ORIGINAL RESEARCH

Antidepressants and Incident Hypertension in Primary Care Patients

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Objective: **Many ADMs can alter blood pressure (BP), but the research on the effect of antidepressant medication (ADMs) on incident hypertension is mixed. We investigated whether the use of ADMs was associated with the subsequent development of hypertension.**

Methods: **A retrospective cohort study was conducted using electronic medical record data from 6224 patients with primary care visits from 2008 to 2015. Prescription orders were used to identify ADM use, and hypertension was defined by medical record diagnosis. Using package insert warnings, a 3-level ADM exposure variable was created: ADMs that increase BP (ADM BP+), ADMs that do not increase BP, and no ADM. Unadjusted and adjusted Cox proportional hazard models were computed to estimate the association between the ADM exposure and incident hypertension.**

Results: **Unadjusted results revealed that ADM BP+ use compared with the no ADM group was significantly associated with incident hypertension (hazard ratio, 1.30; 95% confidence interval, 1.08–1.57). After adjusting for covariates, ADM BP+ use was no longer significantly associated with incident hypertension (hazard ratio, 1.20; 95% confidence interval, 0.97–1.49).**

Conclusions: **Commonly used ADMs were not associated with incident hypertension after controlling for other factors associated with ADM use and hypertension. Research on potential dose and duration effects is warranted. (J Am Board Fam Med 2018;31:22–28.)**

Keywords: **Antidepressive Agents, Blood Pressure, Hypertension, International Classification of Diseases, Primary Health Care, Proportional Hazards Models, Retrospective Studies**

Primary care physicians manage hypertension and antidepressant medications (ADMs) almost every day. The age-adjusted prevalence of hypertension is 29.6% among the adult population in the United States. Of those with hypertension, only 48% achieve control of their blood pressure. Hypertension is directly related to both heart disease and stroke, which are counted as the first and fourth leading causes of death in the United States, respectively.[1] Given the serious outcomes associated with hypertension, physicians must be mindful of iatrogenic causes of hypertension, which can include frequently prescribed medications.

Recent data suggest that 10% to 11% of Americans age 6 years and older are treated with ADMs in a given year.[2,3] Some concern has been expressed as to the safety of ADMs with regard to hypertension, especially when considering certain classes of ADMs. In a cohort of depressed participants with low rates of hypertension at baseline, treatment with ADMs was associated with an increased risk of developing hypertension.[4] The same study showed a stronger link between tricyclic antidepressants (TCAs) and hypertension than between selective serotonin reuptake inhibitors and hypertension. However, that study did not contrast ADMs known to increase blood pressure (BP) against those that do not, and the association of individual ADMs and incident hypertension was not studied.[5] A separate study showed an association between serotonin norepinephrine reuptake inhibitors (SNRIs), espe-

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cially venlafaxine, and severe hypertensive events. However, the study examined only psychiatric inpatients and did not investigate the development of hypertension itself.[6]

Among ADMs associated with increasing BP[7], TCAs are the best studied. SNRIs—venlafaxine in particular—have also been associated with elevated BP.[7] However, a review of the literature revealed little research on whether BP-altering ADMs are associated with an increased risk of hypertension in primary care populations. ADMs are increasingly being prescribed for conditions other than depression, and high rates of prescribing TCAs for insomnia, pain, and migraine could be contributing to hypertension.[8,9] Given the large number of patients exposed to ADMs, determining whether ADMs associated with BP changes are also associated with risk of hypertension would inform prescribing and determine whether some ADMs may lead to adverse physical outcomes, that is, hypertension. This study was designed to estimate the association between the use of ADMs that increase BP, ADMs that have no BP effects, and no ADM use and the risk of incident hypertension.

Methods

Subjects

Data were available from 33,661 patients from the Saint Louis University, Department of Family and Community Medicine's Primary Care Patient Data Registry (PCPD). The PCPD contains deidentified data for patient who visited any of the 3 academic family medicine clinic locations or any of the 3 general internal medicine clinic locations between July 1, 2008, and June 30, 2015. These primary care clinics are in the St. Louis, Missouri, metropolitan area and include both urban and suburban locations.

The PCPD contains patient diagnoses, prescriptions, laboratory results, referrals, social history, vital signs, and demographics. Additional descriptions of the PCPD have been previously reported.[10–19] The creation of the PCPD for primary care research was approved by Saint Louis University's Institutional Review Board.

