Antihypertensive Drug Class and Adherence: An Electronic Monitoring Study

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BACKGROUND

Medication adherence is essential to optimizing blood pressure (BP) control. Prior research has demonstrated differences in pharmacy refill patterns according to antihypertensive drug class. No prior study has assessed the association between drug class and day-to-day adherence.

METHODS

Between 2011 and 2014, we enrolled a convenience sample of 149 patients with persistently uncontrolled hypertension from two inner-city clinics and concurrently measured adherence of up to four antihypertensive medications using electronic pillboxes during the interval between two primary care visits. The main outcome was mean percent of days adherent to each drug. Mixed effects regression analyses were used to assess the association between drug class and adherence adjusting for age, gender, race, ethnicity, education, health insurance, coronary artery disease, heart failure, chronic kidney disease, diabetes, number of medications, days monitored, and dosing frequency.

RESULTS

The mean age was 64 years; 72% women, 75% Hispanic, 88% prescribed ≥1 BP medication. In unadjusted analyses, adherence was lower for beta-blockers (70.9%) compared to angiotensin receptor blocking agents (75.0%, $P = 0.11$), diuretics (75.9%, $P < 0.001$), calcium channel blockers (77.6%, $P < 0.001$) and angiotensin-converting enzyme inhibitors (78.0%, $P < 0.0001$). In the adjusted analysis, only dosing frequency ($P = 0.0001$) but not drug class ($P = 0.71$) was associated with medication adherence.

CONCLUSIONS

Antihypertensive drug class was not associated with electronically measured adherence after accounting for dosing frequency amongst patients with uncontrolled hypertension. Low adherence to beta-blockers may have been due to the common practice of prescribing multiple daily dosing. Providers may consider using once daily formulations to optimize adherence and should assess adherence among all treated patients with uncontrolled hypertension.

Keywords: blood pressure; drug class; hypertension; medication adherence.

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Approximately 50% of US adults are nonadherent to their antihypertensive drug regimens, contributing to uncontrolled hypertension, increased health care costs, and worse cardiovascular prognosis.[1–3] The latest US hypertension guidelines do not discuss whether there is a role for incorporating interclass differences in adherence for prescribing decisions.[4] Pharmacy refill and claims data suggest that there are differences in adherence among the most commonly prescribed antihypertensive medication classes.[5,6] Compared to angiotensin receptor blocking agents (ARB), angiotensin-converting enzyme inhibitors (ACEI), and calcium channel blockers (CCB), thiazide diuretics, and beta-blockers have increased gaps between prescription refills and are more likely to be discontinued, possibly due to increased adverse effects of medications from these classes.[5–7] According to a recent meta-analysis, mean persistence to antihypertensive medications was 65% for ARBs vs. only 28% and 51% for beta-blockers and diuretics, respectively.[6]

These prior studies have focused on patients initiating a single blood pressure (BP) medication and have only examined differences in refill patterns. However, in practice, physicians must often make prescribing decisions among patients who require multiple agents to control their BP, and refilling prescriptions is but one component of adherence behavior.[8–10] Patients must also take their medications on a day-to-day basis to obtain the maximal benefit from their antihypertensive medications.[11] To our knowledge, no prior study has analyzed whether antihypertensive drug class is associated with differences in day-to-day adherence behavior, particularly in patients on multiple chronic BP medications.

The aim of this study was to determine whether interclass differences exist in electronically measured, day-to-day adherence to antihypertensive medications among patients with persistently uncontrolled hypertension. Consistent with the pharmacy refill data, we hypothesized that adherence

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would be lowest in patients prescribed beta-blockers and diuretics.

METHODS

Between February 2011 and June 2014, we enrolled a convenience sample of patients with treated but uncontrolled hypertension attending two urban, academic hospital-based primary care clinics (Columbia University Medical Center and Mount Sinai Medical Center). The study was approved by the Institutional Review Boards at both institutions. Patients were eligible if they were at least 18 years of age, prescribed one or more BP medications and had uncontrolled hypertension (defined as a BP ≥ 140/90 mm Hg or ≥130/80 mm Hg if diabetic or with chronic kidney disease (CKD) based on the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines in place at the time of the study)[12] on at least two consecutively scheduled visits with their primary care provider (PCP). Key exclusion criteria were BP at goal during the recruitment visit, inability to self-manage medications (e.g., due to dementia or severe psychiatric illness), and unavailability for follow-up.

