1), 9 (follow-up visit 2), and 12 (follow-up visit 3) months after enrollment.

Upon enrollment and during follow-up visits, we collected data on socio-demographic factors, the number and doses of antihypertensive medications, drug side effect symptoms, copayment of medications, number of physician visits, hospital admissions, medication use in the year before enrollment, symptoms of depression and anxiety, use of medications for chronic diseases, self-reported health status, physical, sexual, and sleep symptoms, alcohol intake, and current smoking status.

A subset of questions from the Physical Symptoms Distress Index¹⁹ were used to gather data on 24 symptoms related to the use of antihypertensive medications at each visit. The Physical Symptoms Distress Index has been successfully used to evaluate medication side effects in hypertensive patients.²⁰ It asks whether a participant has had a symptom in the past month (yes or no) and, if so, scores its frequency as 1 (1–2 times per month), 2 (1–2 times per week), 3 (often each week), or 4 (almost daily) and its severity as 0 (not at all bothered), 1 (not very bothered), 2 (somewhat bothered), 3 (very bothered), or 4 (extremely bothered). We multiplied the scores for presence, severity, and frequency of each symptom and summed up the resulting values for all symptoms to create an overall symptom distress (OSD) score. This scoring approach has been successfully used in previous studies among hypertensive patients.^{19,20}

For the data analysis we grouped clinically related symptoms in 7 clusters: anticholinergic (dry mouth, blurry vision, and vision problems), gastrointestinal (heartburn and vomiting), genitourinary (increased urination, getting up often during the night to urinate, problems in gaining an erection, and decreased interest in sex), cardio-pulmonary (cough, swelling of feet or ankles, and shortness of breath), functional impairment (fatigue, general weakness, lethargy, and tiredness), neuro-psychiatric and cognitive (numbness or tingling of hand, insomnia, mood swings, feeling depressed, and difficulty remembering things), and miscellaneous (itching, weight gain, and muscle cramp). A similar grouping has been used in a previous study.¹³

Participants were asked to bring their medication bottles to each study visit. Using a pill-count form, data on the

name, number of remaining pills in the bottle, and number of prescribed pills of each antihypertensive medication were collected at each visit. Adherence was measured as the proportion of pills taken out of the total number of pills prescribed between 2 consecutive visits, i.e., the pill count adherence ratio (PCAR) = (pills taken $\div$ pills prescribed) $\times$ 100. Following current practice, participants were considered non-adherent if they took $<80\%$ of the prescribed number of pills (PCAR $< 80\%$). This cut-point has been shown to correlate well with urinary levels of diuretics and changes in BP²¹ and with cause-specific hospitalization in hypertensive patients.² Separate analyses were performed for both PCAR and non-adherence.

We drew *a priori* a directed acyclic graph (DAG)²² and used Pearl's back-door criterion,²³ as implemented in DAGitty²⁴ to select a minimal sufficient adjustment set of variables to control confounding by measured variables, while avoiding selection bias resulting from conditioning on a collider.^{22,25,26} The DAG (Figure 1) was built by identifying all known factors affecting side effects or adherence, and then including all common causes of any pair of variables already in the DAG.^{25,26} Pearl's back-door criterion is based on the identification of noncausal (backdoor) paths connecting the exposure to the outcome. Noncausal paths must be blocked by adjustment/conditioning to obtain a valid association between the exposure and the outcome.²³ The resulting minimal sufficient adjustment set included antihypertensive medication class, number of antihypertensive medications, comorbidity, and use of medications for other diseases as potential confounders. We adjusted for these variables as well as age, sex, and race in all our regression models.

