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Initial Persistence with Antihypertensive Therapies is Associated with Depression Treatment Persistence, But Not Depression

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Abstract

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 non-persistence to antihypertensive therapies in a large, diverse cohort of newly treated hypertension patients. Using a hypertension registry at Kaiser Permanente Northern California, we conducted a retrospective cohort study of 44,167 adults (≥ 18 years) 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 non-persistence (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 socio-demographic and clinical risk factors. Within the group of n=1,484 patients who had evidence of clinical depression in the 12 months prior to the initiation of antihypertensive therapy, we examined the relationship between drug therapy treatment for depression and six-month persistence with antidepressant therapy with early non-persistence with antihypertensive therapies. We found no association between the presence of clinical depression and early non-persistence to antihypertensive therapies after adjustment for individual demographic and clinical characteristics, and neighborhood-level socioeconomic status. However, among the subset of 1,484 patients with documented evidence of clinical depression in the 12 months prior to the initiation of antihypertensive therapy, being prescribed and persistent

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with antidepressant therapy was strongly associated with lower odds of early-non-persistence to antihypertensives (OR=0.64, CI=0.42,0.96). In an integrated delivery system, we 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 CVD risk in these patients.

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in the U.S., and is associated with significant costs to patients, the health care system, and to society.¹⁻³ The appropriate use of clinically efficacious 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 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 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 such as 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 non-persistence is defined as the failure to continue filling an antihypertensive prescription after the initial first fill¹⁵, and accounts for a significant 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 non-persistence 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 non-persistence 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 health care delivery system serving more than 3.3 million people. 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 including nearly 1.3 million patients from the year 2000 through 2009 identified through hypertension diagnosis codes and consecutive elevated blood pressure 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) 2 consecutive elevated blood pressure measurements; (2) 2 ICD-9 diagnostic codes for hypertension recorded on separate dates; (3) 1 diagnostic code for hypertension plus prescription for an antihypertensive medication; or (4) 1 elevated blood pressure measurement plus 1 diagnostic code for hypertension. Among these patients in the hypertension registry, the current study included adults (> 18 years) who were new users of antihypertensive therapy (defined as no evidence of an antihypertensive drug dispensing during the previous eight-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 time period.

Definition of Primary Outcome Measure: Early Non-Persistence—Early non-persistence to antihypertensive medication was defined as filling the first prescription for an antihypertensive medication, but failing to obtain a refill of an antihypertensive medication¹⁵ within 90 days after the days' supply of the first fill had run out (*i.e.* 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 non-persistence.

Key Independent Variable: Depression and Persistence to Antidepressant Therapies—We used the International Classification of Diseases, Ninth Edition (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 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 one or more 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 six months; and equal to '2' if they initiated antidepressant therapy and persisted for six months or more.

Statistical Analysis

We used logistic regression with time-dependent covariates to estimate early non-persistence to antihypertensive medications among patients with hypertension who were new users of antihypertensive therapy with a diagnosis of depression, and initiation and persistence to antidepressant therapy treatment, adjusting for: patient age, gender, 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 SBP reading (<140mmHg, 140–149, 150–159, 160) 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 body mass index (28.2% missing) and baseline systolic blood pressure (6.6% missing)²⁰ and compared the model results with and without imputed values.

All statistical analysis were conducted in SAS Version 9.1.²² This study was approved by the Institutional Review Board at Kaiser Foundation Research Institute.

Results

A total of 44,167 adult hypertension patients who were newly prescribed antihypertensive therapies were eligible for the study (Table 1). Almost half of the cohort was female (49.4%); 41.0% were under age 50; and 37.0% were non-Hispanic White. A total of 1,484 patients (3.4%) had evidence of depression in the prior twelve months based on depression diagnosis or antidepressant medication prescription data. Table 2 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.

After adjustment for patient demographic and clinical characteristics, as well as neighborhood-level income and education level, there was no statistically significant relation between depression and early non-persistence to antihypertensives (OR 1.08, CI=(0.96,1.21)), see Table 3. Race and ethnicity, younger age, male gender, smoking, having a BMI of less than 25, baseline SBP between 140 and 149, lower neighborhood income (<\$40,000), lower neighborhood educational attainment (<10% bachelor's degree), having diabetes, and having three or more medical visits during the 12 months prior to initiation of therapy were all associated with early non-persistence.

Among the subset of 1,484 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-non-persistence

with antihypertensive therapy (OR=0.64, CI=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 non-persistence within this subset.

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 non-persistence 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 ED use and higher hospitalization rates.²⁶ Receiving appropriate treatment for depressive symptoms may be a path towards achieving greater antihypertensive adherence and blood pressure 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 additional limitations that deserve consideration. First, we could not control for unmeasured physiological, behavioral and psychosocial factors such as treatment preferences that may explain some of the observed relationship between antidepressant persistence and early non-persistence 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 versus 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 blood pressures 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 EHR²⁰, it may underestimate the level of depression within the cohort. Finally, as noted above our study takes 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 health care system integration,^{29–31} our results should be generalizable to the coming health care landscape.

