Original Article

Antihypertensive Drugs and Risk of Depression
A Nationwide Population-Based Study

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Abstract—Hypertension, cardiovascular diseases, and cerebrovascular diseases are associated with an increased risk of depression, but it remains unclear whether treatment with antihypertensive agents decreases or increases this risk. The effects of individual drugs are also unknown. We used Danish population-based registers to systematically investigate whether the 41 most used individual antihypertensive drugs were associated with an altered risk of incident depression. Analyses of diuretics were included for comparisons. Participants were included in the study in January 2005 and followed until December 2015. Two different outcome measures were included: (1) a diagnosis of depressive disorder at a psychiatric hospital as an inpatient or outpatient and (2) a combined measure of a diagnosis of depression or use of antidepressants. Continued use of classes of angiotensin agents, calcium antagonists, and β-blockers was associated with significantly decreased rates of depression, whereas diuretic use was not. Individual drugs associated with decreased depression included 2 of 16 angiotensin agents: enalapril and ramipril; 3 of 10 calcium antagonists: amlodipine, verapamil, and verapamil combinations; and 4 of 15 β-blockers: propranolol, atenolol, bisoprolol, and carvedilol. No drug was associated with an increased risk of depression. In conclusion, real-life population-based data suggest a positive effect of continued use of 9 individual antihypertensive agents. This evidence should be used in guiding prescriptions for patients at risk of developing depression including those with prior depression or anxiety and patients with a family history of depression.

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Key Words: antihypertensive agents ■ anxiety disorders ■ depressive disorder ■ diuretics ■ inflammation

Hypertension as a multifactorial pathology is one of the most important cardiovascular risk factors, affecting up to 30% to 40% of the general population.[1] Depression is common in patients with hypertension and cardiovascular and cerebrovascular diseases in general, where it negatively impacts on clinically important outcomes. The prevalence of major depression in hypertension,[2] post-myocardial infarction,[3,4] and post-stroke[5] is ≈30% in each disorder, which is higher than seen in community samples.[6] Both major depression and depressive symptoms are associated with increased mortality, morbidity, poorer quality of life, higher health service utilization, and increased healthcare costs in these comorbid diseases.[3,5,7–10] It is, therefore, important to prevent the development of depression in people with hypertension and cardiovascular and cerebrovascular diseases, and widely used treatment interventions should be thoroughly evaluated.

Four main classes of medications are currently used for hypertension and cardiovascular and cerebrovascular diseases: angiotensin agents (ACE [angiotensin-converting enzyme] inhibitors and angiotensin II receptor blockers [ARBs]), calcium antagonists, β-blockers, and diuretics.[11] Epidemiological studies have shown that depression risk might differ according to the class of these drugs.[12,13]

Low-grade systemic inflammation and neuroinflammation is prevalent in hypertension and cardiovascular and cerebrovascular diseases,[1,14] as well as in depression.[15] Evidence points to increased inflammatory mediators including increased levels of proinflammatory cytokines such as IL (interleukin)-1β, IL-6, IL-8, IL-17, IL-23, TGFβ (transforming growth factor-beta), and TNFα (tumor necrosis factor-alpha) associated with either increased blood pressure or end-organ damage, even in prehypertensive patients.[1] As such, conventional antihypertensive and cardiovascular drugs have shown additional anti-inflammatory effects that could be linked to their blood pressure–lowering properties[1] and concomitantly have an influence on depression.

The renin-angiotensin system is one of the pathways known to modulate inflammation in the central nervous

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system and seems involved in the regulation of the stress response.[16] Angiotensin agents may also exert anti-inflammatory effects.[17] Further, based on a genome-wide association data, angiotensin agents have been suggested as having potential efficacy in mood disorders.[18] A number of observations have linked angiotensin-converting enzyme polymorphisms with depression and the underlying serotonin and dopamine neurotransmitter systems.[19] In a case-control study[16] and in a subsequent case register study,[20] we confirmed that ACE inhibitors were associated with a reduced likelihood for the onset of depression. Use of ACE inhibitors and ARBs for the treatment of hypertension in otherwise healthy adults has been associated with improved mental health domains of quality of life.[21] There are no randomized clinical trials of angiotensin agents and depression.

Dysregulation of intracellular calcium is evident in depression, including receptor-regulated calcium signaling.[22] Calcium antagonists may also have anti-inflammatory effects.[23] Based on genetic associations between voltage-gated calcium channels and major depression,[24] calcium antagonists have been associated with decreased risk of developing depression in a few noncontrolled clinical trials.[25,26]

β-Blockers are the cornerstone treatment for chronic heart failure, reducing mortality and morbidity in patients with heart failure, and are recommended by the American College of Cardiology/American Heart Association guidelines.[27] Nevertheless, early reports linking β-blockers with depression[28] may have limited their use in heart failure patients with comorbid depression. Although randomized controlled trials suggest that some β-blockers such as pindolol may have antidepressants effects[29] and although more recent observational studies have challenged the association between β-blocker therapy and increased risk of depression,[30,31] others have not.[32] There, therefore, is uncertainty and concern about β-blockers in patients with depressive symptoms, leading to possible underutilization.[31] Although preliminary investigations exist, diuretics have not been associated with depression.[13,33]

While the 4 main classes of medications for hypertension and cardiovascular and cerebrovascular diseases within each class share the same overall pharmacological characteristics, each individual drug is characterized by specific pharmacological properties, including selectivity of action depending on the receptors subtypes, intrinsic sympathomimetic activity, lipid solubility, and pharmacokinetic profile,[17,34,35] as well as potential anti-inflammatory properties.[1] These pharmacological and anti-inflammatory characteristics may influence the risk of depression related to the individual drugs, but no study has investigated the effects of individual antihypertensive drugs in relation to depression.

We, therefore, systematically used Danish nationwide population-based registers in the R-WAS (Register Wise Association Study) to investigate whether agents with an a priori preclinical or theoretical evidence base may have effects on depression.[20,36] This approach is predicated on a theoretical construct, that of a shared environmental risks as well as common biological pathways for diverse noncommunicable disorders, which include depression, hypertension, and cardiovascular and cerebrovascular diseases.[37] Based on the abovementioned considerations including shared inflammatory and stress response mechanisms, we systematically studied effects of antihypertensive treatments on depression as part of the R-WAS study.

Aims of the Study

We aimed to use Danish population-based registers to systematically investigate whether the use of antihypertensive drugs is associated with an altered risk of incident depression. To take into account confounding by indication, we estimated the rate of incident depression during successive prescription periods of the drugs, whereas the period with nonuse was included for comparison (see later).

Hypotheses

Due to the overlapping biological including inflammatory pathways involved in the pathogenesis and treatment mechanisms of hypertension and cardiovascular and cerebrovascular diseases and depression, we hypothesized that continued use of ACE inhibitors and ARBs (angiotensin agents) and calcium antagonists (calcium channel blockers) would influence the overall rate of incident depression in line with the number of prescriptions, while we expected no overall effect of continued treatment with β-blockers and of diuretics. Based on the varying pharmacological characteristics of the individual hypertensive drugs, we also hypothesized differential effects of hypertensive drugs such that some drugs within each drug class may influence the rate of incident depression, whereas others may not.

Methods

Anonymized data and materials are available following approval by the Data Agency of the Capital Region of Denmark and contact to the authors.

Registers

Data were obtained by linking Danish population-based registers using a unique personal identification number, which is assigned to all people living in Denmark, thus ensuring accurate linkage of information between registers, irrespective of changes in name and demographics.[38] In this way, the Medicinal Product Statistics[39] was linked with the Danish Medical Register on Vital Statistics,[40] the Danish National Hospital Register,[41] and the Danish Psychiatric Central Register.[42]

The Medicinal Product Statistics contains data on all prescribed medication purchased at pharmacies from January 1, 1995, and onward.[39] The register includes prescription data from all physicians in Denmark, that is, from primary care, including general practice and private specialists, and from secondary outpatient hospital care settings.

The Danish Medical Register on Vital Statistics[40] contains data on deaths. The Danish National Hospital Register[41] contains data on all patients treated at all somatic hospitals as inpatients or outpatients in Denmark from January 1, 1977, and onward as a part of the official Danish health survey.[43] Likewise, from April 1, 1970, and onward, all psychiatric admissions and diagnoses are recorded in the register (as part of the Danish Psychiatric Central Register[42]). Since January 1, 1994, the *International Classification of Diseases* (*ICD*), *Tenth Revision*, has been in use in both registers, and since January 1, 1995, diagnoses from outpatient contacts were included.

Diagnoses from primary care are not included in the registers, but pharmacological treatment from primary care is recorded in the Danish Medical Register on Vital Statistics (as prescriptions from all other physicians).

Study Population

All 5.4 million individuals in Denmark in January 2005 were included in the study.

Exclusion Criteria

The following individuals were excluded: individuals who purchased antidepressants at least once between the start of the medical register in 1995 and the start of our study period (January 1, 2005) and individuals with a diagnosis of depression before entry into the study (back to 1970).

Outcome Measures

Two different outcome measures were included in the analyses: (1) a diagnosis of depressive disorder (*ICD* codes: DF32–DF33.31) given at a psychiatric contact (as inpatient or outpatient) and as identified in the Danish Psychiatric Central Register and (2) a combined end point of either a diagnosis of depressive disorder as specified above or use of antidepressants (Anatomical Therapeutic Chemical Classification: N06A).