Eligibility criteria for this study included age ≥18 years (n = 31,569) and having complete demographic data (n = 30,627). All patients must have had at least 1 visit in the 2-year washout period (July 1, 2008, to June 30, 2010) and at least 1 visit in the 5-year follow-up period (July 1, 2010, to June 20, 2015); these criteria reduced the sample to 10,106. Because the outcome is time to incident hypertension in the follow-up period, patients with existing International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis for hypertension in the washout period were removed, resulting in a final sample size of 6244 primary care patients free of diagnosed hypertension who initiated an ADM at some time during follow-up. Follow-up time was defined as months from July 1, 2010, to the date of incident hypertension or the censored date, which is the date of the last visit in the registry if no incident hypertension was present.

Outcome Variable

Incident hypertension diagnosed after an ADM was initiated was defined by a single instance of ICD-9-CM code 401x, if the code was assigned as the primary reason for the clinic visit.

Exposure Variable

ADM treatment was defined by ≥1 prescription for or the presence on a current medication list, as provided by the patient during the history, of 1 of the following ADMs: selective serotonin reuptake inhibitors (citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline, and vilazodone), SNRIs (venlafaxine, duloxetine, milnacipran, and desvenlafaxine), TCAs (amitriptyline, desipramine, doxepin, imipramine, nortriptyline, trimipramine, clomipramine, maprotiline, protriptyline, amoxapine), nonclassified ADMs (bupropion, nefazodone, trazodone, and mirtazapine), and monamine oxidase inhibitors (selegiline, phenelzine, tranylcypromine, and isocarboxazid). We did not require a minimum dose or duration of treatment and did not measure poly-ADM use.

Based on package insert warnings about effects of the drugs on BP, we classified all monamine oxidase inhibitors, TCAs, SNRIs, and bupropion as ADMs that can increase BP. All other ADMs were considered to not increase BP. We created a 3-level ADM variable: (1) ADMs that can increase BP (ADM BP+), (2) ADMs that do not increase BP (ADM BP−), and (3) no ADM use. ADM use was treated as a time-dependent exposure because it could have started at any time before the incident hypertension or censor date, and, once started, a patient was considered to have continued until the

end of follow-up. ADM exposure status was modeled as an intent-to-treat protocol.

Covariates

We selected covariates based on previous or posited associations with hypertension and depression. Demographics included mean age, race (white vs any other race), gender, marital status (married vs other), and neighborhood socioeconomic status (nSES). nSES uses US Census information and zip codes to compute an nSES index based on zip code–level information such as median income, education, employment, poverty level, and median household value. The nSES index was dichotomized into high and low, based on a median split.[20] Volume of health care use was computed by generating the distribution of mean clinic visits per month and was used to control for detection bias. The distribution was categorized into quartiles, and the top quartile was considered high utilization.

Comorbidities were derived from the ICD-9-CM code given as the primary reason for a clinic visit, with the exception of substance use disorders, which, because of a low prevalence, were derived from all diagnoses, including the problem list. Comorbidity and health behaviors included obesity, depression, any anxiety disorder, substance use disorders, type 2 diabetes, vascular disease, hyperlipidemia, and smoking status.

Obesity was defined as a body mass index ≥30.0 kg/m^2 and/or an ICD-9-CM diagnosis. Many specific anxiety disorders—for example, panic disorder, and social phobia—were uncommon in our data set. Therefore, we created a composite variable called "any anxiety disorder." Any anxiety disorder was defined by ICD-9-CM codes for the following conditions: anxiety disorder unspecified, generalized anxiety disorder, panic disorder, obsessive compulsive disorder, social phobia, or posttraumatic stress disorders. Depression was defined by ICD-9-CM codes 296.2, 296.3, and 311. We required 2 diagnoses within the same 12-month period for both anxiety and depression because this criterion, compared with a single occurrence, has good agreement with chart abstraction and self-report when applied for depression.[21,22] We followed the same logic for anxiety. All other conditions were defined by a single instance of an ICD-9-CM code. Substance use disorder included diagnostic codes for any alcohol or drug abuse or dependence. Vascular disease was a composite variable defining either cardiovascular or cerebrovascular diagnoses. Finally, current smoking status was based on social history data and/or ICD-9-CM diagnosis and was coded as current smoking or not (never and former smokers).

Analytic Approach

This retrospective cohort analysis was conducted using SAS version 9.4 (SAS Institute, Cary, NC) at $\alpha = 0.05$. Bivariate analyses using the χ^2 test for categorical variables and 1-way analysis of variance for continuous variables assessed the relationship of ADM treatment group with incident hypertension (yes vs no) and covariates. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for time to incident hypertension. Crude and adjusted models for the relationship of ADM group and time to incident hypertension were applied before and after adjusting for all covariates. Substance use disorder, depression, any anxiety disorder, obesity, hyperlipidemia, type 2 diabetes, and vascular disease were treated as time-dependent covariates because they could have occurred any time before the end of follow-up.

