Association between common cardiovascular drugs and depression

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Abstract

Objective: Cardiovascular diseases are associated with an increased risk of depression, but it remains unclear whether treatment with cardiovascular agents decreases or increases this risk. The effects of drugs on individual usage are also often unknown. This review aimed to examine the correlation between depression and common cardiovascular drugs, develop more potent interventions for depression in cardiovascular patients, and further research on the bio-behavioural mechanisms linking cardiovascular drugs to depression.

Data sources: The data in this review were obtained from articles included in PubMed, EMBASE, and Web of Science.

Study selection: Clinical trials, observational studies, review literature, and guidelines about depression and cardiovascular drugs were selected for the article.

Results: We systematically investigated whether the seven most used cardiovascular drugs were associated with altered risk of incident depression in this literature review. Statins have been proven to have antidepressant effects. Some studies believe angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blocker (ARB) can exert an antidepressant influence by acting on the renin-angiotensin system, but further clinical trials are needed to confirm this. Beta-blockers have previously been associated with depression, but the current study found no significant association between beta blockers and the risk of depression. Aspirin may have antidepressant effects by suppressing the immune response, but its role as an antidepressant remains controversial. calcium channel blockers (CCBs) can regulate nerve signal transduction by adjusting calcium channels, but whether this effect is beneficial or harmful to depression remains unclear. Finally, some cases have reported that nitrates and diuretics are associated with depression, but the current clinical evidence is insufficient.

Conclusions: Statins have been proven to have antidepressant effect, and the antidepressant effects of ACEIs/ARB and aspirin are still controversial. CCBs are associated with depression, but it is unclear whether it is beneficial or harmful. No association has been found with β-blockers, diuretics, and nitrates.

Keywords: Depression; Cardiovascular drugs; Statins; β-blockers; Calcium channel blocker

Introduction

Depression, one of the most common mental health disorders, is among the leading causes of health-related disability worldwide. Studies have confirmed that depression occurs with even greater frequency in populations suffering from a wide range of cardiovascular conditions, such as coronary heart disease (CHD), hypertension, atrial fibrillation (AF), and heart failure (HF). Depression is two to three times more common in patients with CHD than in the general community,[1] and the research has demonstrated that depression is a risk factor for incident CHD or cardiovascular morbidity and mortality in patients with established CHD.[2] As a multifactorial pathology that affects between 30% and 40% of the general population, hypertension is also an essential risk factor in cardiovascular disease. A cross-sectional comparison study in Ghana and Nigeria suggest the prevalence of depression is high among patients with hypertension in Ghana and Nigeria.[3] Depression affects approximately one-third of hypertensive patients, affecting their quality of life and their prognosis. Thus, effective patient-centered interventions for depression are needed. AF is a clinically common arrhythmia, mostly occurring in patients with other underlying diseases, and mainly caused by ectopic pacemaker activities generated in the atrium during atrial conduction and reentry. Studies have shown that AF patients are more prone to psychological problems than the general healthy population. About 33% of AF patients have associated depression, which can not only increase the recurrence of AF but also seriously affects the quality of life and mortality of patients[4]; among patients with HF, depression and anxiety disorders are common, with

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prevalence markedly higher than that in the general population. A meta-analysis of 36 studies found that clinically significant depressive symptoms affect 21.5% of HF patients, with one-third of HF patients reporting more depressive symptoms on questionnaires.[5]

Cardiovascular diseases are associated with an increased risk of depression, but it remains unclear whether treatment with cardiovascular agents decreases or increases this risk. Accumulated studies have confirmed that some cardiovascular drugs have antidepressant effects. It is accepted that some cardiovascular drugs have anti-inflammatory or anti-oxidant actions, show protective effects toward the vascular endothelium, or alter regulation of neurotransmitters,[6] effects which may be related to their antidepressant mechanisms. At the same time, some studies have demonstrated that certain cardiovascular drugs positively correlate with the development of depression. For instance, reserpine can induce an imbalance in the regulation of monoamine neurotransmitters in the brain, leading to depression and is widely used to induce depression in disease models.[7] By expatiating upon the antidepressant effects of some common cardiovascular drugs, we aim to provide an up-to-date overview of the latest evidence regarding interventions used to treat depression among patients with cardiac disease.