We used random effects logistic regression with non-adherence as the outcome and random effects multiple linear regression with PCAR as the outcome in our analysis. We report random effects estimates, a combination of within and between-individual effects.²⁷ We used robust estimates of the standard errors of the regression coefficients to account for repeated observations of the same participants.²⁷ Four summary measures of side effects were used as exposures in the analysis: (i) the total number of symptoms reported (range: 0–24); (ii) the OSD score (range: 0–384); (iii) the cluster-specific number of side effects; and (iv) the cluster-specific OSD score. Symptoms experienced during the 3rd, 6th, and 9th months were considered relevant exposure for adherence at 3–6, 6–9, and 9–12 months, respectively. Thus, in all analyses the exposure preceded the outcome. All analyses were performed using Stata 13 (StataCorp LP, 2013, College Station, TX).²⁸

The original study included 214 patients. This number decreased to 175, 133, 109, and 91 patients at 3, 6, 9, and 12 months of follow-up, respectively. Based on Twisk's formula,²⁹ our study had a power of 90% to detect a statistically significant increase of 60% in the risk of non-adherence in those who experienced as compared to those who did not experience side effects (50% vs. 31% risk of non-adherence). We assumed an alpha error rate of 5%, a sample size of 175 subjects, and a correlation of 0.55 among the repeated measurements of the outcome.

Figure 1. Directed acyclic graph for the association between drug side effects and adherence among patients starting antihypertensive medications. Exposure variable is drug side effects, outcome variable is drug adherence, variables in circles with gray solid color are ancestors of the exposure and outcome variable, variables in circles with dots are ancestors of the outcome variable, and variables in circles with no shade or dots are ancestors of the exposure variable. Minimal sufficient set of variables needed to estimate the independent association between antihypertensive drug side effects and adherence are antihypertensive drug class, medications for chronic diseases, number of antihypertensive pills, and comorbidity.

Table 1. Characteristics of a cohort of newly treated hypertensive patients at baseline by occurrence of drug side effects

Characteristics	All participants	Side effects		P
	(N = 175)	No (n = 23)	Yes (n = 152)	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Age (years)	50.1 (48.5, 51.6)	50.2 (45.2, 55.3)	50.1 (48.5, 51.7)	0.94
Male (%)	58.0 (50.5, 65.2)	60.9 (38.6, 79.3)	57.6 (49.5, 65.3)	0.74
White (%)	88.5 (82.8, 92.4)	87.0 (64.3, 96.1)	88.7 (82.6, 92.9)	0.79
Above high school (%)	74.7 (67.7, 80.7)	73.9 (50.9, 88.6)	74.8 (67.2, 81.2)	0.91
Antihypertensive drug (%)				
Diuretics	39.7 (32.6, 47.2)	30.4 (14.3, 53.4)	41.1 (33.4, 49.2)	0.33
ACE inhibitors	31.6 (25.1, 39.0)	34.8 (17.4, 57.4)	31.1 (24.2, 39.0)	0.72
Calcium channel blockers	13.8 (9.4, 19.8)	13.0 (3.9, 35.8)	13.9 (9.2, 20.4)	0.91
Other	14.9 (10.3, 21.1)	21.7 (8.7, 44.8)	13.9 (9.3, 20.5)	0.33
Taking other medications (%)	10.9 (7.0, 16.6)	4.4 (0.5, 28.4)	11.9 (7.6, 18.2)	0.28
Number of BP drug	1.4 (1.3, 1.5)	1.3 (1.1, 1.7)	1.4 (1.3, 1.5)	0.83
Systolic BP (mm Hg)	135.1 (132.9, 137.3)	132.0 (127.2, 136.7)	135.6 (133.1, 138.0)	0.28
Diastolic BP (mm Hg)	85.1 (83.6, 86.6)	82.2 (78.6, 85.7)	85.6 (83.9, 87.2)	0.13

Abbreviations: CI, confidence interval; ACE, angiotensin-converting enzyme; BP, blood pressure.

RESULTS

Data for at least 1 follow-up visit were available for 175 participants. At baseline (the first follow-up visit of the parent study), participants had a mean age of 50 years (range: 23–69), 58.0% were male, 88.5% were White, and 74.7% had

an education level above high school (Table 1). The most frequently used antihypertensive drugs at baseline were diuretics (39.7%) and angiotensin-converting enzyme inhibitors (31.6%). Participants who reported at least 1 side effect had higher systolic and diastolic BP and were more likely to take diuretics and medications for other conditions.