Results

The distribution of covariates and the cumulative incidence of hypertension for the entire cohort and by ADM group is shown in Table 1. In the entire cohort, the mean age ± standard deviation of patients was 46.4 ± 15.6 years; 68.8% were white, 63.2% were female, 47.5% were married, and 58.4% had a high nSES.

As shown in Table 1, the cumulative incidence of hypertension was 12.4% during the observation period. The cumulative incidence of hypertension, which ranged from 12.1% to 13.5% in patients without ADM and in those taking ADM-BP+, was not significantly associated with ADM group. Older age, white race, female sex, and high nSES were significantly more common among patients who received an ADM. Married patients were significantly more common among patients not exposed to an ADM. Current smoking, substance use disorder, depression, any anxiety disorder, obesity, hyperlipidemia, type 2 diabetes, and vascular disease were all significantly more common among patients who received an ADM than among those who did not receive an ADM.

Table 1. Distribution of Sociodemographics, Covariates, and 5-Year (2010–2015) Cumulative Incidence of Hypertension Among Adult Primary Care Patients, Overall and by ADM Exposure ($n = 6244$)

Variable	Total ($n = 6244$)	No ADM (n = 4182)	ADM-BP− (n = 1008)	ADM-BP+ (n = 1054)	*P* Value
Hypertension, cumulative incidence	774 (12.4)	507 (12.1)	125 (12.4)	142 (13.5)	.494
Age (years), mean (SD)	46.4 (15.6)	46.0 (16.0)	47.2 (15.7)	47.2 (13.8)	.012
White race	4297 (68.8)	2713 (64.9)	772 (76.6)	812 (77.0)	<.0001
Female sex	3949 (63.2)	2449 (58.6)	706 (70.0)	794 (75.3)	<.0001
Married	2968 (47.5)	2058 (49.2)	426 (42.3)	484 (45.9)	<.001
High neighborhood SES	3649 (58.4)	2378 (56.9)	618 (61.3)	653 (62.0)	.001
High clinic utilization	1380 (22.1)	628 (15.0)	297 (29.5)	455 (43.2)	<.0001
Current smoker	1164 (18.6)	620 (14.8)	214 (21.2)	330 (31.3)	<.0001
Substance use disorder	190 (3.0)	65 (1.6)	51 (5.1)	74 (7.0)	<.0001
Depression	771 (12.4)	24 (0.6)	337 (33.4)	410 (38.9)	<.0001
Any anxiety disorder	665 (10.7)	92 (2.2)	289 (28.7)	284 (26.9)	<.0001
Obese	2365 (37.9)	1480 (35.4)	413 (41.0)	472 (44.8)	<.0001
Hyperlipidemia	1429 (22.9)	898 (21.5)	261 (25.9)	270 (25.6)	.001
Type 2 diabetes	391 (6.3)	228 (5.4)	79 (7.8)	84 (8.0)	.001
Vascular disease	605 (9.7)	356 (8.5)	110 (10.9)	139 (13.2)	<.0001

Data are n (%) unless otherwise indicated.
ADM, antidepressant medication; BP−, no effect on blood pressure; BP+, increases blood pressure; SD, standard deviation; SES, socioeconomic status.

Results from Cox proportional hazard models of the association between ADM groups and time to incident hypertension are shown in Table 2. Unadjusted results revealed that the ADM-BP+ group were significantly more likely than the no ADM group to develop hypertension (HR, 1.30; 95% CI, 1.08–1.57). No association was found between ADM-BP− and incident hypertension. After adjusting for all covariates, the association between the ADM-BP+ group and incident hypertension was no longer statistically significant (HR, 1.20; 95% CI, 0.97–1.49).

Discussion

In a cohort of 6244 primary care patients without hypertension at baseline, we observed that the use of ADMs traditionally associated with increased BP corresponded to a 30% increased risk of incident hypertension. After adjusting for covariates, however, this association decreased in magnitude and was no longer statistically significant as a class.