Data synthesis

We conducted a literature search of PubMed, EMBASE, and Web of Science from January 1990 through May 2021, including clinical trials, observational studies, review literature, and guidelines limited to studies published in English. To explore the following topics: (1) pathophysiological mechanisms of cardiovascular drugs and depression, (2) the role of statins in depression, (3) the role of β-blockers in depression, (4) the role of antiplatelet medications in depression, (5) the role of calcium channel blocker (CCBs) in depression, (6) the role of angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) in depression, (7) the role of diuretics in depression, and (8) the role of nitrate drugs in depression. After excluding duplicate studies, other publication types, those not relevant to the topic, or having insufficient sample size for significant conclusions, a total of 623 records were eligible for final reviewing. We picked out the controlled clinical trials as listed in Table 1. The screening process used was as illustrated in Figure 1. The representative articles selected are summarized as follows:

Pathophysiological mechanisms of cardiovascular drugs and depression

As we know, the link between depression and cardiovascular disease is bidirectional. Both have common pathophysiology and behavior as their basis [Figure 2]. Cardiovascular drugs can improve the emotional state of cardiovascular patients, which indicates a close relationship to the regulation of a common pathogenic cause between depression and cardiovascular disease. Within each of the seven main classes of medication for cardiovascular disease, the active compounds show different overall pharmacological characteristics. Each drug is characterized by specific pharmacological properties, including selectivity of action dependent on receptor subtypes, intrinsic sympathomimetic activity, lipid solubility, and pharmacokinetic profile, as well as potential anti-inflammatory properties. Thus, by reducing blood lipids and affecting cholesterol synthesis, statins can regulate metabolism in the nervous system.[8] Concurrently, studies have confirmed that statins can reduce inflammatory factors, suggesting that statins can play an antidepressant role by reducing the inflammatory response.[9] Previous studies had linked β-blockers use with an increased risk of depression, but more recent studies have found no significant association between the two.[10] Antiplatelet drugs, such as aspirin, may reduce the risk of depression by reducing inflammation,[11] but this remains controversial. CCBs modulate nerve cell signaling by regulating calcium channels, but whether this effect is beneficial or harmful in depression remains unclear. ACEI/ARB targeting-drugs may regulate the body's response to stress by regulating the renin-angiotensin system (RAS), thus reducing the risk of depression,[12] but there is still no solid clinical evidence to support this. Some cases have reported that nitrates and diuretics are associated with depression, but the current clinical evidence for this is insufficient.

Common cardiovascular drugs in depression

Currently, the main cardiovascular drugs used in clinical practice include lipid-lowering drugs such as statins, antiplatelet drugs such as aspirin and clopidogrel, ACEIs and ARBs, β-blockers, CCBs, diuretics, and nitrate ester drugs. We will now explore the correlation between the above medications and depression.

The role of statins in depression

Statins are commonly prescribed lipid-lowering drugs used primarily to treat high cholesterol and cardiovascular disease. In 1992, Lechleitner *et al*[13] reported four cases with primary hypercholesterolemia who developed severe depressive symptoms during treatment with pravastatin. This association between depression and statins has subsequently drawn much attention from researchers. Initially, the main viewpoint was that statins were associated with increased risk of depression. This perspective may be based on reports of a reduction of cholesterol synthesis in the brain on statin exposure.[14] Cholesterol is a membrane component that may bind to and alter the behavior of specific G-protein-coupled receptors, including α1A-adrenergic, β2-adrenergic, adenosine A2A, dopamine D1, and 5-HT1A receptors; and reports suggested that decreasing cholesterol can induce psychological disease.[15] However, subsequent controlled clinical studies did not find statins to be associated with an increased risk of symptoms of depression. Results from 14 controlled trials conducted by Bristol Myers Squibb do not support an association between pravastatin therapy and depressive symptoms. There was no difference between patients treated with pravastatin or placebo for up to 2 years.[16] A prospective cohort study that included 1631 subjects discovered that regular aspirin or statin at outset

Table 1: Major clinical trials investigating relationships between common cardiovascular drugs and depression.