The proportion of participants who experienced at least 1 drug-related side effect (85.5%; 95% confidence interval (CI): 82.1, 88.9) and the median number of side effects (4; 95% CI: 3.6, 4.4)³⁰ were consistent across study periods. The median OSD score was 7 at baseline, 6 at visits 1 and 2, and 5 at visit 3. On average, the PCAR was 95.1% (95% CI: 91.5%, 99.1%) across all visits: 94.8% between baseline and visit 1, 96.2% between visits 1 and 2, and 94.2% between visits 2 and 3. The risk of becoming non-adherent was 21.4% between baseline and visit 1, 15.8% between visits 1 and 2, and 19.2% between visits 2 and 3. The cumulative risk of non-adherence calculated using the actuarial method³¹ was 34.5% (95% CI: 23.1%, 48.9%) for the whole length of the study. Average PCAR and the risk of non-adherence by number and severity of side effects are reported in [Supplementary Table 1](#).

Before and after adjusting for confounders, PCAR and risk of non-adherence were not significantly different in participants in the 2nd, 3rd, and 4th quartiles of the number of side effects, as compared to those in the 1st quartile ([Table 2](#)). Individuals with >4 symptoms (above the median) had 6.0 percentage points (95% CI: -11.8, -0.2) lower adherence and twice the risk of non-adherence (odds ratio = 2.01, 95% CI: 1.03, 3.92) than those with ≤4 symptoms. No significant differences in PCAR and risk of non-adherence were found when individuals with symptoms were compared with those without symptoms. Moreover, the OSD score was not associated with PCAR or risk of non-adherence in the crude and the adjusted analyses, regardless of how OSD was categorized ([Table 2](#)). An increasing risk of non-adherence was observed across the quartiles of both the number of symptoms and the OSD score, but these trends failed to reach

statistical significance (trend test *P*-values of 0.10 and 0.61, respectively).

Out of all the clusters of symptoms evaluated, only the cluster of genitourinary symptoms was significantly associated with adherence ([Table 3](#)). Participants with at least 1 genitourinary symptom had 7.1 percentage points (95% CI: -12.5, -1.2) lower adherence, after adjusting for confounders, than individuals with no such symptoms. The cluster of genitourinary symptoms (at least 1 vs. none) was marginally associated with the risk of non-adherence (adjusted odds ratio = 1.90, *P* = 0.09). Also, participants with an OSD score above the median for genitourinary symptoms had 7.3 percentage points (95% CI: -13.2, -1.5) lower adherence than those with OSD below the median ([Table 3](#)). An OSD score for these symptoms (above vs. below median) was marginally associated with non-adherence (adjusted odds ratio = 1.85, *P* = 0.08). Further analyses using the number of symptoms within a cluster as a continuous variable showed similar results, with the genitourinary cluster being the only significant predictor of adherence.

Regarding specific genitourinary symptoms, we found that participants who experienced excessive urination or a decrease in sexual drive had 6.5 percentage points (95% CI: -13.2, 0.2, *P* = 0.06) and 7.6 percentage points (95% CI: -13.6, -1.6, *P* = 0.01) lower adherence, respectively, than individuals who had not experienced these symptoms ([Table 4](#)). Participant with an OSD score above the median for a decrease in sexual drive had 8.3 percentage points (95% CI: -14.9, -1.8) lower adherence than those with an OSD score below the median, but the OSD score for specific genitourinary symptoms was not associated with the risk of non-adherence.