Follow-Up Period

Individuals were followed from entry into the study until either the date of death; date of a diagnosis of organic mental disorders, mental disorders due to psychoactive substance use, schizophrenia, and mania/bipolar disorder (DF00–DF31.9 incl); or December 31, 2015 (end of the study period), whatever came first.

Exposure Drugs

Angiotensin agents, calcium channel blockers, β-blockers, and diuretics within each class and separately for each drug are listed in Table 1.

Comorbidity

Somatic diagnoses were categorized within 9 *ICD*, *Eighth Revision* and *Tenth Revision*, defined somatic disease chapters (I: infections; II: neoplasms; III: diseases of the blood; IV+IX+X: endocrine, nutritional, and metabolic diseases and diseases of the circulatory or respiratory system; VI–VIII: diseases of the nervous system, eye, and ear; XI: diseases of the digestive system; XII: diseases of the skin and subcutaneous tissue; XIII: diseases of the musculoskeletal system; XIV: diseases of the genitourinary system and pregnancy, child birth, and the puerperium) and separately within each of these disease areas.

Design of the Analyses

There are 2 main potential sources of errors in the planned analyses that we proactively addressed: confounding by indication may occur if an unobserved variable (eg, some somatic comorbidity) is a risk factor for the studied outcome (depression) and at the same time is an indication of the drug of interest.[44] More specifically, confounding by indication may occur as hypertension,[2] myocardial infarction[3,4] and stroke[5] are risk factors for depression, and at the same time are indications for treatment with the antihypertensive drugs of interest. Detection bias may occur if subjects who are prescribed antihypertensives are more likely to be diagnosed with the outcome disease (depression) or to get antidepressants than subjects unexposed to antihypertensives. However, strategic sampling designs may be used to ameliorate these risks, for example, based on the self-controlled case series method as previously done in pharmacoepidemiological studies by our group. This will allow us under certain circumstances to substantially mitigate or at least assess the magnitude of the bias. To control for confounding effects and detection bias and to estimate the effect of duration of treatment, rates were compared during successive prescriptions of the exposure drug as in prior studies (eg, by Kessing et al[20,45]).

Statistical Analyses

The association between drug exposure and the rate of incident depression was analyzed separately for each drug using Cox regression with time-dependent exposure. We fitted these models using a nested case-control design with 10 age- and sex-matched controls for each depression case. In these analyses, the principle is that each follow-up day where a subject is at risk for experiencing the outcome is categorized according to the current values of the drug exposure defined in the current exposure window. The exposure window was defined as the 10-year period before the case date. The models were adjusted for the potential confounders evaluated at the start of the exposure window. The drug exposure on a given day during follow-up was defined as the number of prescriptions of the candidate drug during the last 10 years in appropriate categories. The number and width of categories were chosen dependent on the general usage of the candidate drug. The category 1 to 2 prescriptions was used as the reference category in all analyses. The exposure category was evaluated for each case and the corresponding matched controls on the case's date of depression diagnosis. To note the cumulation of exposure in the fixed 10-year period, all analyses of the outcomes were restricted to the calendar years 2005 to 2015 (the Danish Medical Product Statistics Register starts in 1995).

All analyses were matched for current age, sex, and current calendar date and also adjusted for additive effects of current employment status (working or student: reference, unemployed, age pension, disability pension, other)=partially adjusted analyses. Additional analyses were performed in which we also adjusted for additive effects of the time-dependent comorbidity status with additive effects of 9 dummy variables indicating the 9 comorbidity groups listed under section 2.7, which were regarded as the fully adjusted analyses. The comorbidity status was always evaluated 10 years previously to avoid time interference between exposure status and comorbidity.

Hazard ratios (HRs) with 95% confidence limits and exposure trend tests obtained were reported with a likelihood ratio test comparing a Cox regression model without drug exposure to a model that assumes a linear increase in outcome hazard rate between the exposure categories (excluding the nonuse category). Data are reported for each of the 4 drug classes: angiotensin agents, calcium antagonists, β-blockers, and diuretics, respectively (Table 2), and for the 41 most used individual antihypertensive drugs within each drug class (Tables 3 through 5). Due to multiple testing in relation to individual drugs, we Bonferroni-adjusted *P* for the number of drugs within each drug class in these analyses. To be considered statistically significant, the following *P* should be survived for each individual drug: $P<0.003$ for angiotensin agents (16 drugs), $P<0.005$ for calcium antagonists (10 drugs), and $P<0.003$ for β-blockers (15 drugs).

All analyses were performed with R.

Statement of Ethics

Ethical approval of anonymous register studies is not needed according to the Danish law.

Data Approval

The study was approved by the Data agency of the Capital Region of Denmark.

Results

A total of 3 747 190 subjects were exposed to an antihypertensive drug during the exposure period from 2005 to 2015. Table 1 shows the number of subjects exposed for the 4 drug classes and for each individual drug for which there were >100 users included (n), age, and female sex proportion at first prescription. Table 2 presents HRs according to prescription number of each of the 4 drug classes, adjusted for age, sex, employment status, and calendar year (partially adjusted), and additionally adjusted for somatic diagnoses (fully adjusted) and trend tests. Results of analyses for which the outcome measure was a diagnosis of depression are at the left side of the table whereas results from analyses with a diagnosis of depression or use of antidepressants as the outcome measure are shown on the right side of the table.

Table 1. Number of Individuals Exposed in Total and for Each Drug During the Exposure Period 2005 to 2015, Age, and Female Sex Proportion at the Date of First Prescription

Drug	n	Age, y; Median (Quantiles)	Female Sex Proportion, %
Angiotensin agents	1 000 683	64 (54–73)	50
Calcium antagonists	833 281	63 (51–74)	54
β-Blockers	777 038	65 (56–75)	52
Diuretics	1 136 188	67 (56–77)	60
Angiotensin agents			
Captopril, C09AA01	8517	67 (57–76)	47
Enalapril, C09AA02	452 366	63 (54–73)	50
Lisinopril, C09AA03	45 304	62 (53–72)	52
Perindopril, C09AA04	54 769	67 (58–77)	44
Ramipril, C09AA05	253 800	65 (55–74)	45
Quinapril, C09AA06	1642	68 (59–77)	52
Benazepril, C09AA07	441	67 (59–76)	51
Fosinopril, C09AA09	916	66 (58–76)	51
Trandolapril, C09AA10	40 425	69 (59–78)	42
Losartan, C09CA01	363 785	65 (56–74)	53
Eprosartan, C09CA02	6332	68 (59–77)	59
Valsartan, C09CA03	25 122	65 (56–74)	53
Irbesartan, C09CA04	25 904	64 (56–73)	51
Candesartan, C09CA06	86 903	63 (53–73)	58
Telmisartan, C09CA07	19 902	64 (55–73)	53
Olmesartan medoxomil, C09CA08	5877	64 (55–73)	55
Calcium antagonists			
Amlodipine, C08CA01	39 367	78 (57–51)	59
Fedipin, C08CA02	6398	65 (81–62)	64
Isradipin, C08CA03	502	76 (69–78)	64
Nifedipin, C08CA05	3304	78 (55–44)	62
Nitrendipin, C08CA08	192	51 (67–82)	64
Lacidipin, C08CA09	404	72 (51–55)	70
Lercanidipin, C08CA13	2408	83 (65–71)	66
Verapamil, C08DA01	7483	80 (46–52)	62
Verapamil combinations, C08DA51	130	58 (70–70)	51
Diltiazem, C08DB01	4266	66 (78–73)	60
β-Blockers			
Pindolol, C07AA03	779	44 (76–79)	71
Propranolol, C07AA05	18 268	20 (26–77)	76
Timolol, C07AA06	111	61 (80–60)	67
Sotalol, C07AA07	2580	73 (63–59)	53
Metoprolol, C07AB02	40 772	59 (62–33)	60
Atenolol, C07AB03	8565	75 (38–42)	67
Acebutolol, C07AB04	104	61 (73–76)	67
Betaxolol, C07AB05	102	72 (66–41)	72
Bisoprolol, C07AB07	4117	58 (84–77)	58
Nebivolol, C07AB12	306	74 (52–59)	61
Labetalol, C07AG01	1086	28 (73–29)	87
Carvedilol, C07AG02	4632	78 (71–68)	49
Metoprolol and thiazides, C07BB02	460	67 (43–44)	70
Atenolol and other diuretics, C07CB03	757	53 (52–63)	69
Metoprolol and felodipine, C07FB02	216	76 (70–78)	62

(*Continued*)

Table 1. Continued

As can be seen, for all 4 antihypertensive classes and in nearly all analyses, the hazard rate of depression and the hazard rate of depression or use of antidepressants, respectively, were significantly lower in subjects with zero prescriptions (nonuse of the target antihypertensive drug or class) compared with 1 to 2 prescriptions of the target drug/class, reflecting that patients with hypertension and cardiovascular and cerebrovascular diseases are at increased risk of developing depression.[2–5] For angiotensin agents, calcium antagonists, and β-blockers, hazard rates were decreased during prescription period 3 to 5, 6 to 10, and >10, respectively, compared with the reference period 1 to 2 with highly statistically significant trend test (P<0.001) in all 4 analyses, that is, with a diagnosis of depression and a diagnosis of depression or use of antidepressant as the outcome measures, respectively, and partially and fully adjusted, respectively. In contrast, no effects were found of diuretics.