Author/year	Drug	Country/sample size	Design	Depression diagnosis	Related to depression risk
Glaus *et al* 2015[17]	Aspirin and statin	Switzerland/1631	Prospective cohort	CES-D	Aspirin (*) Statin (*)
Berk *et al* 2020[18]	Rosuvastatin and aspirin	USA/130	RCT	MADRS	Aspirin (*) Rosuvastatin (+)
Soh *et al* 2020[19]	Atorvastatin	Canada/60	RCT	MADRS	Atorvastatin (*)
Agustini *et al* 2019[20]	Statin	Australia and USA/19114	Cross-sectional study	CES-D	Statin (*)
Stewart *et al* 2000[21]	Pravastatin	Australia and New Zealand/1130	RCT	GHQ	Pravastatin (*)
Muldoon *et al* 2000[22]	Lovastatin	USA/209	RCT	HDRS	Lovastatin (*)
Chan *et al* 2017[23]	Simvastatin	England/140	RCT	HAM-D	Simvastatin (+)
Redlich *et al* 2014[24]	Statin	Sweden/4,607,990	Cohort study	ICD	Statin (−)
Hoogwegt *et al* 2013[25]	Statin	Netherlands/409	Prospective study	HADS	Statin (−)
Young-Xu *et al* 2003[26]	Statin	USA/761	RCT	Kellner scale	Statin (−)
Yeh *et al* 2019[27]	Statin	China/9193	Cohort study	ICD	Statin (−)
Harrison and Ashton 1994[29]	Simvastatin and pravastatin	England/25	RCT	HADS	Simvastatin (−) Pravastatin (−)
Haghighi *et al* 2014[30]	Atorvastatin	Switzerland/60	RCT	HDRS	Atorvastatin (−)
van Melle *et al* 2006[10]	β-blockers	Multinational/381	Multicenter study	BDI	β-blockers (*)
Sorgi *et al* 1991[39]	β-blockers	USA/50	RCT	HDRS	β-blockers (*)
Rosenberg *et al* 2017[40]	Propranolol	USA/202	RCT	BDI	Propranolol (*)
Pérez-Stable *et al* 2000[41]	Propranolol	USA/312	RCT	BDI	Propranolol (*)
Liu *et al* 2017[42]	Metoprolol	China/154	Prospective study	HADS	Metoprolol (+)
Duch *et al* 1992[43]	β-blockers	Spain/25	RCT	BDI and Zung self-rating depression	β-blockers (+)
Hu *et al* 2020[46]	Aspirin	Sweden/316,904	Cohort study	ICD	Aspirin (−)
Weir *et al* 1996[59]	Amlodipine, Bisoprolol, Enalapril	USA/218	RCT	Zung self-rating depression	Amlodipine (*) Bisoprolol (*) Enalapril (*)
Rathmann *et al* 1999[60]	CCB, β-blocker, and ACE inhibitor	Germany/1944	Case-control study	ICD	CCB (+) β-blocker (+) ACE inhibitor (*)
Kessing *et al* 2020[70]	Antihypertensive drugs	Denmark/3,747,190	Cohort study	Comprehensive diagnostic methods	Angiotensin agents (−) Calcium antagonists (−) β-blockers (−) Diuretic (*)
Potempa *et al* 1993[71]	Pindolol, propranolol, and hydrochlorothiazide	Chicago/41	Case-control study	BDI	Pindolol (+) Propranolol (*) Hydrochlorothiazide (*)