Table 2. Adjusted mean difference in pill count adherence ratio (PCAR) and odds ratio of non-adherence (PCAR < 80%) to antihypertensive medications by number of side effect symptoms and by overall symptom distress score in newly treated hypertensive patients

Exposure	Outcome: PCAR		Outcome: Non-adherence	
	Mean difference ^a (95% CI)	<i>P</i>	Odds ratio ^a (95% CI)	<i>P</i>
<i>Number of side effects</i>				
1st quartile (0–2)	0		1	
2nd quartile (3–4)	2.93 (–3.48, 9.34)	0.37	0.39 (0.12, 1.24)	0.11
3rd quartile (5–8)	–5.92 (–12.26, 0.43)	0.07	1.33 (0.56, 3.15)	0.52
4th quartile (9–23)	–3.61 (–13.42, 6.19)	0.47	1.96 (0.83, 4.64)	0.12
Above the median ^b	–6.00 (–11.84, –0.16)	0.04	2.01 (1.03, 3.92)	0.04
At least 1	1.27 (–7.28, 9.82)	0.77	0.78 (0.33, 1.85)	0.57
<i>Overall symptom distress</i>				
1st quartile (0–0)	0		1	
2nd quartile (1–6)	0.79 (–6.73, 8.31)	0.84	0.64 (0.23, 1.79)	0.39
3rd quartile (7–17)	–3.57 (–10.42, 3.29)	0.31	1.15 (0.49, 2.69)	0.74
4th quartile (18–204)	–0.73 (–10.31, 8.84)	0.88	1.14 (0.52, 2.54)	0.74
Above the median ^c	–2.38 (–7.59, 2.82)	0.37	1.32 (0.71, 2.43)	0.38

Abbreviations: CI, confidence interval.

^aModels adjusted for age, sex, race, antihypertensive drug class, number of antihypertensive drugs, and other medications. ^bMedian score for number of side effects was 4 at all visits. ^cMedian score for overall symptom distress score was 7 at visits 1 and 6 at visits 2 and 3.

Table 3. Adjusted mean difference in pill count adherence ratio (PCAR) and odds ratio of non-adherence (PCAR < 80%) to antihypertensive medications for clusters of related side effect symptoms in newly treated hypertensive patients

Exposure	Outcome: PCAR	P	Outcome: Non-adherence	P
	Mean difference ^a (95% CI)		Odds ratio ^a (95% CI)	
At least 1 vs. no symptom				
Anticholinergic	−1.85 (−7.96, 4.25)	0.55	1.62 (0.83, 3.15)	0.16
Gastrointestinal	−2.92 (−8.88, 3.05)	0.34	1.59 (0.82, 3.07)	0.17
Genitourinary	−7.11 (−13.12, −1.10)	0.02	1.90 (0.89, 4.07)	0.09
Cardio-pulmonary	−0.69 (−5.80, 4.42)	0.79	0.97 (0.53, 1.79)	0.93
Functional impairment	−2.24 (−7.37, 2.89)	0.39	1.41 (0.77, 2.60)	0.27
Neuro-psych-cognitive	−0.15 (−5.65, 5.34)	0.96	0.80 (0.41, 1.54)	0.50
Miscellaneous	−4.30 (−9.95, 1.34)	0.14	1.66 (0.89, 3.08)	0.11
Overall symptom distress				
(above vs. below median ^b)				
Anticholinergic	0.31 (−7.08, 7.71)	0.93	1.15 (0.57, 2.32)	0.70
Gastrointestinal	−2.67 (−9.10, 3.76)	0.42	1.28 (0.65, 2.50)	0.48
Genitourinary	−7.31 (−13.17, −1.46)	0.01	1.85 (0.93, 3.68)	0.08
Cardio-pulmonary	−0.42 (−6.07, 5.23)	0.88	1.17 (0.63, 2.20)	0.62
Functional impairment	−1.48 (−7.23, 4.28)	0.62	1.23 (0.68, 2.23)	0.49
Neuro-psych-cognitive	−1.10 (−6.72, 4.51)	0.70	1.13 (0.62, 2.04)	0.69
Miscellaneous	−1.11 (−7.22, 5.01)	0.72	1.15 (0.62, 2.14)	0.66

Anticholinergic (dry mouth, blurry vision, and vision problems); Gastrointestinal (heartburn and vomiting); Genitourinary (increased urination, getting up often during the night to empty bladder, problems in gaining an erection, and decreased interest in sex); Cardio-pulmonary (cough, swelling of feet or ankles, and shortness of breath); Functional impairment (fatigue, general weakness, lethargy, and tiredness); Neuro-psychiatric and cognitive (numbness or tingling of hand, insomnia, mood swings, feeling depressed, and difficult remembering things); Miscellaneous (itching, weight gain, and muscle cramp).

