Initial Persistence With Antihypertensive Therapies Is Associated With Depression Treatment Persistence, But Not Depression

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The purpose of this study was to examine the relationship between the presence of clinical depression and persistence to drug therapy treatment for depression with early nonpersistence to antihypertensive therapies in a large, diverse cohort of newly treated hypertension patients. Using a hypertension registry at Kaiser Permanente Northern California, the authors conducted a retrospective cohort study of 44,167 adults (18 years and older) with hypertension who were new users of antihypertensive therapy in 2008. We used multivariate logistic regression analysis to model the relationships between the presence of clinical depression and early nonpersistence (defined as failing to refill the first prescription within 90 days after the end of the first fill days' supply) to antihypertensive therapies, controlling for sociodemographic and clinical risk factors. Within the group of 1484 patients who had evidence of clinical depression in the 12 months prior to the initiation of antihypertensive therapy, the authors examined the relationship between drug therapy treatment for depression and 6-month persistence with antidepressant therapy with early nonpersistence with antihypertensive therapies. No association was found between the presence of clinical depression and early nonpersistence to antihypertensive therapies after adjustment for individual demographic and clinical characteristics and neighborhood-level socioeconomic status. However, among the subset of 1484 patients with documented evidence of clinical depression in the 12 months prior to the initiation of antihypertensive therapy, being prescribed and persistence with antidepressant therapy was strongly associated with lower odds of early nonpersistence to antihypertensive medications (odds ratio, 0.64; confidence interval, 0.42–0.96). In an integrated delivery system, the authors found that treatment for depression was associated with higher levels of antihypertensive persistence. Improving quality of depression care in patients with comorbid hypertension may be an important strategy in decreasing cardiovascular disease risk in these patients. *J Clin Hypertens (Greenwich).* 2014;16:412–417.

Cardiovascular disease (CVD) is the leading cause of mortality in the United States and is associated with significant costs to patients, the health care system, and society.[1–3] The appropriate use of clinically effective therapies is a key component to reducing adverse CVD outcomes in patients at high risk for CVD, such as those with hypertension.[4] However, poor adherence to antihypertensive medications is a significant barrier to managing hypertension,[5] and only about one half of patients with hypertension achieve recommended levels of blood pressure (BP) control.[6]

Clinical depression has been identified as a potential barrier to medication adherence in a wide range of chronic diseases,[7] and evidence suggests that there may be a relationship between the presence of clinical depression and poor adherence to antihypertensive therapies in patients with hypertension.[7–14] However, since the results of these studies have been mixed[8,14] and have often employed heterogeneous methods and approaches,[14] more research to clarify the relationship between depression and antihypertensive adherence is needed.[14] Many previous studies have focused on self-reported adherence measures;[12] are based on relatively small sample sizes;[10,11,13] and do not adequately control for factors such as comorbidities, socioeconomic status, or biometric data including body mass index that may confound the relationship between depression and medication adherence.[7,9,11,14] No studies of the relationship between depression and adherence to antihypertensive therapies have been conducted in large, integrated delivery systems with extensive electronic health record (EHR) data on patient characteristics and clinical data on the treatment of both hypertension and depression.

Early nonpersistence is defined as the failure to continue filling an antihypertensive prescription after the initial first fill,[15] and accounts for a significant

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proportion of the underuse of appropriate antihypertensive therapies.[16] However, no study has examined the specific relationship between the persistence to drug therapy treatment for depression with early nonpersistence to antihypertensive therapies. Since long-term adherence is dependent upon persistence with therapy at an early stage of treatment,[16] understanding factors associated with early nonpersistence to antihypertensives may provide key opportunities for identifying practices with the potential to improve CVD outcomes in hypertension patients.

The purpose of this study is to examine the relationship between the presence of clinical depression, and persistence to drug therapy treatment for that depression, with early nonpersistence to antihypertensive therapies in a large, integrated delivery system using EHR data.