Individual drugs are highlighted for which statistically significant associations with incident depression were found in all 4 analyses, that is, analyses with a diagnosis of depression and a diagnosis of depression or use of antidepressant as the outcome measures, respectively, and partially and fully adjusted, respectively.

Table 3 shows results for the 16 most used individual angiotensin agents. Across all 4 analyses, 2 drugs, enalapril, and ramipril were associated with decreased rates of depression.

Table 4 shows results for the 10 most used individual calcium antagonists. Across all 4 analyses, amlodipine, verapamil, and verapamil combinations were associated with decreased rates of depression.

Table 5 shows results for the 15 most used individual β-blockers. Across all 4 analyses, 4 drugs, propranolol, atenolol, bisoprolol, and carvedilol, were associated with decreased rates of depression.

All analyses of the abovementioned individual drugs survived Bonferroni correction as all P values were <0.001 except in 1 analysis for verapamil (P=0.004) and 2 for verapamil combinations (P=0.022 and P=0.020).

Discussion

This is the first study ever using population-based health data to investigate the association between individual

Table 2. Prescription Number of Angiotensin Agents, Calcium Antagonists, β-Blockers, and Diuretics; HRs of Diagnosis of Depression and Diagnosis of Depression or Use of Antidepressants, respectively; and Trend Tests, adjusted for Age, Sex, Employment Status, and Calendar Year (Partially Adjusted) and Additionally Adjusted for Somatic Diagnoses (Fully Adjusted)

Drug	Prescription No.	HR (95% CI), Partially Adjusted	Trend Test	HR (95% CI), Fully Adjusted	Trend Test	HR (95% CI), Partially Adjusted	Trend Test	HR (95% CI), Fully Adjusted	Trend Test
		Outcome measure: diagnosis of depression				Outcome measure: diagnosis of depression or use of antidepressant			
Angiotensin agents	1–2	1.00	0.98 (0.96–0.99), *P*=0.001*	1.00	0.97 (0.96–0.99), *P*<0.001*	1.00	0.98 (0.97–0.99), *P*<0.001*	1.00	0.97 (0.96–0.98), *P*<0.001*
	0	0.57 (0.55–0.60)		0.64 (0.61–0.67)		0.60 (0.58–0.61)		0.63 (0.61–0.65)	
	3–5	0.96 (0.90–1.02)		0.97 (0.91–1.04)		0.95 (0.91–0.99)		0.95 (0.91–0.99)	
	6–10	0.92 (0.87–0.98)		0.94 (0.88–1.00)		0.89 (0.86–0.93)		0.89 (0.86–0.93)	
	>10	0.92 (0.88–0.97)		0.92 (0.88–0.97)		0.92 (0.89–0.95)		0.91 (0.88–0.94)	
Calcium antagonists	1–2	1.00	0.96 (0.95–0.98), *P*<0.001*	1.00	0.97 (0.95–0.98), *P*<0.001*	1.00	0.96 (0.95–0.97), *P*<0.001*	1.00	0.96 (0.95–0.97), *P*<0.001*
	0	0.54 (0.52–0.57)		0.61 (0.59–0.64)		0.57 (0.56–0.59)		0.61 (0.59–0.62)	
	3–5	0.92 (0.86–0.98)		0.93 (0.87–1.00)		0.92 (0.88–0.96)		0.94 (0.89–0.98)	
	6–10	0.85 (0.79–0.91)		0.87 (0.81–0.94)		0.85 (0.81–0.89)		0.86 (0.82–0.90)	
	>10	0.88 (0.83–0.92)		0.89 (0.85–0.94)		0.88 (0.85–0.91)		0.89 (0.86–0.92)	
β-Blockers	1–2	1.00	0.91 (0.90–0.92), *P*<0.001*	1.00	0.90 (0.89–0.91), *P*<0.001*	1.00	0.94 (0.93–0.95), *P*<0.001*	1.00	0.94 (0.93–0.94), *P*<0.001*
	0	0.47 (0.46–0.48)		0.52 (0.51–0.54)		0.55 (0.54–0.56)		0.59 (0.57–0.60)	
	3–5	0.98 (0.93–1.03)		0.95 (0.90–1.00)		0.97 (0.93–1.01)		0.96 (0.93–1.00)	
	6–10	0.84 (0.79–0.89)		0.82 (0.77–0.87)		0.83 (0.80–0.87)		0.84 (0.80–0.87)	
	>10	0.76 (0.73–0.79)		0.74 (0.71–0.77)		0.83 (0.81–0.85)		0.83 (0.80–0.85)	
Diuretics	1–2	1.00	0.99 (0.98–1.01), *P*=0.403	1.00	0.99 (0.98–1.00), *P*=0.079	1.00	1.01 (1.00–1.02), *P*=0.040	1.00	1.00 (1.00–1.01), *P*=0.250
	0	0.60 (0.58–0.62)		0.71 (0.69–0.74)		0.63 (0.62–0.65)		0.69 (0.67–0.70)	
	3–5	1.00 (0.95–1.06)		1.00 (0.95–1.05)		0.95 (0.91–0.98)		0.94 (0.91–0.98)	
	6–10	0.96 (0.91–1.01)		0.95 (0.90–1.01)		0.89 (0.86–0.92)		0.89 (0.86–0.92)	
	>10	0.99 (0.95–1.03)		0.97 (0.93–1.01)		1.02 (0.99–1.04)		1.01 (0.98–1.03)	

HR indicates hazard ratio.
*Statistically significant.

antihypertensive agents and depression. Using Danish nationwide population-based registers, we confirmed our overall hypothesis that continued use of classes of angiotensin agents and calcium antagonists was associated with decreased rates of incident depression, whereas use of diuretics was not. Surprisingly, β-blockers as a group were also associated with decreased rates of depression. We further confirmed the hypothesis of differential effects of 9 individual drugs out of 41 investigated drugs, with decreased rates of depression across all 4 analyses comprising 2 of 16 angiotensin agents: enalapril and ramipril; 3 of 10 calcium antagonists: amlodipine, verapamil, and verapamil combinations; and 4 of 15 β-blockers: propranolol, atenolol, bisoprolol, and carvedilol.

Strengths of the Study

First, the study is a systematic investigation of all 5.4 million persons in Denmark, including 3 747 190 subjects who used

Table 3. Prescription Number of Angiotensin Agents; HRs of Diagnosis of Depression and Diagnosis of Depression or Use of Antidepressants, Respectively; and Trend Tests, Adjusted For Age, Sex, Employment Status, and Calendar Year (Partially Adjusted) and Additionally Adjusted for Somatic Diagnoses (Fully Adjusted)

Drug	Prescription No.	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test
		Outcome measure: diagnosis of depression				Outcome measure: diagnosis of depression or use of antidepressant			
Captopril, C09AA01	1–2	1.00	0.96 (0.86–1.07), *P*=0.481	1.00	0.96 (0.87–1.07), *P*=0.478	1.00	1.04 (0.97–1.12), *P*=0.280	1.00	1.03 (0.96–1.11), *P*=0.382
	0	0.96 (0.72–1.29)		1.15 (0.86–1.54)		1.19 (0.97–1.47)		1.25 (1.01–1.54)	
	3–5	1.24 (0.79–1.96)		1.37 (0.86–2.16)		1.26 (0.91–1.73)		1.26 (0.91–1.74)	
	6–10	0.87 (0.54–1.39)		0.89 (0.56–1.43)		0.77 (0.52–1.12)		0.77 (0.53–1.13)	
	>10	0.95 (0.67–1.34)		0.97 (0.69–1.36)		1.18 (0.93–1.49)		1.15 (0.91–1.47)	
Enalapril, C09AA02	1–2	1.00	0.95 (0.93–0.97), *P*<0.001*	1.00	0.94 (0.92–0.96), *P*<0.001*	1.00	0.97 (0.96–0.99), *P*<0.001*	1.00	0.97 (0.96–0.99), *P*<0.001*
	0	0.60 (0.57–0.63)		0.65 (0.61–0.68)		0.62 (0.60–0.64)		0.65 (0.63–0.67)	
	3–5	1.02 (0.94–1.10)		1.02 (0.94–1.10)		0.96 (0.91–1.01)		0.95 (0.90–1.00)	
	6–10	0.92 (0.85–1.00)		0.93 (0.85–1.01)		0.92 (0.87–0.97)		0.91 (0.86–0.97)	
	>10	0.86 (0.81–0.92)		0.85 (0.79–0.91)		0.92 (0.88–0.96)		0.92 (0.88–0.96)	
Lisinopril, C09AA03	1–2	1.00	0.91 (0.85–0.97), *P*=0.003*	1.00	0.91 (0.85–0.97), *P*=0.005*	1.00	0.99 (0.95–1.04), *P*=0.756	1.00	0.99 (0.95–1.03), *P*=0.612
	0	0.54 (0.47–0.62)		0.59 (0.51–0.67)		0.67 (0.61–0.74)		0.70 (0.64–0.77)	
	3–5	0.63 (0.49–0.82)		0.63 (0.48–0.81)		0.86 (0.73–1.02)		0.84 (0.71–1.00)	
	6–10	0.78 (0.60–1.01)		0.76 (0.58–0.99)		0.96 (0.81–1.14)		0.97 (0.81–1.15)	
	>10	0.72 (0.59–0.87)		0.72 (0.60–0.88)		0.96 (0.85–1.09)		0.94 (0.83–1.07)	
Perindopril, C09AA04	1–2	1.00	0.96 (0.92–1.01), *P*=0.11	1.00	0.97 (0.92–1.01), *P*=0.167	1.00	0.95 (0.92–0.99), *P*=0.005	1.00	0.95 (0.92–0.99), *P*=0.006
	0	0.64 (0.57–0.72)		0.71 (0.63–0.81)		0.68 (0.63–0.73)		0.72 (0.66–0.78)	
	3–5	0.99 (0.82–1.20)		1.01 (0.83–1.23)		0.86 (0.75–0.98)		0.87 (0.76–1.00)	
	6–10	0.88 (0.72–1.08)		0.91 (0.74–1.11)		0.77 (0.67–0.88)		0.78 (0.68–0.90)	
	>10	0.90 (0.77–1.04)		0.91 (0.78–1.06)		0.86 (0.77–0.95)		0.86 (0.77–0.95)	
Ramipril, C09AA05	1–2	1.00	0.92 (0.89–0.95), *P*<0.001*	1.00	0.92 (0.89–0.95), *P*<0.001*	1.00	0.96 (0.94–0.97), *P*<0.001*	1.00	0.95 (0.93–0.97), *P*<0.001*
	0	0.57 (0.53–0.61)		0.62 (0.58–0.67)		0.58 (0.55–0.61)		0.61 (0.58–0.64)	
	3–5	0.87 (0.77–0.97)		0.87 (0.77–0.98)		0.79 (0.73–0.86)		0.79 (0.73–0.85)	
	6–10	0.84 (0.74–0.95)		0.83 (0.74–0.95)		0.83 (0.77–0.90)		0.84 (0.77–0.91)	
	>10	0.76 (0.70–0.84)		0.76 (0.69–0.84)		0.85 (0.80–0.90)		0.83 (0.78–0.89)	