Abbreviations: CI, confidence interval.

^aModels adjusted for age, sex, race, antihypertensive drug class, number of antihypertensive drugs, and other medications. ^bMedian score for overall symptom distress score was 7 at visits 1 and 6 at visits 2 and 3.

DISCUSSION

We found that an increased number of antihypertensive drug side effects was independently associated with lower treatment adherence in the next 3 months. Individuals with more than 4 side effects had 6.0 percentage points lower adherence and twice higher risk of non-adherence as compare to those with a lower number of side effects. When exploring different clusters of side effects, the association persisted only among patients experiencing genitourinary side effects.

Our findings are consistent with those from previous cross-sectional^{6,12,16} and cohort¹⁵ studies. However, the association between side effects and adherence was weaker in our study, a finding that could be partly explained by the selection of patients <70 years, without major comorbidities and by the fewer and less bothersome side effects of newer antihypertensive drugs.³² Lin *et al.*¹⁶ found that hypertensive patients who experienced any drug side effects in the past 6 months were 77% less likely to be adherent than those who did not experience side effects. Toyoshima *et al.*¹² and Morgado *et al.*⁶ also found that individuals who reported having side-effect symptoms at the time of an interview were 1.37 times and 3.70 times, respectively, more likely to be non-adherent

at that time than individuals with no symptoms. However, these studies were cross-sectional and thus were prone to reverse causality bias.³³ Moreover, it is likely that positive correlated errors, resulting from measuring symptoms and adherence by self-report during the same interview, resulted in overestimation of the association between symptoms and non-adherence.^{17,18}

Our findings are also in support of those from the only published prospective study to date.¹⁵ Indeed, in Gregoire's *et al.*¹⁵ study, the risk of non-adherence in the next 3 months was 90% higher among newly treated hypertensive patients who experienced at least 1 drug side effect. However, the validity of those findings could have been compromised by the use of self-reported adherence. In fact, in contrast to Gregoire *et al.*,¹⁵ we found a significantly higher risk of non-adherence among individuals with a number of side effects above as compared to below the median, but not in those who reported only one side effect, as compared to no side effects.

In hypertensive patients, lack of motivation to comply with treatment could arise from concerns about potential treatment side effects.³⁴ Drug side effects appear to be more frequent and adherence lower in patients using diuretics and β -blockers, as compare to other antihypertensive drugs.^{12,35}

Table 4. Adjusted mean difference in pill count adherence ratio (PCAR) and odds ratio of non-adherence (PCAR < 80%) to antihypertensive medications for genitourinary symptoms in newly treated hypertensive patient

Exposure	Outcome: PCAR		Outcome: Non-adherence	
	Mean difference ^a (95% CI)	P	Odds ratio ^a (95% CI)	P
<i>Presence vs. Absence of symptom</i>				
Genitourinary symptoms				
Increased urination	-6.52 (-13.21, 0.17)	0.06	1.93 (0.81, 4.57)	0.14
Urinating at night	-4.09 (-10.50, 2.32)	0.21	1.88 (0.91, 3.89)	0.09
Erection problems	-3.63 (-11.28, 4.03)	0.35	1.32 (0.35, 4.97)	0.68
Decrease in sex drive	-7.60 (-13.57, -1.64)	0.01	1.54 (0.73, 3.25)	0.26
<i>Overall symptom distress</i>				
<i>(above vs. below median^b)</i>				
Genitourinary symptoms				
Increased urination	-4.69 (-13.12, 3.75)	0.28	1.75 (0.71, 4.29)	0.22
Urinating at night	-4.75 (-12.45, 2.94)	0.23	1.57 (0.72, 3.43)	0.26
Erection problems	-2.30 (-8.71, 4.10)	0.48	0.55 (0.22, 1.39)	0.21
Decrease in sex drive	-8.34 (-14.86, -1.81)	0.01	1.75 (0.79, 3.85)	0.17

Abbreviations: CI, confidence interval.