(−): increase; (+): decrease; (*): not related. aHR: Adjusted hazard ratio; BDI: Beck Depression Inventory; CBI: Copenhagen Burnout Inventory; CCB: Calcium channel blocker; CES-D: Center Epidemiological Studies of Depression; CI: Confidence interval; GEE analysis: Generalised estimating equation analysis; GHQ: General Health Questionnaire; HADS: Hospital Anxiety and Depression Scale; HAM-D: Hamilton Depression Rating Scale; HDRS: Hamilton Depression Rating Scale; HR: Hazard ratio; ICD: International Classification of Diseases; ICSs: Inhaled corticosteroids; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: Major depressive disorder; NSAIDs: Nonsteroidal anti-inflammatory drugs; OSs: Oral steroids

did not reduce the incidence of major depressive disorder (MDD) during a 3-year follow-up.[17] Another 12-week triple-blind, randomized, controlled trial enrolled 130 participants with moderate to severe MDD (aged 15–25 years old); participants were randomized to receive aspirin ($n = 40$), rosuvastatin ($n = 48$), or placebo, and the results indicated that neither aspirin nor rosuvastatin conferred any beneficial effect over and above routine treatment for depression in young people.[18] Soh *et al*[19] conducted a randomized, double-blind clinical trial that enrolled 60 bipolar disorder and MDD patients using lithium. Their experimental data show that depression relapse during a 12-week follow-up was not significantly different between groups. A double-blind investigation carried by Glaus *et al*[17] also found that there was no significant effect of lovastatin in treatment for depression ($P > 0.2$). Similar results were obtained by Agustini *et al*[20], Stewart *et al*,[21] and Muldoon *et al*[22] There are even some studies that have found that statins increase the risk of depression. For example, Chan *et al*[23] found that after 24 months of statin treatment, there was an increase of 2.8 points (1.5–4.0) on the Hamilton Depression Rating scale ($P < 0.0001$), although 64 (68%) of 94 patients' scores at 24 months still suggested either no depression or mild depression. The differences in these results may be related to the criteria for depression and the dosages of statins.

However, accumulated studies have confirmed that statins are related to a reduced risk of depression in people with cardiovascular disease. A Swedish national cohort study showed that the use of statins was shown to reduce the odds of depression by 8% compared to individuals not using statin medications.[24] Hoogwegt *et al*[25] found that statin therapy can improve psychological conditions in people with an implantable cardioverter defibrillator. Furthermore, after adjusting for the relative statin dosage, there were no significant differences between statin types and effects on psychological function. With annual follow-up in the outpatient cardiology clinic, Young-Xu *et al*[26] reported that the use of statin was associated with a lower risk of elevated depression scores (Odds Ratio[OR] 0.63, 95% confidence interval [CI] 0.43–0.93) in patients with