(*Continued*)

Table 3. Continued

Drug	Prescription No.	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test
Quinapril, C09AA06	1–2	1.00	0.98 (0.76–1.27), *P*=0.892	1.00	0.98 (0.76–1.26), *P*=0.848	1.00	1.25 (1.05–1.49), *P*=0.014*	1.00	1.24 (1.04–1.49), *P*=0.019*
	0	1.33 (0.56–3.20)		1.43 (0.63–3.25)		2.55 (1.17–5.59)		2.58 (1.15–5.76)	
	3–5	2.14 (0.62–7.42)		2.02 (0.59–6.90)		2.36 (0.84–6.64)		2.40 (0.82–7.05)	
	6–10	1.75 (0.56–5.49)		1.80 (0.59–5.45)		5.05 (2.06–12.39)		5.41 (2.17–13.49)	
	>10	1.19 (0.45–3.16)		1.15 (0.45–2.94)		2.89 (1.28–6.54)		2.88 (1.25–6.65)	
Benazepril, C09AA07	1–2	1.00	0.87 (0.62–1.23), *P*=0.434	1.00	0.88 (0.63–1.23), *P*=0.462	1.00	1.18 (0.87–1.61), *P*=0.294	1.00	1.17 (0.86–1.59), *P*=0.317
	0	0.33 (0.15–0.76)		0.36 (0.16–0.80)		1.74 (0.45–6.73)		1.75 (0.48–6.43)	
	3–5	0.91 (0.22–3.78)		0.88 (0.23–3.39)		4.26 (0.93–19.45)		4.18 (0.94–18.65)	
	6–10	0.21 (0.03–1.79)		0.26 (0.03–2.53)		1.38 (0.26–7.19)		1.46 (0.29–7.37)	
	>10	0.68 (0.25–1.85)		0.70 (0.26–1.87)		3.05 (0.74–12.50)		2.99 (0.76–11.73)	
Fosinopril, C09AA09	1–2	1.00	1.08 (0.80–1.46), *P*=0.607	1.00	1.09 (0.81–1.46), *P*=0.588	1.00	0.84 (0.70–1.00), *P*=0.045	1.00	0.84 (0.70–1.00), *P*=0.048
	0	1.30 (0.49–3.47)		1.40 (0.55–3.57)		0.52 (0.35–0.79)		0.52 (0.34–0.81)	
	3–5	2.26 (0.60–8.44)		2.14 (0.60–7.61)		0.67 (0.33–1.32)		0.59 (0.30–1.19)	
	6–10	1.47 (0.37–5.87)		1.40 (0.39–4.99)		0.68 (0.34–1.35)		0.72 (0.36–1.43)	
	>10	1.59 (0.53–4.76)		1.58 (0.55–4.57)		0.56 (0.33–0.95)		0.54 (0.31–0.93)	
Trandolapril, C09AA10	1–2	1.00	0.97 (0.91–1.02), *P*=0.231	1.00	0.96 (0.91–1.02), *P*=0.215	1.00	0.97 (0.93–1.00), *P*=0.086	1.00	0.97 (0.93–1.01), *P*=0.125
	0	0.70 (0.60–0.82)		0.79 (0.67–0.92)		0.75 (0.68–0.83)		0.80 (0.72–0.89)	
	3–5	1.08 (0.85–1.38)		1.15 (0.90–1.47)		0.82 (0.69–0.97)		0.83 (0.70–0.99)	
	6–10	0.90 (0.70–1.16)		0.92 (0.71–1.20)		0.72 (0.60–0.87)		0.74 (0.61–0.89)	
	>10	0.93 (0.77–1.11)		0.93 (0.77–1.13)		0.87 (0.77–0.98)		0.88 (0.78–0.99)	
Losartan, C09CA01	1–2	1.00	0.97 (0.94–1.00), *P*=0.042*	1.00	0.97 (0.95–1.00), *P*=0.073	1.00	0.97 (0.95–0.99), *P*=0.002*	1.00	0.97 (0.95–0.99), *P*<0.001*
	0	0.58 (0.54–0.62)		0.63 (0.59–0.67)		0.62 (0.59–0.65)		0.64 (0.62–0.68)	
	3–5	0.97 (0.87–1.08)		0.98 (0.88–1.09)		0.93 (0.87–1.00)		0.93 (0.86–1.00)	
	6–10	0.93 (0.83–1.03)		0.95 (0.85–1.06)		0.89 (0.83–0.96)		0.89 (0.83–0.96)	
	>10	0.92 (0.84–1.00)		0.92 (0.84–1.01)		0.91 (0.86–0.96)		0.90 (0.85–0.96)	
Eprosartan, C09CA02	1–2	1.00	0.94 (0.82–1.07), *P*=0.344	1.00	0.94 (0.82–1.08), *P*=0.384	1.00	0.94 (0.85–1.03), *P*=0.195	1.00	0.95 (0.86–1.05), *P*=0.314
	0	0.73 (0.53–1.01)		0.77 (0.55–1.06)		0.61 (0.49–0.76)		0.67 (0.54–0.84)	

(*Continued*)