Each participant was then given a 4-compartment electronic pillbox (MedSignals; MedSignals Corporation) that records the date and time each compartment is opened. Each BP medication was stored in a separate compartment and participants were monitored during the interval between recruitment and the subsequent clinic visit with the PCP. BP was measured by a research assistant according to a standard protocol using an automatic BP machine (BpTRU, VSM MedTech, Vancouver, Canada)[13] and was defined as the average of the second and third BP measured.

Measures

The main outcome variable was class level medication adherence, a continuous variable defined as the percent of monitored days that the patient took the correct number of doses of a particular medication. If a participant took 1 out of 2 doses on a given day, this counted as 50% adherence that day. Participants were not penalized for taking extra doses. Days on which patients were hospitalized or had a clear history of traveling without their electronic pillbox were censored. In descriptive analyses, adherence was defined as a dichotomous variable, and patients who took medications as prescribed less than 80% of days monitored were categorized as nonadherent.[14] The main predictor was antihypertensive drug class as assessed by review of the electronic medical record. Antihypertensive medications were assigned to one of the following classes: thiazide diuretics, beta-blockers, ARBs, ACEIs, CCBs, or other. Medications that combined medications in one pill were included in the "other" category.

Age, gender, race, ethnicity, years of schooling, and health insurance status were assessed by self-report. Comorbidities, including diabetes mellitus, coronary artery disease (CAD), and heart failure, as well as total number of BP medications were based on chart review, and in the case of CKD, the most recent labs.

Cohort assembly

A total of 522 patients were screened. Of the patients who were screened, only 8.8% declined to participate and 198 participants consented and completed a baseline interview following their PCP visit. Compared to those who consented, those who declined to participate were less likely to be Hispanic (56.1% vs. 76.9%, $P < 0.001$) and more likely to be black (70.7% vs. 48.2%; $P < 0.001$), but did not differ by gender. Of these 198 participants, we included 149 patients in the final analyses due to incomplete electronic adherence data (24.7%).

Statistical analysis

Descriptive statistics were used to describe the overall study population. To account for multiple BP medications within patients, mixed effects regression analyses were used to assess the association between drug class and mean percent of days adherent. Based on prior systematic reviews of predictors of adherence to cardiovascular medications,[6,15] we adjusted for age, gender, ethnicity, race, health insurance status, years of schooling, number of BP medications, and frequency of dosing. We additionally adjusted for comorbidities with indications for specific drug classes in recent hypertension guidelines (i.e., CAD, heart failure, CKD, diabetes). We performed a sensitivity analysis in which we limited our analysis to participants with at least two weeks of adherence monitoring. As this did not significantly change any of our results, we only display the results on the complete set of participants with any adherence monitoring. Additionally, as the distribution of mean percent of days adherent was negatively skewed, we performed a sensitivity analysis in which we transformed our measure of adherence to a measure of nonadherence (i.e., one adherence) and then applied a square-root transformation so that our dependent variable approached a normal distribution. There were no differences in the pattern of the relationship between drug class and adherence. As such, we present data for the untransformed measure of adherence in order to simplify the interpretation of our findings.

RESULTS

Data pertaining to a total of 353 BP medications prescribed by 33 PCPs among 149 participants were analyzed. The mean age was 64.2 years; 72% female, 41% Black, and 75% Hispanic (See Supplementary Table S1 online). The mean systolic BP at baseline was 158 (20) mm Hg; 15% had CAD, 9% heart failure, and 58% diabetes. On average, participants were monitored for 55 days, range 6–365 days, and 93.3% had at least two weeks of adherence monitoring. Beta-blockers were the most commonly prescribed drug class (55%). The mean (SD) number of BP medications was 2.5 (0.93), and 88% were prescribed more than one BP medication.