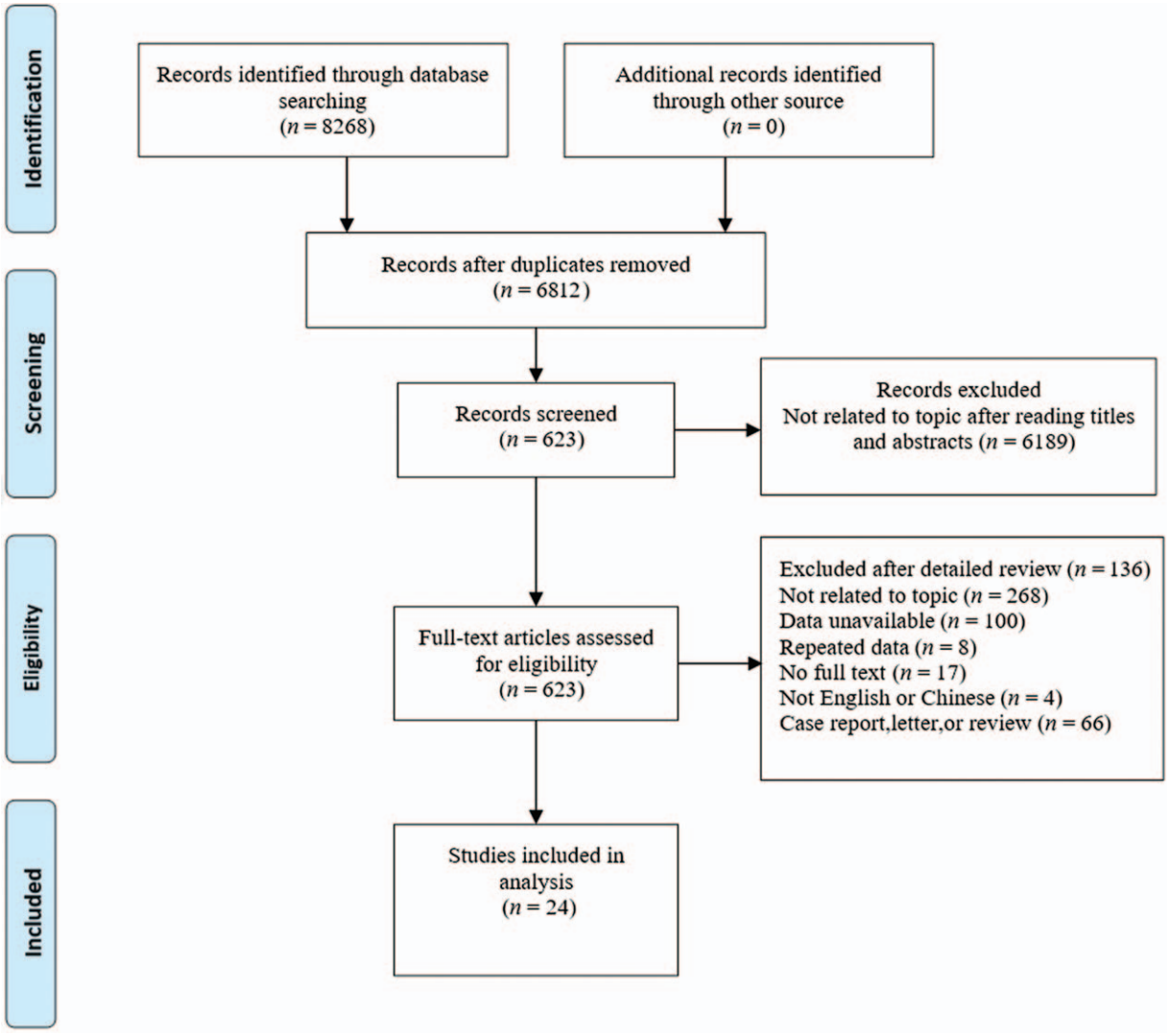

Figure 1: The screening progress of the study on association between common cardiovascular drugs and depression.

CHD. Recent studies show that statins are related to lower risk in patients with other systemic diseases. A trial enrolling 465 stroke patients supports the conclusion that statin use was not associated with poststroke depression (PSD) status at outset but was significantly associated with reductions in PSD and significant PSD risk, specifically at follow-up. By enrolling two asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) cohorts, one taking statins ($n = 1252$) and one comprised of non-statin users, matched by age, sex, and index date ($n = 7887$), Yeh *et al*[27] found that the ACOS cohort using statins had lower risks of anxiety and depression. The incidence of anxiety and depression was relatively low among users of statins with inhaled corticosteroids or oral steroids in the ACOS cohort. However, the association between statin use and depression is complex as research findings have been mixed. The possible mechanism underlying the antidepressant effect of statins may predominantly include the anti-inflammatory, anti-oxidant, and lipid-lowering properties of this drug class. An animal study has found that treating mice orally with vehicle (saline, 0.9%, control group) compared to 1 or 10 $mg \cdot kg^{-1}$ day^{-1} of atorvastatin or fluoxetine for seven days, the mice treated with atorvastatin presented lower depressive status than the placebo group; this was associated with the prevention of lipopolysaccharide (LPS)-induced depressive-like state and of an LPS-induced increase in tumor necrosis factor-α level and reduction in brain derived nerve factor level in the hippocampus and prefrontal cortex.[28] A clinical trial enrolling 217 coronary artery disease (CAD) patients reported that the patients treated with statin showed reduced Interleukin-1β (IL-1β) and Nuclear factor kappa B (NF-κB) levels. By comparing the correlation between simvastatin and pravastatin and depression, Harrison and Ashton[29] found that both kinds of statins could relieve the symptoms of depression, and the effect of simvastatin was greater than that of pravastatin. In a randomized, double-blind clinical trial, Haghighi *et al*[30] also found that statins had an antidepressant effect. Statins may function as anti-inflammatory agents in therapy for depression in patients with CAD via downregulation of IL-1β and NF-κB.[31]