Table 3. Continued

Drug	Prescription No.	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test
	3–5	1.65 (1.01–2.68)		1.59 (0.96–2.62)		1.04 (0.74–1.46)		1.09 (0.77–1.52)	
	6–10	0.69 (0.36–1.33)		0.71 (0.36–1.39)		0.60 (0.40–0.90)		0.61 (0.40–0.92)	
	>10	0.94 (0.60–1.46)		0.95 (0.61–1.47)		0.88 (0.66–1.19)		0.93 (0.69–1.25)	
Valsartan, C09CA03	1–2	1.00	1.02 (0.95–1.10), *P*=0.571	1.00	1.02 (0.95–1.10), *P*=0.607	1.00	1.01 (0.96–1.06), *P*=0.654	1.00	1.01 (0.96–1.06), *P*=0.750
	0	0.71 (0.60–0.85)		0.74 (0.61–0.89)		0.69 (0.62–0.77)		0.71 (0.63–0.79)	
	3–5	0.98 (0.73–1.32)		0.95 (0.70–1.29)		0.88 (0.72–1.06)		0.88 (0.72–1.07)	
	6–10	1.13 (0.84–1.51)		1.10 (0.82–1.48)		1.01 (0.84–1.23)		1.01 (0.83–1.23)	
	>10	1.05 (0.83–1.32)		1.04 (0.82–1.32)		1.01 (0.87–1.17)		1.00 (0.86–1.16)	
Irbesartan, C09CA04	1–2	1.00	0.94 (0.88–1.01), *P*=0.098	1.00	0.95 (0.88–1.02), *P*=0.133	1.00	0.98 (0.93–1.03), *P*=0.380	1.00	0.98 (0.93–1.03), *P*=0.440
	0	0.64 (0.53–0.76)		0.69 (0.58–0.83)		0.70 (0.62–0.80)		0.74 (0.65–0.84)	
	3–5	1.02 (0.77–1.36)		1.02 (0.76–1.36)		0.89 (0.73–1.09)		0.88 (0.72–1.07)	
	6–10	1.18 (0.90–1.54)		1.18 (0.90–1.55)		0.99 (0.81–1.19)		0.99 (0.81–1.20)	
	>10	0.84 (0.67–1.05)		0.85 (0.67–1.06)		0.91 (0.79–1.06)		0.92 (0.78–1.07)	
Candesartan, C09CA06	1–2	1.00	0.95 (0.91–0.99), *P*=0.024	1.00	0.96 (0.92–1.01), *P*=0.109	1.00	0.96 (0.93–0.99), *P*=0.003*	1.00	0.96 (0.93–0.99), *P*=0.007*
	0	0.54 (0.49–0.60)		0.61 (0.55–0.68)		0.65 (0.60–0.70)		0.69 (0.64–0.75)	
	3–5	0.82 (0.70–0.97)		0.91 (0.76–1.07)		1.00 (0.89–1.12)		1.04 (0.92–1.17)	
	6–10	0.78 (0.66–0.92)		0.81 (0.69–0.96)		0.90 (0.80–1.01)		0.91 (0.81–1.02)	
	>10	0.84 (0.74–0.96)		0.89 (0.78–1.02)		0.89 (0.81–0.97)		0.90 (0.82–0.99)	
Telmisartan, C09CA07	1–2	1.00	1.03 (0.95–1.13), *P*=0.448	1.00	1.05 (0.96–1.14), *P*=0.303	1.00	1.03 (0.97–1.09), *P*=0.347	1.00	1.02 (0.96–1.08), *P*=0.524
	0	0.74 (0.60–0.92)		0.82 (0.66–1.02)		0.69 (0.60–0.79)		0.72 (0.63–0.83)	
	3–5	1.24 (0.89–1.73)		1.33 (0.95–1.87)		1.04 (0.83–1.30)		1.08 (0.86–1.35)	
	6–10	1.00 (0.71–1.41)		0.99 (0.69–1.42)		0.91 (0.73–1.14)		0.93 (0.74–1.16)	
	>10	1.16 (0.88–1.52)		1.22 (0.93–1.62)		1.10 (0.92–1.31)		1.08 (0.91–1.29)	
Olmesartan medoxomil, C09CA08	1–2	1.00	1.02 (0.85–1.23), *P*=0.849	1.00	1.05 (0.86–1.28), *P*=0.635	1.00	0.93 (0.82–1.06), *P*=0.282	1.00	0.93 (0.82–1.06), *P*=0.311
	0	0.72 (0.47–1.10)		0.85 (0.54–1.34)		0.54 (0.41–0.70)		0.57 (0.44–0.75)	
	3–5	1.13 (0.57–2.24)		1.25 (0.62–2.53)		0.71 (0.43–1.17)		0.72 (0.43–1.19)	
	6–10	0.97 (0.49–1.90)		1.12 (0.55–2.27)		0.60 (0.38–0.96)		0.63 (0.39–1.01)	
	>10	1.09 (0.61–1.94)		1.19 (0.64–2.21)		0.83 (0.57–1.20)		0.83 (0.57–1.22)	

HR indicates hazard ratio.
*Statistically significant.

Table 4. Prescription Number of Calcium Antagonists; HRs of Diagnosis of Depression and Diagnosis of Depression or Use of Antidepressants, respectively; and Trend Tests, Adjusted for Age, Sex, Employment Status, and Calendar Year (Partially Adjusted) and Additionally Adjusted for Somatic Diagnoses (Fully Adjusted)

Drug	Prescription No.	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test
		Outcome measure: diagnosis of depression				Outcome measure: diagnosis of depression or use of antidepressant			
Amlodipine, C08CA01	1–2	1.00	0.95 (0.93–0.97), *P*<0.001*	1.00	0.96 (0.94–0.97), *P*<0.001*	1.00	0.94 (0.92–0.95), *P*<0.001*	1.00	0.94 (0.92–0.95), *P*<0.001*
	0	0.52 (0.50–0.55)		0.58 (0.55–0.61)		0.56 (0.54–0.58)		0.59 (0.57–0.61)	
	3–5	0.87 (0.81–0.94)		0.88 (0.82–0.95)		0.95 (0.90–0.99)		0.94 (0.90–0.99)	
	6–10	0.86 (0.80–0.93)		0.88 (0.82–0.95)		0.84 (0.80–0.88)		0.84 (0.80–0.88)	
	>10	0.84 (0.80–0.89)		0.86 (0.81–0.91)		0.82 (0.79–0.86)		0.82 (0.79–0.86)	
Felodipin, C08CA02	1–2	1.00	0.97 (0.93–1.02), *P*=0.266	1.00	0.99 (0.94–1.04), *P*=0.722	1.00	1.02 (0.98–1.05), *P*=0.315	1.00	1.02 (0.99–1.05), *P*=0.212
	0	0.67 (0.59–0.75)		0.73 (0.65–0.83)		0.69 (0.64–0.75)		0.73 (0.67–0.79)	
	3–5	1.08 (0.89–1.31)		1.08 (0.89–1.32)		0.90 (0.78–1.03)		0.89 (0.78–1.02)	
	6–10	0.81 (0.66–0.99)		0.83 (0.68–1.02)		1.05 (0.92–1.20)		1.05 (0.92–1.20)	
	>10	0.95 (0.82–1.10)		1.00 (0.86–1.16)		1.02 (0.93–1.13)		1.03 (0.93–1.14)	
Isradipin, C08CA03	1–2	1.00	0.95 (0.81–1.12), *P*=0.543	1.00	1.00 (0.84–1.17), *P*=0.952	1.00	0.94 (0.84–1.06), *P*=0.314	1.00	0.93 (0.83–1.05), *P*=0.238
	0	0.57 (0.37–0.88)		0.73 (0.47–1.13)		0.72 (0.51–1.04)		0.76 (0.53–1.09)	
	3–5	0.97 (0.47–2.03)		1.10 (0.52–2.31)		2.00 (1.19–3.37)		1.96 (1.16–3.33)	
	6–10	0.78 (0.37–1.66)		0.87 (0.39–1.93)		1.18 (0.70–1.99)		1.17 (0.69–1.98)	
	>10	0.86 (0.52–1.44)		1.00 (0.60–1.68)		1.04 (0.70–1.54)		1.01 (0.67–1.50)	
Nifedipin, C08CA05	1–2	1.00	0.92 (0.87–0.98), *P*=0.011*	1.00	0.93 (0.87–0.99), *P*=0.021*	1.00	0.96 (0.92–1.00), *P*=0.073	1.00	0.98 (0.93–1.02), *P*=0.257
	0	0.64 (0.57–0.72)		0.77 (0.67–0.87)		0.62 (0.57–0.68)		0.69 (0.63–0.75)	
	3–5	0.86 (0.66–1.11)		0.88 (0.67–1.16)		0.62 (0.51–0.75)		0.66 (0.54–0.80)	
	6–10	0.71 (0.53–0.96)		0.76 (0.55–1.03)		0.64 (0.52–0.80)		0.68 (0.55–0.84)	
	>10	0.80 (0.66–0.96)		0.80 (0.66–0.98)		0.89 (0.78–1.00)		0.93 (0.82–1.05)	
Nitrendipin, C08CA08	1–2	1.00	0.75 (0.56–1.01), *P*=0.055	1.00	0.80 (0.59–1.08), *P*=0.139	1.00	1.13 (0.89–1.42), *P*=0.311	1.00	1.15 (0.91–1.46), *P*=0.235
	0	0.46 (0.21–1.04)		0.57 (0.24–1.35)		1.39 (0.64–3.02)		1.49 (0.67–3.29)	
	3–5	0.40 (0.08–1.98)		0.45 (0.09–2.23)		1.44 (0.48–4.33)		1.44 (0.47–4.39)	
	6–10	1.04 (0.36–3.05)		1.34 (0.43–4.11)		1.85 (0.71–4.80)		1.88 (0.71–4.96)	
	>10	0.37 (0.14–0.99)		0.45 (0.16–1.27)		1.60 (0.69–3.72)		1.70 (0.72–4.02)	

(*Continued*)