METHODS

Study Design and Population

This retrospective cohort study was conducted at Kaiser Permanente Northern California (KPNC), an integrated healthcare delivery system that serves more than 3.3 million patients. Full details on the specifications for this cohort are provided elsewhere,[16] and outlined briefly as follows. Eligible patients were selected from a hypertension registry that included nearly 1.3 million patients from the year 2000 through 2009 identified through hypertension diagnosis codes and consecutive elevated BP measurements.[16–18] The hypertension registry included clinical data on inpatient, outpatient, and pharmacy utilization extracted from integrated electronic medical records at KPNC. Patients were considered hypertensive and eligible to be in the registry on the date they first met 1 of the following criteria: (1) two consecutive elevated BP measurements; (2) two *International Classification of Diseases, Ninth Edition* (*ICD-9*) diagnostic codes for hypertension recorded on separate dates; (3) one diagnostic code for hypertension plus prescription for an antihypertensive medication; or (4) one elevated BP measurement plus one diagnostic code for hypertension. Among these patients in the hypertension registry, the current study included adults (18 years and older) who were new users of antihypertensive therapy (defined as no evidence of an antihypertensive drug dispensing during the previous 80-year period) in 2008. We excluded patients who were not continuously enrolled and who did not have an active drug benefit on the date therapy was started and continuing for at least 250 days following the therapy start date to ensure adequate follow-up. We also excluded patients who were hospitalized at any point in that same period.

Definition of Primary Outcome Measure: Early Nonpersistence

Early nonpersistence to antihypertensive medication was defined as filling the first prescription for an antihypertensive medication but failing to obtain a refill of an antihypertensive medication[15] within 90 days after the days' supply of the first fill had run out (ie, not obtaining the refill by the date of first fill + first fill days' supply +90 days). Patients who switched medications within the first 90 days of initiating therapy were not included in the calculation of early nonpersistence.

Key Independent Variable: Depression and Persistence to Antidepressant Therapies

We used the *ICD-9*[19] to identify the presence of depression based on one inpatient or two outpatient diagnoses observed prior to the date of initiation of antihypertensive therapy. Given the challenges in identifying depression using medical records,[20] we only counted depression diagnoses that occurred during the 12-month period prior to the initiation of antihypertensive medication, and also used the dispensing of select antidepressant classes (tricyclics, serotonin reuptake inhibitors, norepinephrine reuptake inhibitors) within the 12 months to identify patients with possible depression.

To assess drug treatment for depression within hypertension patients with a history of depression, we assessed whether a patient had been prescribed ≥1 antidepressant classes to identify patients with possible depression in the 12 months prior to the initiation of antihypertensive therapies. Antidepressant treatment status was equal to "0" if the patient had no antidepressant use, "1" if they initiated antidepressant therapy but did not persist for at least 6 months, and equal to "2" if they initiated antidepressant therapy and persisted for 6 months or more.

Statistical Analysis

We used logistic regression with time-dependent covariates to estimate early nonpersistence to antihypertensive medications among patients with hypertension who were new users of antihypertensive therapy with a diagnosis of depression, and initiation and persistence to antidepression therapy, adjusting for patient age, sex, race/ethnicity, neighborhood-level median household income, and average educational attainment obtained from each patient's US Census 2000 block group of residence; the most recent systolic BP (SBP) reading (<140 mm Hg, 140–149 mm Hg, 150–159 mm Hg, ≥160 mm Hg) recorded prior to the initiation of antihypertensive treatment; physical and mental health comorbidities; the number of medical office visits during the 12 months prior to starting antihypertensive therapy; patient-reported smoking status (yes/no); and clinically assessed body mass index (BMI).

As a sensitivity analysis, we used multiple imputation to address missing values for BMI (28.2% missing) and baseline SBP (6.6% missing)[21] and compared the model results with and without imputed values.

All statistical analyses were conducted with SAS version 9.1.[22] This study was approved by the institutional review board at Kaiser Foundation Research Institute.

TABLE I. Characteristics of Kaiser Permanente Northern California Enrollees Newly Initiated on Antihypertensive Medications in 2008 (N=44,167)

Characteristic	No. (%)
Age, y	
<50	18,122 (41.0)
50–64	18,817 (42.6)
65–74	4966 (11.2)
75+	2262 (5.1)
Race/ethnicity	
White	16,343 (37.0)
Black	3036 (6.9)
Latino	4479 (10.1)
Asian	3893 (8.8)
Other/mixed/unknown	16,416 (37.2)
Sex	
Male	22,371 (50.7)
Female	21,796 (49.4)
Current smoker	
Yes	4653 (10.5)
BMI, kg/m^2	
<18.5	179 (0.6)
18.5–24.99	5959 (18.8)
25–29.99	10,893 (34.4)
≥30	14,668 (46.3)
Missing	12,468 (28.2)
Household income, $	
<40,000	8304 (18.9)
40,000–74,999	24487 (55.7)
≥75,000	11146 (25.4)
Missing	230 (0.5)
College degree, %	
<10	9316 (21.2)
10–19	14960 (33.4)
20–29	11973 (27.5)
≥30	7955 (18.1)
Missing	353 (0.5)
Drug copay, $	
0–5	13833 (31.6)
6–10	24434 (55.8)
>10	5547 (12.7)
Missing	353 (0.8)
Comorbid condition	
Diabetes	3152 (7.1)
Prior cardiovascular disease	959 (2.2)
Chronic kidney disease	909 (2.1)
Schizophrenia	147 (0.3)
Bipolar disorder	338 (0.8)
Anxiety	2641 (6.0)
Depression	1484 (3.4)
Total outpatient visits (SD)[a]	5.9 (10.2)
Mean SBP (SD)[b]	144.3 (17.1)