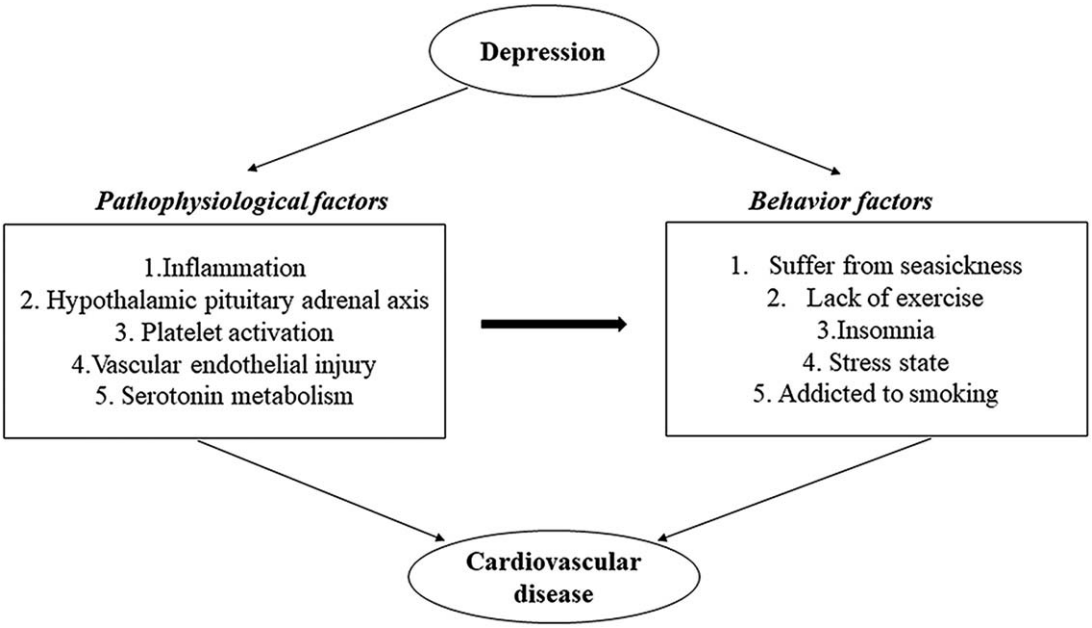

Figure 2: Relationships related to depression and cardiovascular disease.

The role of β blockers in depression

β-blockers are a family of agents widely used to treat hypertension, angina pectoris, and cardiac arrhythmias.[32] They are widely used in patients with cardiovascular disease. The first β-blocker to be implicated in depression was propranolol, whose lipophilic structure and penetration of the blood-brain barrier (BBB) could explain its role in depression.[33] β-blockers can be divided into two types, fat-soluble and water-soluble. Compared with water-soluble β-blockers, fat-soluble blockers can more easily permeate into the central nervous system (CNS) through the BBB to reach high concentrations. Studies suggested that β-blockers can be used in the treatment of essential tremors and have unique therapeutic significance, and previous work supports that they can induce depression, insomnia, dreaming, and other side effects.[34] In a 1967 article published in the British Medical Journal, Fitzgerald *et al*[35] reported on a case group of 89 hypertensive patients who were being treated for arrhythmia. Results of subsequent research on the link between β-blockers and depression have been mixed, prompting more research on the subject.