Table 4. Continued

Drug	Prescription No.	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test
Lacidipin, C08CA09	1–2	1.00	1.04 (0.85–1.28), *P*=0.709	1.00	1.02 (0.82–1.26), *P*=0.862	1.00	1.02 (0.89–1.17), *P*=0.726	1.00	1.03 (0.89–1.18), *P*=0.723
	0	1.00 (0.54–1.86)		1.06 (0.57–2.00)		0.58 (0.42–0.80)		0.59 (0.43–0.82)	
	3–5	1.61 (0.70–3.73)		1.46 (0.63–3.39)		0.32 (0.16–0.63)		0.31 (0.16–0.60)	
	6–10	0.92 (0.33–2.52)		0.83 (0.29–2.33)		0.82 (0.49–1.38)		0.78 (0.46–1.31)	
	>10	1.30 (0.64–2.62)		1.19 (0.58–2.44)		0.85 (0.58–1.25)		0.84 (0.57–1.25)	
Lercanidipin, C08CA13	1–2	1.00	0.89 (0.83–0.96), *P*=0.003*	1.00	0.90 (0.83–0.97), *P*=0.007*	1.00	0.99 (0.94–1.03), *P*=0.547	1.00	0.98 (0.94–1.03), *P*=0.504
	0	0.50 (0.42–0.58)		0.53 (0.45–0.62)		0.62 (0.56–0.70)		0.65 (0.58–0.73)	
	3–5	0.74 (0.56–0.98)		0.75 (0.56–0.99)		1.15 (0.96–1.37)		1.15 (0.96–1.37)	
	6–10	0.79 (0.61–1.03)		0.80 (0.61–1.05)		1.03 (0.86–1.24)		1.03 (0.86–1.24)	
	>10	0.69 (0.55–0.87)		0.71 (0.56–0.89)		0.98 (0.84–1.14)		0.98 (0.84–1.14)	
Verapamil, C08DA01	1–2	1.00	0.92 (0.88–0.96), *P*<0.001*	1.00	0.92 (0.88–0.96), *P*<0.001*	1.00	0.96 (0.93–0.99), *P*=0.004*	1.00	0.96 (0.93–0.99), *P*=0.006*
	0	0.53 (0.48–0.58)		0.60 (0.54–0.66)		0.62 (0.58–0.66)		0.65 (0.61–0.70)	
	3–5	0.70 (0.59–0.83)		0.69 (0.58–0.83)		0.72 (0.64–0.82)		0.72 (0.64–0.82)	
	6–10	0.85 (0.71–1.01)		0.87 (0.73–1.04)		0.85 (0.76–0.96)		0.87 (0.76–0.98)	
	>10	0.74 (0.65–0.84)		0.75 (0.66–0.85)		0.85 (0.78–0.93)		0.85 (0.79–0.93)	
Verapamil, combinations, C08DA51	1–2	1.00	0.62 (0.41–0.93), *P*=0.022*	1.00	0.61 (0.40–0.92), *P*=0.020*	1.00	0.71 (0.58–0.88), *P*=0.001*	1.00	0.69 (0.56–0.86), *P*<0.001*
	0	0.38 (0.22–0.67)		0.41 (0.24–0.71)		0.35 (0.25–0.51)		0.37 (0.25–0.54)	
	3–5	0.45 (0.14–1.38)		0.38 (0.12–1.13)		0.52 (0.24–1.12)		0.52 (0.23–1.19)	
	6–10	0.20 (0.03–1.56)		0.16 (0.02–1.19)		0.52 (0.22–1.24)		0.46 (0.19–1.13)	
	>10	0.28 (0.09–0.85)		0.28 (0.09–0.82)		0.36 (0.19–0.66)		0.33 (0.17–0.63)	
Diltiazem, C08DB01	1–2	1.00	0.96 (0.91–1.02), *P*=0.195	1.00	0.97 (0.91–1.03), *P*=0.316	1.00	1.04 (1.00–1.08), *P*=0.080	1.00	1.05 (1.00–1.09), *P*=0.040
	0	0.65 (0.56–0.77)		0.76 (0.65–0.90)		0.80 (0.72–0.90)		0.86 (0.77–0.97)	
	3–5	1.07 (0.82–1.40)		1.09 (0.82–1.43)		0.82 (0.67–1.01)		0.81 (0.66–1.00)	
	6–10	0.83 (0.62–1.10)		0.82 (0.61–1.09)		0.92 (0.76–1.13)		0.94 (0.76–1.15)	
	>10	0.91 (0.76–1.09)		0.93 (0.77–1.12)		1.07 (0.94–1.21)		1.09 (0.95–1.24)	

HR indicates hazard ratio.
*Statistically significant.

the 41 most prescribed antihypertensives during a study period of 10 years. More than 450 000 patients were included in the analyses of enalapril alone.

Second, it confirms the validity of the R-WAS methodology, that in broad concordance with the literature, we as hypothesized detected a positive overall effect of continued

Table 5. Prescription Number of β-Blockers; HRs of Diagnosis of Depression and Diagnosis of Depression or Use of Antidepressants, respectively; and Trend Tests, Adjusted for Age, Sex, Employment Status, and Calendar Year (Partially Adjusted) and Additionally Adjusted for Somatic Diagnoses (Fully Adjusted)

Drug	Prescription No.	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test
		Outcome measure: diagnosis of depression				Outcome measure: diagnosis of depression or use of antidepressant			
Pindolol, C07AA03	1–2	1.00	0.78 (0.70–0.87), *P*<0.001*	1.00	0.80 (0.72–0.90), *P*<0.001*	1.00	0.98 (0.90–1.08), *P*=0.736	1.00	0.99 (0.90–1.09), *P*=0.85
	0	0.37 (0.29–0.46)		0.41 (0.32–0.53)		0.73 (0.59–0.91)		0.78 (0.62–0.97)	
	3–5	0.90 (0.55–1.48)		0.91 (0.55–1.50)		0.79 (0.50–1.26)		0.79 (0.49–1.27)	
	6–10	0.55 (0.31–0.97)		0.60 (0.33–1.09)		0.84 (0.52–1.35)		0.87 (0.54–1.40)	
	>10	0.48 (0.34–0.67)		0.53 (0.37–0.75)		0.93 (0.70–1.23)		0.95 (0.71–1.26)	
Propranolol, C07AA05	1–2	1.00	0.95 (0.93–0.98), *P*<0.001*	1.00	0.93 (0.91–0.96), *P*<0.001*	1.00	0.90 (0.88–0.91), *P*<0.001*	1.00	0.89 (0.87–0.91), *P*<0.001*
	0	0.46 (0.45–0.48)		0.52 (0.50–0.54)		0.60 (0.58–0.61)		0.64 (0.62–0.66)	
	3–5	0.97 (0.88–1.06)		0.91 (0.83–1.01)		0.92 (0.85–0.99)		0.90 (0.83–0.97)	
	6–10	0.84 (0.74–0.96)		0.79 (0.69–0.90)		0.77 (0.69–0.85)		0.75 (0.68–0.84)	
	>10	0.88 (0.81–0.96)		0.84 (0.77–0.92)		0.72 (0.68–0.77)		0.72 (0.67–0.77)	
Timolol, C07AA06	1–2	1.00	0.89 (0.63–1.24), *P*=0.492	1.00	0.82 (0.58–1.17), *P*=0.278	1.00	1.10 (0.86–1.39), *P*=0.460	1.00	1.08 (0.86–1.35), *P*=0.531
	0	0.67 (0.25–1.78)		0.57 (0.20–1.62)		1.00 (0.51–1.96)		1.01 (0.53–1.90)	
	3–5	1.90 (0.53–6.83)		1.70 (0.43–6.73)		0.70 (0.16–3.16)		0.70 (0.15–3.25)	
	6–10	0.35 (0.04–3.16)		0.29 (0.03–2.75)		1.97 (0.79–4.90)		1.99 (0.82–4.84)	
	>10	0.92 (0.29–2.90)		0.72 (0.22–2.38)		1.26 (0.57–2.76)		1.20 (0.57–2.53)	
Sotalol, C07AA07	1–2	1.00	0.94 (0.87–1.01), *P*=0.095	1.00	0.92 (0.86–1.00), *P*=0.043*	1.00	0.98 (0.93–1.03), *P*=0.496	1.00	0.98 (0.93–1.03), *P*=0.483
	0	0.71 (0.60–0.84)		0.74 (0.62–0.88)		0.82 (0.72–0.92)		0.85 (0.75–0.96)	
	3–5	0.95 (0.68–1.33)		0.86 (0.61–1.20)		0.96 (0.77–1.20)		0.95 (0.76–1.19)	
	6–10	0.64 (0.44–0.93)		0.61 (0.42–0.88)		0.93 (0.74–1.18)		0.93 (0.74–1.18)	
	>10	0.84 (0.67–1.05)		0.80 (0.64–1.00)		0.95 (0.81–1.10)		0.94 (0.81–1.10)	
Metoprolol, C07AB02	1–2	1.00	0.88 (0.87–0.90), *P*<0.001*	1.00	0.88 (0.86–0.89), *P*<0.001	1.00	0.93 (0.92–0.94), *P*<0.001	1.00	0.93 (0.92–0.94), *P*<0.001
	0	0.47 (0.45–0.49)		0.51 (0.49–0.54)		0.53 (0.51–0.54)		0.56 (0.54–0.57)	
	3–5	0.94 (0.88–1.01)		0.93 (0.87–1.00)		0.90 (0.86–0.95)		0.90 (0.86–0.94)	
	6–10	0.78 (0.73–0.84)		0.77 (0.72–0.84)		0.80 (0.76–0.84)		0.80 (0.76–0.84)	
	>10	0.69 (0.66–0.73)		0.68 (0.65–0.72)		0.80 (0.77–0.83)		0.79 (0.76–0.82)	

(*Continued*)