^aModels adjusted for age, sex, race, antihypertensive drug class, number of antihypertensive drugs, and other medications. ^bMedian score was zero for all individual side effects symptoms during each visit.

Individuals who were taking diuretics in our study were more likely to experience side effects than those taking other antihypertensive drugs (41% vs. ≤30%). This suggests that the observed association between side effects and adherence could be explained, at least partly, by a higher frequency of side effects among patients taking diuretics and β -blockers. Unfortunately, our sample size was too small to allow informative comparisons across different types of antihypertensive drugs. In spite of its association with the number of side effect symptoms, we did not observe an association between adherence and OSD scores. Combining symptoms that significantly predicted adherence with those that did not into 1 composite score might have averaged out the association between OSD and adherence, making it nonsignificant.

In contrast to previous cross-sectional studies^{6,12,16} the longitudinal nature of our study allowed capturing the correct temporal relationship between drug side effects and adherence. To our knowledge, ours is the first study to assess the association between side effects distress (severity and frequency) and adherence to antihypertensive drugs. In addition, unlike previous studies based on self-report,^{6,12,15,16} we used an objective measurement of adherence (pill count), likely reducing error in the measurement of the outcome. In fact, the sensitivity of pill count compared to electronic cap bottles is 93%³⁶ and there is a high correlation between adherence measured by electronic cap bottles and pill count (concordance rate = 89%).³⁷

In view of the selection criteria used in the parent study, our findings may not be applicable to hypertensive patients who are already under treatment, those ≥70 years old, those with chronic diseases, those taking mood-modifying drugs, and those without high levels of adherence. Also, these exclusions may have made the study cohort too homogenous

regarding adherence and, therefore, less amenable to detect significant differences in adherence. The low level of non-adherence observed in our cohort (about 35% as compared to 50% in other cohorts³⁻⁵) was probably a consequence of “cooperative” patients being more likely both to participate in a cohort study and to comply with prescribed treatment. Though this selective participation was unlikely to introduce bias, since both exposure (side effect symptoms) and outcome (adherence) occurred after the decision to participate,³⁸ it limits the extrapolability of our findings to patients with high levels of adherence. On the other hand, our study included newly treated patients and those who restarted treatment after stopping for ≥2 months. This should induce no bias, since previous treatment may exert an effect on non-adherence through either the exposure (side effects) or variables included in our regression models (i.e., those in the minimal sufficient adjustment set). In contrast, including previously treated patients likely enhanced the generalizability of our results.

Our modest sample size, coupled with consistently high levels of adherence across study visits likely decreased the power of our study to detect statistically significant associations between side effect symptoms and adherence, as suggested by the wide CIs in Tables 2–4. Non-differential error in the measurement of the exposure and the outcome could have also decreased study power. Particularly, pill count is an objective measure of adherence, but it is known to overestimate adherence.^{39,40} This type of measurement error was likely independent of drug side effects and, therefore, may have resulted in bias toward the null, further compromising study power. Finally, due to the observational nature of our study, we cannot rule out the possibility of confounding by unmeasured variables, such as incident health conditions

that may influence both side effects and adherence to antihypertensive medications.

In conclusion, individuals with higher number of antihypertensive drug-related side effects had lower adherence to medication. Of all the side effects, only genitourinary symptoms, specifically excessive urination and a decrease in sexual drive, predicted adherence in the next 3 months. These symptoms may potentially be used as markers to screen out patients at high risk of non-adherence. Nevertheless, further studies on the role of side effect symptoms are warranted, not only to replicate our findings, but also to assess if they could be extrapolated to other populations, such as patients already under treatment and with concomitant diseases, and to develop accurate and easy to use side effect based screening tools to predict adherence in the clinical setting.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (<http://ajh.oxfordjournals.org>).

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DISCLOSURE

The authors declared no conflict of interest.

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