Conclusions

Our study suggests that in an integrated delivery system with a diverse population of hypertension patients, early non-persistence 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 non-persistence to antihypertensive medications. This suggests that the quality of mental health care 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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Table 1

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

Characteristic	N (%)
Age:	
<50	18,122 (41.0)
50–64	18,817 (42.6)
65–74	4,966 (11.2)
75+	2,262 (5.1)
Race/Ethnicity:	
White	16,343 (37.0%)
Black	3,036 (6.9%)
Latino	4,479 (10.1%)
Asian	3,893 (8.8%)
Other/Mixed/Unknown	16,416 (37.2)
Gender:	
Male	22,371 (50.7)
Female	21,796 (49.4)
Current Smoker:	
Yes	4,653 (10.5)
BMI* (kg/m ²)	
<18.5	179 (0.6)
18.5–24.99	5,959 (18.8)
25–29.99	10,893 (34.4)
30	14,668 (46.3)
Missing (%)	12,468 (28.2)
Household Income:	
< \$40K	8304 (18.9)
\$40–74,999	24487 (55.7)
\$75K	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)

Characteristic	N (%)
\$6–10	24434 (55.8)
> \$10	5547 (12.7)
<i>Missing (%)</i>	353 (0.8)
Comorbid condition:	
Diabetes	3,152 (7.1)
Prior Cardiovascular Disease	959 (2.2)
Chronic Kidney Disease	909 (2.1)
Schizophrenia	147 (0.3)
Bipolar Disorder	338 (0.8)
Anxiety	2,641 (6.0)
Depression	1,484 (3.4)
Total outpatient visits [†] (sd)	5.9(10.2)
Mean SBP [‡] (sd)	144.3(17.1)

* BMI-Body Mass Index;

[†] All outpatient visits during the 12 months prior to initiation of antihypertensive medication.;

[‡] Most recent systolic blood pressure (SBP) reading prior to initiation of antihypertensive medication.

Table 2

Characteristics of Sub-cohort of Patients with Depression in Past 12 Months by Method of Identification (Dx only, Dx and Rx, Rx only)

	ALL	Dx only	Dx & Rx	Rx only
	1484	177	363	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%
Oth/mix/unk	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%
Gender:				
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/m²)^{†**}				
< 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 **	15.8%)	14.1%	25.1%	12.6%
Baseline SBP ^{†***} (sd)	141.8 (15.7)	138.4 (16.8)	141.6 (16.1)	142.6 (15.3)

[†] Proportions exclude missing data; the number missing and proportion of the total shown in the last row.

** p <= 0.01.

[†] Most recent reading prior to initiation of antihypertensive medication.

Table 3

Multivariable Logistic Regression Results Predicting Early Non-Adherence to Antihypertensives

Class	% Early Non- Persistence to Antihypertensives	Odds Ratios (95% CI)
Race:		
White	30.6	Referent
Black	42.5	1.58 (1.45 – 1.72)**
Asian	38.1	1.38 (1.27 – 1.49)*
Hispanic	41.1	1.47 (1.37 – 1.59)**
Other/Mixed/Unknown	11.3	1.06 (1.01 – 1.12)**
Age:		
<50	39.1	
50–64	28.7	0.67 (0.64 – 0.70)**
65–74	28.1	0.66 (0.61 – 0.71)**
75+	31.1	0.76 (0.68 – 0.85)
Gender:		
Male	33.1	
Female	32.8	0.92 (0.88 – 0.96)**
Current Smoker:		
No	32.3	Referent
Yes	38.8	1.16 (1.09 – 1.24)**
BMI:		
<24.99	37.3	Referent
Overweight (25– 29.99)	35.7	0.90 (0.84 – 0.97)**
Obese (30)	36.2	0.84 (0.79 – 0.90)
Missing	24.8	0.63 (0.58 – 0.69)**
Baseline SBP		
<140	33.5	
140 – 149	36.4	1.07 (1.02 – 1.13)**
150 – 159	33.3	0.96 (0.90 – 1.02)*
160+	32.2	0.99 (0.93 – 1.06)
Household Income:		
< \$40K	35.9	Referent
\$40K – \$ 74.9K	33	0.90 (0.85 – 0.95)
\$75K	30.9	0.86 (0.80 – 0.91)*
Missing	32.1	1.10 (0.79 – 1.52)
Drug Copay		
<\$6	32.9	Referent

Class	% Early Non- Persistence to Antihypertensives	Odds Ratios (95% CI)
\$6–10	33.9	1.06 (1.01 – 1.11)**
\$11+	29.1	0.96 (0.88 – 1.04)
Comorbid Conditions:		
Diabetes	37.9	1.09 (1.00 – 1.18)*
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 to 2	34.6	1.03 (0.97 – 1.10)**
3 to 5	36.3	1.09 (1.02 – 1.18)
6 to 15	40.9	1.30 (1.19 – 1.43)**

* p-value 0.05

** p-value 0.01

Table 4

Multivariable Logistic Regression Results Predicting Early Non-persistence to Antihypertensives Among Patients with History of Depression

Class	Proportion non-persist	
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:		
<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)
Gender:		
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	42.5	
Overweight (25– 29.99)	39.4	0.91 (0.64 – 1.29)
Obese (30)	38.5	0.85 (0.61 – 1.19)
Missing	26.4	0.72 (0.38 – 1.38)
Baseline SBP:		
<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:		
< \$40K	39.9	
\$40 – \$ 74.9K	37.8	0.97 (0.72 – 1.31)
\$75K	38.5	1.01 (0.71 – 1.43)
Copay: <\$6		
\$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)

Class	Proportion non-persist	
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 to 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)
No Antidepressant use	43	
Antidepressant use; not persistent for 6 months	42.8	0.92 (0.61 – 1.37)
Antidepressant use; persistent for 6 months	32.1	0.64 (0.42 – 0.96)**

*
p-value 0.05

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p-value 0.01