Table 5. Continued

Drug	Prescription No.	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test
Atenolol, C07AB03	1–2	1.00	0.88 (0.84–0.91), *P*<0.001*	1.00	0.88 (0.85–0.92), *P*<0.001*	1.00	0.92 (0.90–0.95), *P*<0.001*	1.00	0.93 (0.90–0.95), *P*<0.001*
	0	0.53 (0.49–0.58)		0.58 (0.54–0.63)		0.63 (0.60–0.67)		0.67 (0.63–0.71)	
	3–5	0.79 (0.67–0.93)		0.80 (0.68–0.94)		0.88 (0.78–0.98)		0.86 (0.77–0.97)	
	6–10	0.62 (0.52–0.75)		0.61 (0.51–0.74)		0.77 (0.68–0.87)		0.77 (0.68–0.87)	
	>10	0.68 (0.61–0.76)		0.70 (0.62–0.78)		0.78 (0.73–0.85)		0.80 (0.74–0.86)	
Acebutolol, C07AB04	1–2	1.00	1.27 (0.83–1.94), *P*=0.264	1.00	1.37 (0.88–2.14), *P*=0.158	1.00	0.75 (0.58–0.97), *P*=0.025*	1.00	0.78 (0.61–1.00), *P*=0.053
	0	0.74 (0.24–2.30)		0.95 (0.27–3.29)		0.57 (0.33–1.00)		0.69 (0.40–1.19)	
	3–5	1.21 (0.20–7.31)		1.25 (0.16–10.00)		1.00 (0.33–3.04)		1.32 (0.43–4.03)	
	6–10	0.63 (0.11–3.80)		0.87 (0.12–6.16)		0.31 (0.07–1.33)		0.47 (0.11–2.08)	
	>10	1.87 (0.54–6.46)		2.37 (0.62–9.03)		0.45 (0.21–0.95)		0.52 (0.24–1.10)	
Betaxolol, C07AB05	1–2	1.00	0.72 (0.50–1.06), *P*=0.095	1.00	0.77 (0.53–1.14), *P*=0.189	1.00	1.00 (0.79–1.27), *P*=0.991	1.00	1.03 (0.81–1.31), *P*=0.793
	0	0.50 (0.22–1.12)		0.62 (0.26–1.48)		1.32 (0.61–2.87)		1.52 (0.69–3.33)	
	3–5	0.64 (0.13–3.21)		0.79 (0.15–4.22)		1.76 (0.58–5.28)		1.86 (0.61–5.64)	
	6–10	0.94 (0.28–3.11)		1.14 (0.33–3.99)		2.66 (1.05–6.78)		3.08 (1.20–7.87)	
	>10	0.29 (0.07–1.18)		0.36 (0.09–1.48)		1.06 (0.41–2.74)		1.17 (0.45–3.04)	
Bisoprolol, C07AB07	1–2	1.00	0.87 (0.82–0.92), *P*<0.001*	1.00	0.86 (0.81–0.91), *P*<0.001*	1.00	0.90 (0.87–0.94), *P*<0.001*	1.00	0.90 (0.87–0.94), *P*<0.001*
	0	0.53 (0.47–0.60)		0.60 (0.52–0.68)		0.61 (0.56–0.67)		0.65 (0.59–0.71)	
	3–5	0.77 (0.61–0.97)		0.79 (0.63–1.00)		0.99 (0.85–1.15)		0.99 (0.85–1.15)	
	6–10	0.79 (0.63–1.00)		0.79 (0.62–1.00)		0.76 (0.65–0.90)		0.76 (0.65–0.90)	
	>10	0.63 (0.53–0.75)		0.63 (0.53–0.75)		0.76 (0.67–0.85)		0.75 (0.67–0.84)	
Nebivolol, C07AB12	1–2	1.00	0.91 (0.73–1.13), *P*=0.406	1.00	0.94 (0.76–1.17), *P*=0.575	1.00	1.01 (0.86–1.18), *P*=0.929	1.00	0.99 (0.84–1.16), *P*=0.855
	0	0.38 (0.27–0.54)		0.43 (0.30–0.61)		0.57 (0.42–0.76)		0.60 (0.44–0.82)	
	3–5	0.61 (0.30–1.23)		0.63 (0.31–1.27)		1.13 (0.69–1.86)		1.14 (0.68–1.89)	
	6–10	0.86 (0.43–1.72)		0.85 (0.42–1.74)		0.97 (0.59–1.62)		0.95 (0.56–1.59)	
	>10	0.75 (0.38–1.48)		0.85 (0.44–1.63)		1.06 (0.64–1.73)		0.99 (0.59–1.65)	
Labetalol, C07AG01	1–2	1.00	0.94 (0.84–1.06), *P*=0.325	1.00	0.94 (0.83–1.06), *P*=0.278	1.00	0.89 (0.82–0.97), *P*=0.007*	1.00	0.88 (0.81–0.96), *P*=0.005*
	0	0.67 (0.55–0.81)		0.76 (0.63–0.93)		0.59 (0.52–0.68)		0.64 (0.55–0.74)	

(*Continued*)

Table 5. Continued

Drug	Prescription No.	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test	HR (0.95% CI), Partially Adjusted	Trend Test	HR (0.95% CI), Fully Adjusted	Trend Test
	3–5	0.98 (0.68–1.40)		1.03 (0.71–1.49)		0.87 (0.67–1.14)		0.90 (0.69–1.18)	
	6–10	1.19 (0.79–1.79)		1.18 (0.76–1.83)		0.88 (0.64–1.21)		0.88 (0.64–1.21)	
	>10	0.75 (0.50–1.11)		0.73 (0.48–1.09)		0.69 (0.53–0.90)		0.67 (0.51–0.88)	
Carvedilol, C07AG02	1–2	1.00	0.92 (0.87–0.97), *P*=0.001*	1.00	0.92 (0.87–0.97), *P*=0.003*	1.00	0.94 (0.91–0.97), *P*<0.001*	1.00	0.94 (0.90–0.97), *P*<0.001*
	0	0.53 (0.46–0.61)		0.60 (0.52–0.69)		0.60 (0.55–0.67)		0.64 (0.58–0.71)	
	3–5	1.15 (0.93–1.43)		1.17 (0.93–1.46)		1.02 (0.88–1.19)		1.05 (0.91–1.23)	
	6–10	1.03 (0.83–1.28)		1.05 (0.84–1.31)		0.97 (0.84–1.12)		0.97 (0.83–1.12)	
	>10	0.82 (0.69–0.97)		0.82 (0.69–0.98)		0.85 (0.76–0.95)		0.84 (0.75–0.95)	
Metoprolol and thiazides, C07BB02	1–2	1.00	0.86 (0.71–1.03), *P*=0.109	1.00	0.87 (0.72–1.06), *P*=0.162	1.00	0.84 (0.75–0.95), *P*=0.004*	1.00	0.83 (0.74–0.94), *P*=0.002*
	0	0.52 (0.33–0.82)		0.56 (0.35–0.90)		0.55 (0.42–0.72)		0.56 (0.43–0.74)	
	3–5	0.47 (0.21–1.07)		0.51 (0.22–1.18)		0.35 (0.18–0.67)		0.37 (0.19–0.72)	
	6–10	0.83 (0.41–1.70)		0.91 (0.44–1.88)		0.87 (0.56–1.35)		0.87 (0.55–1.35)	
	>10	0.55 (0.31–0.97)		0.59 (0.33–1.05)		0.53 (0.37–0.75)		0.51 (0.36–0.73)	
Atenolol and other diuretics, C07CB03	1–2	1.00	0.88 (0.76–1.00), *P*=0.058	1.00	0.92 (0.79–1.05), *P*=0.220	1.00	1.03 (0.94–1.13), *P*=0.463	1.00	1.05 (0.95–1.15), *P*=0.329
	0	0.57 (0.42–0.79)		0.64 (0.45–0.89)		0.63 (0.50–0.79)		0.66 (0.53–0.84)	
	3–5	0.65 (0.34–1.21)		0.69 (0.36–1.30)		0.74 (0.49–1.12)		0.74 (0.48–1.13)	
	6–10	0.76 (0.42–1.37)		0.88 (0.48–1.61)		0.54 (0.35–0.82)		0.55 (0.36–0.84)	
	>10	0.64 (0.42–0.97)		0.73 (0.47–1.13)		1.03 (0.79–1.34)		1.06 (0.81–1.39)	
Metoprolol and felodipine, C07FB02	1–2	1.00	0.73 (0.55–0.98), *P*=0.035*	1.00	0.75 (0.57–0.99), *P*=0.040*	1.00	1.04 (0.86–1.27), *P*=0.672	1.00	1.06 (0.87–1.28), *P*=0.580
	0	0.48 (0.27–0.88)		0.52 (0.29–0.92)		0.60 (0.36–1.01)		0.65 (0.39–1.07)	
	3–5	0.42 (0.12–1.52)		0.46 (0.13–1.71)		0.52 (0.22-1.21)		0.54 (0.23–1.28)	
	6–10	0.39 (0.11–1.38)		0.39 (0.11–1.32)		0.56 (0.22–1.43)		0.59 (0.24–1.46)	
	>10	0.38 (0.17–0.86)		0.40 (0.18–0.89)		0.90 (0.51–1.59)		0.94 (0.53–1.65)	

Depression is common in patients with hypertension. We identified a total of 9 of 41 antihypertensive drugs that should be used in individuals at increased risk of depression. HR indicates hazard ratio.