These findings are not entirely in line with previously published data on this topic. Prior studies showed a positive relationship between SNRIs/TCAs and elevated BP.[5,23,34] In the case of SNRIs, this relationship was dose-dependent: higher doses were associated with a greater magnitude of BP elevation. The most significant effects have been noted at doses typically considered to be supratherapeutic.[23,24] Such doses would be less likely in a primary care setting, which may help explain why our findings differ. In fact, several studies showed no change in BP in patients treated with therapeutic doses of venlafaxine.[25–27] Studies of duloxetine showed no or clinically insignificant blood pressure elevations with therapeutic dosing.[28–30] The literature on TCAs varies and includes findings ranging from elevated BP to orthostatic hypotension.[31–35]

A study by Licht et al[5] showed increased rates of BP elevation in patients taking SNRIs and TCAs. Our study differs in that we relied on a diagnosis of hypertension to identify patients, whereas Licht et al relied on BP measurements at a single clinic visit. By using the diagnosis of hypertension, we decreased the likelihood that spurious BP elevations, which are not uncommon in normotensive patients, were diagnosed as hypertension. The use of a diagnosis code also enabled us to capture instances of masked hypertension, which would be missed with BP checks at a single visit. Similar to our results, Licht and colleagues found a diminished effect after adjusting for covariates, though their findings did remain significant after adjustment.

Table 2. Survival Models, Hazard Ratios, and 95% Confidence Intervals of the Relationship of Antidepressant Medication Treatment Group and Time to Incident Hypertension among Adult Primary Care Patients ($n = 6244$), 2010–2015*

	Crude HR (95% CI)	Overall adjusted HR (95% CI)
ADM		
None	1.00	1.00
BP−	1.10 (0.90–1.34)	1.08 (0.87–1.33)
BP+	1.30 (1.08–1.57)	1.20 (0.97–1.49)
Age		1.04 (1.03–1.05)
White race		0.60 (0.52–0.71)
Female sex		0.93 (0.80–1.08)
Married		1.08 (0.93–1.26)
High neighborhood SES		0.93 (0.79–1.09)
High clinic utilization		1.37 (1.17–1.61)
Current smoker		1.43 (1.21–1.70)
Substance use disorder		1.19 (0.80–1.76)
Depression		0.88 (0.68–1.13)
Any anxiety disorder		0.90 (0.68–1.18)
Obese		1.78 (1.54–2.07)
Hyperlipidemia		1.07 (0.91–1.26)
Type 2 diabetes		1.62 (1.31–1.99)
Vascular disease		0.99 (0.81–1.22)

ADM, antidepressant medication; BP−, no effect on blood pressure; BP+, increases blood pressure; CI, confidence interval; HR, hazard ratio; SES, socioeconomic status.
*ADM treatment and comorbidities were treated as time-dependent variables.

TCAs are now infrequently used to treat depression and anxiety. In fact, a recent study surveying prescribing data from 2006 to 2015 in Quebec, Canada, found that TCAs are prescribed for depression and anxiety only 2.7% and 1.5% of the time, respectively. Some of the most common uses for TCAs include chronic pain, insomnia, and migraine.[9] Similarly, SNRIs have indications outside the realm of depression and anxiety. It is possible that prior studies, which primarily focused on patients in a psychiatric setting, would have had fewer patients taking ADMs for nonpsychiatric purpose and more patients taking higher doses. This may partly account for the inconsistent findings in our primary care sample compared with results from studies using a primarily psychiatric population.

Limitations

While the use of the 3-level exposure variable allowed us to compare ADMs with BP effects versus those without, we lacked a sufficient sample size to estimate the risk of hypertension due to a specific ADM class or individual medication. Other limitations are intrinsic to the retrospective cohort design. We did not have access to data for filled ADM prescriptions (vs those prescribed), and it is not possible to draw conclusions regarding the duration of ADM use associated with incident hypertension. We recognize that a single prescription does not fully account for characteristics of ADM exposure and does not capture characteristics of ADM use, such as duration, which may contribute to hypertension. Additional research is necessary to determine whether higher dose and longer duration of use of an ADM-BP+ are associated with incident hypertension. The limited geographic region and academic medical setting limit generalizability. Finally, a risk of misclassification exists if patients left our health care system and developed hypertension. This possibility would bias results to the null and thus our HRs may be conservative.

Conclusions

Our results suggest that patient characteristics associated with receiving an ADM may account for the observation that ADMs with BP-altering effects could lead to hypertension. We lacked a sufficient

number of patients to model the risk of hypertension as a function of specific ADMs and we were unable to test whether ADM duration or dose were associated with incident hypertension. Our findings are hypothesis generating, and future research should focus on the potential of long-term use of ADMs with strong BP effects to lead to hypertension in primary care. Given the differences between prior prospective controlled studies and our real-world analysis, further investigation into the relationship between these extremely common parts of primary care practice is warranted.

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