Abbreviations: BMI, body mass index; SD, standard deviation. [a]All outpatient visits during the 12 months prior to initiation of antihypertensive medication. [b]Most recent systolic blood pressure (SBP) reading prior to initiation of antihypertensive medication.

RESULTS

A total of 44,167 adult hypertension patients who were newly prescribed antihypertensive therapies were eligible for the study (Table I). Almost half of the cohort was female (49.4%), 41.0% were younger than 50, and 37.0% were non-Hispanic white. A total of 1484 patients (3.4%) had evidence of depression in the prior 12 months based on depression diagnosis or antidepressant medication prescription data. Table II shows the demographics of this subgroup with depression; there was almost no variation across the groups based on whether pre-existing depression was based on diagnosis data, prescription data, or both.

TABLE II. Characteristics of Subcohort of Patients With Depression in the Past 12 Months by Method of Identification (Dx Only, Dx and Rx, or Rx Only)

	All, % 1484	Dx Only, % 177	Dx and Rx, % 363	Rx Only, % 944
Race				
White	47.5	43.5	50.4	47.1
Black	7.0	9.6	7.2	6.5
Asian	6.9	7.3	4.4	7.7
Hispanic	12.3	15.3	13.5	11.3
Other/mixed/unknown	26.3	24.3	24.5	27.3
Age				
<50	45.2	44.6	45.7	45.1
50–64	40.6	39.6	43.0	39.9
65–74	9.1	11.3	6.9	9.5
75+	5.1	4.5	4.4	5.4
Sex				
Male	38.5	36.7	34.4	40.4
Female	61.5	63.3	65.6	59.6
Current smoker				
Yes	17.9	11.9	19.8	18.2
BMI, kg/m^{2a,c}				
<25	19.1	11.3	16.6	21.5
25–29.99	32.0	31.5	29.5	33.1
≥30	49.0	57.2	53.9	45.4
Missing, %	8.5			
Comorbidity				
Diabetes	7.6	9.6	8.5	6.9
CKD	2.4	1.7	1.9	2.7
Schizophrenia	0.5	0.6	0.8	0.4
Bipolar disorder	1.9	1.7	1.7	2.0
ADD	1.0	1.1	1.9	0.6
Anxiety[c]	15.8	14.1	25.1	12.6
Baseline SBP (SD)[b,c]	141.8 (15.7)	138.4 (16.8)	141.6 (16.1)	142.6 (15.3)

Abbreviations: ADD, attention deficit disorder; CKD, chronic kidney disease; Dx, diagnosis; Rx, prescription; SBP, systolic blood pressure; SD, standard deviation. [a]Proportions exclude missing data; the number missing and proportion of the total shown in the last row. [b]Most recent reading prior to initiation of antihypertensive medication. [c]$P \leq .01$.

TABLE III. Multivariable Logistic Regression Results Predicting Early Nonadherence to Antihypertensives