The mean percent of days adherent for each drug class was lowest for beta-blockers (70.9%) compared to ARBs (75.0%, $P = 0.11$), diuretics (75.9%, $P < 0.001$), CCBs (77.6%, $P < 0.001$), and ACEIs (78.0%, $P < 0.0001$) (See

Supplementary Figure S1 online). The proportion of individuals who were adherent, defined as taking their medications more than 80% of days monitored, was lowest for beta-blockers (48%), followed by ARBs (50%), diuretics (56%), CCBs (60%), and ACEIs (70%). In the mixed effects analyses, a significant association between drug class and mean percent of days adherent was observed. In the unadjusted model, adherence to beta-blockers was lower than all other drug classes (4.2% lower than ARBs ($P = 0.11$), 5.0% lower than diuretics ($P < 0.001$), 6.7% lower than CCBs ($P < 0.001$), and 7.1% lower than ACEIs ($P < 0.0001$). In the adjusted model, dosing frequency was strongly associated with medication adherence (B (SE) = −10.5 (2.1), $P = 0.0001$) (Table 1).

In *post hoc* analyses, we observed that once a day formulations comprised 100% of diuretics, 98.3% of ACEIs, 98.7% of CCBs, 97.5% of ARBs, 72.7% of "other" drugs, and 39.0% of beta-blockers. We additionally compared the fully adjusted model excluding dosing frequency with a model that included dosing frequency. The association between beta-blockers and adherence was diminished only after adding dosing frequency to the model (Table 1). Additionally, we stratified by frequency. Drug class was not related to adherence amongst those taking medications with once daily dosings ($P = 0.41$) or multiple daily dosings ($P = 0.58$). Finally, we stratified by number of BP medications. Amongst those on more than one BP agent, there was a significant relationship between drug class and adherence ($P = 0.01$), which diminished by a similar magnitude after adjusting for frequency ($P = 0.64$). Only 18 individuals were on monotherapy and we did not have sufficient power to assess class differences in this subgroup ($P = 0.54$).

DISCUSSION

Among patients with persistently uncontrolled hypertension on predominantly multi-BP drug regimens, we found suboptimal adherence across all classes of BP medications, but particularly for beta-blockers. The association between beta-blockers and nonadherence was likely explained by the increased propensity for beta-blockers to be prescribed as multiple doses per day. To our knowledge, this is the first study to compare and comprehensively electronically measure adherence to the near complete BP regimen simultaneously. Physicians often rely on beta-blockers to treat hypertension in patients with established cardiovascular disease or those already on several agents,[16] such as our cohort where beta-blockers were the most frequently prescribed antihypertensive medication. In the United States, twice a day formulations of beta-blockers continue to be more commonly prescribed than once a day formulations,[17] also demonstrated in our cohort. Given recent studies supporting reduced adherence to beta-blockers and the now widespread availability of generic extended-release formulations,[18] physicians should consider beta-blockers with proven efficacy and once daily dosing.[16]

Table 1. Mixed regression analysis of the association between antihypertensive drug class and mean % of days adherent to antihypertensive medications (estimate (SD), *P* value)