*Statistically significant.

use of angiotensin agents and calcium antagonists and not of diuretics. The study design and type of statistical analyses used in the present study is part of the validated R-WAS methodology to confirm whether agents with an a priori preclinical or theoretical evidence base may have effects in depression. These include low-dose aspirin, statins, allopurinol, and angiotensin agents,[20] as well as metformin.[36]

It is clear from Tables 3 through 5 that findings for the individual drugs vary a lot, some showing increased, some decreased, and some no association with depression,

minimizing the possibility that they are a result of systematic or general bias or confounding. Thus, in the prespecified plan of analyses, we decided to address bias or confounding by indication of antihypertensives in 2 different ways: by (1) the design of the study and by (2) the adjustment methods. Regarding design, the study was designed to estimate the rate of depression during successive prescription periods of the drug compared with the rate during prescription period 1 to 2. We generally confirmed that the prescription period 1 to 2 was associated with increased HR of depression compared with the period with the nonuse period (Table 3) illustrating confounding by indication since drugs were prescribed for hypertension, cardiovascular, and cerebrovascular diseases that share an increased risk of depression.[2–5] Regarding covariate adjustment, in addition to adjustments for sex, age, employment status, and calendar period, we adjusted the analyses for all physical comorbidities recorded in the Danish National Hospital Register, as many patients experience multiple diseases (eg, co-occurrence of hypertension, myocardial infarction, stroke, diabetes mellitus, or chronic pain[46,47]), aiming to reduce unknown or residual confounding.

It should further be noted that results of the analyses of the individual drugs were not a matter of statistical power: among the 9 individual drugs that were found to be associated with a decreased risk of depression, drugs with a beneficial effect such as verapamil combinations included 130 individuals, only (Table 1), resulting in decreased statistical power, whereas many frequently used drugs such as perindopril (n=54 769) or metoprolol (n=40 772), resulting in increased statistical power, showed no statistical significant associations with depression.

Third, 2 different outcome measures were included: (1) a diagnosis of depressive disorder at a psychiatric hospital contact as inpatient or outpatient and (2) a combined measure of a diagnosis of depression or use of antidepressants. The first outcome measure likely comprises more severe cases with depression referred only to psychiatric hospital care. The second outcome measure includes the broader illness spectrum from severe to milder cases of depression, as this measure, in addition to a hospital diagnosis of depression, includes drug prescription data from all physicians in Denmark, that is, from primary care including general practice and private specialists and from secondary outpatient hospital care. In most analyses, the results with the 2 outcome measures were very similar, serving to support the internal and external validity of the findings.

Fourth, potential reverse causation is substantively minimized as only incident depression/use of antidepressants was included in the analyses, since we excluded individuals who received antidepressants (from 1995 to 2005) or had a diagnosis of depression (back to 1970) before use of the drug class of interest.

Finally, population-based data as those included in the present study reflect real-life, so-called naturalistic data adding to increase the generalizability of findings.[48] By contrast, a large proportion of real-life patients are excluded from randomized controlled trials due to the strict inclusion and exclusion criteria often deployed. Among patients with depression in clinical practice, ≈25% meet usual eligibility requirements for an antidepressant efficacy trial.[49]

Limitations

The first outcome measure, a diagnosis of depression, was not research based but based on clinical diagnoses. However, the *ICD*, *Tenth Revision*, diagnosis of depression recorded in the Danish Psychiatric Central Research Register has a high validity as compared with a research diagnostic interview with the Clinical Assessment in Neuropsychiatry.[50] Further, we included analyses with a combined outcome measure on a diagnosis of depression or the use of antidepressants overall confirming results from the first analyses with a diagnosis of depression as the outcome measure. We did not include continued use of antidepressants as a separate outcome measure as antidepressants are prescribed for other conditions than depression.

As with all other registers including nationwide medication data, the Danish Medicinal Product Statistics includes no information on drug indication, as well as adherence or dose of the exposure drugs, although repeat prescriptions are a reasonable proxy of adherence.[39] As we estimated the rate of incident depression during successive prescription periods within each drug class/individual drug, it is unlikely that indications or nonadherence substantially confounded our results. Regarding drug indications, it should be stressed that we did not compare rates of depression across drugs but within different prescription periods within each drug, and further, we included analyses with adjustments for all physical comorbidities. Notably, these HRs adjusted for physical comorbidities (fully adjusted in Tables 2 through 5) did not deviate much from HRs without (partially adjusted in Tables 2 through 5), also not for β-blockers (Table 5) mainly being prescribed for cardiac infarction and insufficiency and as second- or third-line antihypertensives.

Residual confounding by unmeasured variables remains possible. For example, around 40% of hypertension remains undiagnosed and untreated.[51] Factors such as high health literacy, high socioeconomic status, and high levels of other adaptive health behaviors such as physical activity, high-quality diet, and not smoking may thus be associated with prophylactic antihypertensive therapy and may moderate relationships with depression. We considered antihypertensive drugs individually, drug by drug, as well as within the 4 main classes of medications (angiotensin agents, calcium channel blockers, and β-blockers). This approach does not directly adjust analyses for combinations of ≥1 other antihypertensive drugs (polypharmacy) but instead adjusts for diverse morbidity for which antihypertensive may be prescribed such as hypertension and cardiovascular and cerebrovascular diseases, as well as all other potential comorbidity, by including the 9 morbidity groups listed in *ICD*, *Tenth Revision*. Future research may more specifically address risk of depression with monotherapy versus polypharmacy of antihypertensives. One final factor may be sequencing; some drugs are generally used as first-line therapies and others, second- or third-line therapies depending on the indication in the individual case. As hypertension and cardiovascular and cerebrovascular diseases are progressive disorders, one might expect people who settle on first-line therapy to have simpler and more benign illness, whereas those needing second- or third-line therapy may have more complex illness.

Pharmacological Properties of Individual Drugs

There is no prior research on individual angiotensin agents, calcium antagonists, or β-blockers and their associations with inflammation or depression. The pharmacological properties of the 9 identified drugs that were associated with a decreased rate of incident depression differ in many ways including lipid solubility; some are lipid soluble and have an ability to cross the blood-brain barrier and some are not. It is possible that these 9 drugs possess other off-target receptor or anti-inflammatory properties that they do not share with the remaining 32 antihypertensives, but we are not aware of studies specifically investigating potential anti-inflammatory effects of these 9 drugs.

Angiotensin Agents

Among the 2 angiotensin agents showing antidepressant effects, ramipril is a lipid-soluble angiotensin-converting enzyme inhibitor that has the ability to cross the blood-brain barrier in contrast to enalapril that is a noncentrally active angiotensin-converting enzyme inhibitor that works mainly by lowering blood pressure.[17] These data support the ongoing development of angiotensin agents for mood disorders.

Calcium Antagonists

Calcium antagonists are not interchangeable because of their heterogeneity of structure, binding site, and action.[34] Among the 3 calcium antagonists showing antidepressant effects, amlodipine is a selective calcium blocker and verapamil and verapamil combination are phenylalkymine calcium channel blockers. As lipophilic substances, amlodipine and verapamil cross the blood-brain barrier. Calcium channel antagonists have been explored for utility in bipolar disorder[52]—a related mood disorder but not depression.

β-Blockers

The main pharmacological properties of the 4 β-blockers showing antidepressant effects differ: propranolol being a first generation, nonselective β-blocker with high lipid solubility, atenolol, and bisoprolol being second generation, selective β-blockers with low lipid solubility and carvedilol being a third generation, and nonselective β-blocker with moderate lipid solubility.[35] Lipophilic β-blockers, such as propranolol, may passively cross the blood-brain barrier.[53] Nevertheless, also hydrophilic β-blockers, such atenolol and bisoprolol, may have central effects due to NO and hydrogen peroxide release independently of their ability to cross the blood-brain barrier.[53] Notably, pindolol did not display a potentially beneficial effect in accordance with results from a meta-analysis.[29]

Conclusions

In this population-based register study data from all 5.4 million persons in Denmark, we systematically investigated whether the 41 most used antihypertensive drugs were associated with an altered risk of incident depression. Analyses of diuretics were included for comparisons. Continued use of classes of angiotensin agents, calcium antagonists, and β-blockers was associated with decreased rates of depression, whereas diuretics were not. As the first study on individual antihypertensives and risk of depression, we found a decreased risk of depression associated with 9 drugs, including 2 of 16 angiotensin agents: enalapril and ramipril; 3 of 10 calcium antagonists: amlodipine, verapamil, and verapamil combinations; and 4 of 15 β-blockers: propranolol, atenolol, bisoprolol, and carvedilol, whereas no antihypertensive drug increased the risk of depression. The findings should be replicated in well-designed larger randomized controlled trials and in other population-based registers using similar designs and statistical analyses to address selection and confounding factors.

Perspectives

As hypertension and cardiovascular and cerebrovascular diseases are associated with increased risk of depression and due to the detrimental effects of depression, it is recommended that clinicians use one of the identified individual 9 drugs depending on the somatic indication, especially in patients at increased risk of developing depression, including patients with prior depression or anxiety and patients with a family history of depression.

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Novelty and Significance

What Is New?

- This study is the first to investigate the association between individual antihypertensives and incidence of depression.

What Is Relevant?

- Depression is common in patients with hypertension, but antihypertensives may differentially affect the risk of depression.

Summary

No drug was associated with increased risk of depression. A total of 9 of 41 drugs were associated with decreased risk of depression. These drugs should specifically be used in patients at increased risk of developing depression, including patients with prior depression or anxiety and patients with a family history of depression.