Class	Early Nonpersistence to Antihypertensives, %	Odds Ratios (95% CI)
Race		
White	30.6	Referent
Black	42.5	1.58 (1.45–1.72)[a]
Asian	38.1	1.38 (1.27–1.49)[b]
Hispanic	41.1	1.47 (1.37–1.59)[a]
Other/mixed/unknown	11.3	1.06 (1.01–1.12)[a]
Age, y		
<50	39.1	
50–64	28.7	0.67 (0.64–0.70)[a]
65–74	28.1	0.66 (0.61–0.71)[a]
75+	31.1	0.76 (0.68–0.85)
Sex		
Male	33.1	
Female	32.8	0.92 (0.88–0.96)[a]
Current smoker		
No	32.3	Referent
Yes	38.8	1.16 (1.09–1.24)[a]
BMI		
<24.99 (normal)	37.3	Referent
25–29.99 (overweight)	35.7	0.90 (0.84–0.97)[a]
≥30 (obese)	36.2	0.84 (0.79–0.90)
Missing	24.8	0.63 (0.58–0.69)[a]
Baseline SBP, mm Hg		
<140	33.5	
140–149	36.4	1.07 (1.02–1.13)[a]
150–159	33.3	0.96 (0.90–1.02)[b]
160+	32.2	0.99 (0.93–1.06)
Household income, $		
<40,000	35.9	Referent
40,000–74,999	33	0.90 (0.85–0.95)
≥75,000	30.9	0.86 (0.80–0.91)[b]
Missing	32.1	1.10 (0.79–1.52)
Drug copay, $		
<6	32.9	Referent
6–10	33.9	1.06 (1.01–1.11)[a]
11+	29.1	0.96 (0.88–1.04)
Comorbid conditions		
Diabetes	37.9	1.09 (1.00–1.18)[b]
CKD	33.6	1.02 (0.88–1.19)
Prior CVD	31.8	0.91 (0.79–1.06)
Concurrent depression	38.4	1.08 (0.96–1.21)
Ever schizophrenia	32.4	0.77 (0.53–1.11)
Ever bipolar disorder	38.1	1.03 (0.81–1.32)
Ever anxiety	38.9	1.09 (1.00–1.19)
Total outpatient visits		
0	27.7	Referent
1 or 2	34.6	1.03 (0.97–1.10)[a]
3 to 5	36.3	1.09 (1.02–1.18)
6 to 15	40.9	1.30 (1.19–1.43)[a]

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; SBP, systolic blood pressure. [a]$P \leq .01$. [b]$P \leq .05$.

After adjustment for patient demographic and clinical characteristics, as well as neighborhood-level income and education level, there was no statistically significant relationship between depression and early nonpersistence to antihypertensives (odds ratio, 1.08; confidence interval, 0.96–1.21; Table III). Race and ethnicity, younger age, male sex, smoking, having a BMI <25, baseline SBP between 140 and 149 mm Hg, lower neighborhood income (<$40,000), lower neighborhood educational attainment (<10% bachelor's degree), having diabetes, and having ≥3 medical visits during the 12 months prior to initiation of therapy were all associated with early nonpersistence.

Among the subset of 1484 patients with documented evidence of clinical depression in the 12 months prior to the initiation of antihypertensive therapy, being prescribed and persistent to antidepressant therapy was strongly associated with lower rates of early nonpersistence with antihypertensive therapy (odds ratio, 0.64; confidence interval, 0.42–0.96) after adjusting for demographic, clinical, and socioeconomic characteristics. Race/ethnicity, younger age, and history of anxiety were also associated with early nonpersistence within this subset (Table IV).

Our results were robust to the inclusion of imputed values for BMI and baseline SBP (data not shown).

DISCUSSION

Our study showed no association between evidence of depression in the 12 months prior to the initiation of antihypertensive therapy and early nonpersistence to antihypertensive therapies. Unlike in prior studies that have found a relationship between depression and antihypertensive therapy use, our study had a large sample size (n=44,167) and was able to use EHR and geocoded socioeconomic data to adjust for a wide range of patient characteristics. This study took place in an integrated delivery system setting, where access to integrated health record data and coordination of mental and physical health care may attenuate a potential negative impact of depression on antihypertensive use.[5,23,24]

We found that within the subset of patients who had evidence of depression, persistent use of antidepressants in the period prior to antihypertensive initiation was a strong predictor of early persistence to new antihypertensive therapy. Inadequate treatment of depression and depressive symptoms has been shown to be associated with lower antihypertensive adherence in prior studies[11,25] and also with other adverse health outcomes such as higher emergency department and hospitalization rates.[26] Receiving appropriate treatment for depressive symptoms may be a path towards achieving greater antihypertensive adherence and BP control in depressed patients.[4] Pilot studies have suggested that integrating the treatment of depression with hypertension care is a promising approach to improve hypertension outcomes.[23] Our findings suggest that this approach is worth pursuing.