Drug class	Model 1	Model 2	Model 3
Beta-blockers	**Ref**	**Ref**	**Ref**
ARB	4.2 (2.6), $P = 0.12$	4.7 (2.7), $P = 0.09$	−2.5 (2.9), $P = 0.41$
ACEI	**7.1 (1.4), $P < 0.0001$**	**6.3 (1.4), $P < 0.0001$**	0.5 (1.7), $P = 0.76$
Diuretics	**5.0 (1.6), $P < 0.001$**	**7.4 (1.6), $P < 0.0001$**	0.5 (1.9), $P = 0.80$
CCB	**6.7 (1.7), $P < 0.001$**	**7.9 (1.6), $P < 0.0001$**	−0.4 (2.2), $P = 0.87$
Age		0.3 (0.3), $P = 0.21$	0.3 (0.3), $P = 0.19$
Gender		−5.3 (5.2), $P = 0.31$	−4.1 (5.1), $P = 0.43$
Race		0.2 (5.3), $P = 0.98$	0.5 (5.2), $P = 0.91$
Ethnicity		−4.1 (6.6), $P = 0.54$	−6.3 (6.6), $P = 0.33$
# BP meds		−2.3 (2.4), $P = 0.38$	−2.4 (2.4), $P = 0.32$
CAD		−6.8 (6.6), $P = 0.31$	−4.4 (6.5), $P = 0.50$
Heart failure		−6.0 (7.3), $P = 0.42$	−5.3 (7.3), $P = 0.46$
DM		0.97 (4.7), $P = 0.84$	0.6 (4.7), $P = 0.90$
CKD		1.3 (4.7), $P = 0.79$	2.2 (4.7), $P = 0.64$
Days[a]		−0.001 (0.1), $P = 0.99$	0.02 (0.1), $P = 0.78$
Medicaid		5.5 (6.6), $P = 0.41$	5.8 (6.6), $P = −0.33$
Education		−0.5 (0.6), $P = 0.43$	−0.5 (0.6), $P = 0.38$
Dosing frequency			**−10.5 (2.1), $P = 0.0001$**

Abbreviations: ARB, angiotensin II type 1 receptor blocking agents; ACEI, angiotensin II converting enzyme inhibitors; CCB, calcium channel blockers; CAD, coronary artery disease; CKD, chronic kidney disease. Significant terms are in bold.

[a]Number of days monitored.

In contrast with our hypothesis, adherence to thiazide diuretics was not lower than adherence to other drug classes. We postulated that diuretics would be skipped or discontinued more frequently due to side effects and electrolyte abnormalities. It is possible that side-effects are less discernable in multidrug regimens or that there was too short a period to observe discontinuation for electrolyte abnormalities; it may also have been that participants with this cause of early discontinuation had already switched to different classes of drugs[5] given that the majority of our patients were on long-term regimens. In contrast with prior studies using refill data, ARBs did not account for the highest adherence rates in our sample, possibly due to the small sample of patients prescribed ARBs in our cohort. It may be that the newness of product, financial incentives, market availability, and selection bias previously attributed to the superiority of ARB adherence compared to other classes[6,19,20] in older studies have diminished over time.

There were several strengths to our study. We used electronic monitors to objectively measure medication adherence, widely considered to be an optimal approach to measuring adherence. We also enrolled a racially and ethnically diverse sample from two primary care clinics. There were some limitations, however. Firstly, our findings in this primarily Medicaid, Hispanic population attending academic hospital-based clinics may not be generalizable to other populations. However, this is an understudied population in whom little is known about adherence patterns. Though the majority of participants had Medicaid, we were unable to assess whether differences in co-pays or drug costs affected adherence. Also, unlike studies of pharmacy refill data, we had relatively short monitoring periods. While persistence rates have been shown to diminish over time,[5] we were unable to assess whether drug classes differed in terms of persistence, discontinuation, and class change. Further, our method of measuring adherence via an electronic pillbox may have altered participants' usual adherence behavior, as patients were aware they were being monitored and that this information might be relayed to their PCPs. Nevertheless, we still observed substantial non-adherence in our participants. Unlike large pharmacy refill data sets, our sample size was limited. Nonetheless, this is the first study to electronically measure adherence to multiple BP medications concurrently in such a large group of patients.

Despite these limitations, using electronic monitoring, we found suboptimal adherence across all drug classes and further research should be directed at interventions that improve these rates. Clinicians should carefully assess for nonadherence in patients with uncontrolled hypertension regardless of the class of antihypertensive medication prescribed. Strategies such as education, addressing barriers, and motivational interviewing have been used to address medication nonadherence with variable success.[9] Our results also remind clinicians to consider once-daily beta-blockers whenever possible, carefully ensuring that the once-per-day formulation is affordable to the patient. Future studies should seek to better understand why beta-blockers are more likely to be prescribed as a multiple daily dose drug and could explore interventions that remind physicians of the availability of extended release formulations.

SUPPLEMENTARY MATERIAL

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

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DISCLOSURES

The authors declared no conflict of interest. Dr Kronish received an honoraria from Integritas Communications Group for speaking at a continuing medical education conference.

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