Study Limitations

This study has limitations that deserve consideration. First, we could not control for unmeasured physiological,

TABLE IV. Multivariable Logistic Regression Results Predicting Early Nonpersistence to Antihypertensive Agents Among Patients With a History of Depression

Class	Proportion Nonpersistent	Odds Ratios (95% CI)
Race		
White	36.3	
Black	50.5	1.65 (1.02–2.66)
Asian	46.5	1.42 (0.89–2.27)
Hispanic	39.4	0.97 (0.66–1.41)
Other/missing	36.5	1.07 (0.81–1.42)
Age, y		
<50	43.8	
50–64	33.1	0.65 (0.51–0.84)
65–74	34.4	0.62 (0.39–0.98)
75+	41.9	0.82 (0.45–1.49)
Sex		
Male	37.4	
Female	39	1.04 (0.81–1.32)
Smoker		
No	38.2	
Yes	39.1	1.02 (0.75–1.39)
BMI		
<24.99 (normal)	42.5	
25–29.99 (overweight)	39.4	0.91 (0.64–1.29)
≥30 (obese)	38.5	0.85 (0.61–1.19)
Missing	26.4	0.72 (0.38–1.38)
Baseline SBP, mm Hg		
<140	38.6	
140–149	39.6	1.05 (0.79–1.40)
150–159	36.2	0.94 (0.68–1.31)
160+	42.8	1.22 (0.84–1.77)
Household income, $		
<40,000	39.9	
40,000–74,999	37.8	0.97 (0.72–1.31)
≥75,000	38.5	1.01 (0.71–1.43)
Copay, $		
<6	36.9	
6–10	38.9	1.10 (0.85–1.42)
11+	38.5	1.15 (0.74–1.77)
Comorbidity		
Diabetes	39.1	1.01 (0.65–1.57)
CKD	39.4	0.88 (0.37–2.08)
Prior CVD	46.3	1.84 (0.92–3.67)
Ever schizophrenia	25	0.25 (0.03–2.20)
Ever bipolar disorder	29.6	0.64 (0.26–1.61)
Ever anxiety	42.3	1.11 (0.80–1.52)
Total visits		
0	25.5	
1 or 2	35.4	1.08 (0.57–2.05)
3 to 5	40.3	1.20 (0.63–2.31)
6 to 15	42.5	1.27 (0.65–2.50)
Antidepressant use		
No antidepressant use	43	
Not persistent for 6 mo	42.8	0.92 (0.61–1.37)
Persistent for 6 mo	32.1	0.64 (0.42–0.96)[b]

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; SBP, systolic blood pressure. [a]$P \leq .05$. [b]$P \leq .01$.

behavioral, and psychosocial factors such as treatment preferences that may explain some of the observed relationship between antidepressant persistence and early nonpersistence to antihypertensive therapies; for example, it is possible that patients who are persistent to antihypertensives are inherently more likely to be persistent to antidepressants. However, previous research has shown that medication persistence within individuals varies markedly across different medications and over time.[27,28] In addition, while the use of pharmacy records to estimate adherence is well-supported, we did not directly observe patient behavior. Therefore, to the extent that there is greater variation in actual vs estimated adherence, our findings may be biased. While it is possible that we misclassified some patients as having hypertension who did not have the condition, we believe that this possibility was reduced through the application of a complex algorithm requiring diagnosis codes or elevated BPs to identify patients with hypertension and reduce any potential bias or noise relating to misdiagnosis.[17,18] Our definition of depression required one inpatient or two outpatient diagnoses observed prior to the date of initiation of antihypertensive therapy within the 12-month period prior to the initiation of antihypertensive medication and/or the use of specific antidepressant medication classes within that interval. While this conservative definition of depression allows for more certainty in identifying depression from the her,[20] it may underestimate the level of depression within the cohort. Finally, as noted above, our study took place in a large, integrated health delivery system with detailed EHR data. These findings might not be generalizable to other settings; however, in the context of greater requirements for both the meaningful use of EHRs and greater healthcare system integration,[29–31] our results should be generalizable to the coming healthcare landscape.

CONCLUSIONS

Our study suggests that in an integrated delivery system with a diverse population of hypertension patients, early nonpersistence with antihypertensives is not associated with a history of clinical depression prior to antihypertensive initiation. However, among these patients with a history of depression, persistence to prescribed antidepressants is significantly associated with lower odds of early nonpersistence to antihypertensive medications. This suggests that the quality of mental healthcare among depressed hypertension patients can improve antihypertensive use and may be a path to reducing CVD events in this high-risk population. Future research should continue to clarify the relationship between adequate treatment of depression and antihypertensive persistence, and develop interventions that ensure optimal concurrent management of both mental and physical health conditions.

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