We feel that the association between depression and β-blockers may need to be further explored due to the possibilities of publication bias and use of different criteria for depression assessment. Since Stoudemire *et al*[36] posed, in 1984, that there is very little evidence to link propranolol with mood disturbance, subsequent studies have consistently challenged the dogma that β-blockers cause depression. Recent studies in patients with heart disease have tended to sever the link between β-blockers and depression, treatment with β-blockers even being associated with a lower risk of depression in some cases. A retrospective cohort study of 6915 patients, in a multicenter integrated healthcare system, diagnosed with HF between 2008 and 2014, found that among them, 1252 had a diagnosis of depression. During a mean follow-up of 2.6 years, the authors reported that depressed patients not treated with a β-blocker had higher mortality than non-depressed patients (adjusted hazard ratio [aHR], 1.4, 95% CI 1.09–1.70, $P < 0.05$). When treated with β-blockers, their risk of mortality was attenuated (hazard ratio [HR] 1.1, 95% CI 0.97–1.20, $P = 0.14$).[37] Randomized trials of β-blockers used in the treatment of myocardial infarction (MI), HF, or hypertension were identified by searching the MEDLINE database for English-language articles (1966–2001). A paper published in JAMA also supports the idea that there is no significant increased risk of depressive symptoms and only small increased risks of fatigue and sexual dysfunction.[38] In a multicenter study, 381 MI patients were assessed for depressive symptoms using the Beck Depression Inventory at outset and at $t = 3$ months, 6 months, and 12 months post-MI; patients were matched using the frequency matching procedure according to age, gender, hospital of admission, presence of baseline depressive symptoms, and left ventricular function. No significant differences were found between non-β-blocker users and β-blocker users in the presence of depressive symptoms.[10] Additionally, the results of Sorgi *et al*,[39] Rosenberg *et al*,[40] and Pérez-Stable *et al*[41] also support this view. There are also some studies suggesting that the use of β-blockers increased the risk of depression. For example, Liu *et al*[42] analyzed the correlation between metoprolol use and depression in patients with chronic HF. It was found that their Hospital Anxiety and Depression Scale and the Copenhagen Burnout Inventory (CBI) scale scores significantly increased from baseline throughout the study's timeframe. Similar results were found by Duch *et al*'s[43] study. The differences in these results may be related to the quantity of β-blocker crossing the BBB. The amount of a fat-soluble β-blocker crossing the BBB is determined by plasma protein-binding (low uptake) and fat-solubility. The potency of action is determined by

the local concentration of the drug, the number of receptors, and the affinity for the relevant receptors.[44]

The role of antiplatelet medications in depression

Aspirin is a commonly used antiplatelet drug in the clinic. In addition to its inhibitory effect on platelet aggregation, it can also be used as an anti-inflammatory and analgesic agent.[45] Numerous clinical and animal studies have confirmed that aspirin treatment has a specific correlation with reduction in signs of depression. A cohort study involving all patients in Sweden diagnosed with a first primary malignancy between July 2006 and December 2013, found that among 316,904 patients identified, 5613 patients received a diagnosis of depression, anxiety, or stress-related disorder within 1 year after a cancer diagnosis. Compared with those with no use of nonsteroidal anti-inflammatory drugs, the use of aspirin alone was associated with a lower rate of depression, anxiety, and stress-related disorders (HR, 0.88; 95% CI 0.81–0.97).[46] Bhatt *et al*[47] demonstrated in animal studies that aspirin improved depression in sprague-dawleyrats both in combination with dexamethasone and alone. The animals treated with aspirin showed increased sucrose preference, decreased immobility-time in the forced swim test, decreased serum cortisol, and increased brain serotonin levels signifying antidepressant action. Studies have shown that aspirin's antidepressant mechanisms are closely related to its anti-inflammatory effects. Many clinical trials and observational studies have been conducted based on the premise that the anti-inflammatory effect of aspirin may prevent depression. Inflammatory processes associated with persistent infection have long been discussed as etiological factors in psychiatric disorders. Studies have found that people with major depression have higher levels of pro-inflammatory cytokines, such as IL-1, IL-6, tumor necrosis factor-alpha, and C-reactive protein. After antidepressant treatment for depression, a decrease in IL-4, IL-6, and IL-10 cytokine levels was observed in serum.[48-50] These observations raise the possibility that the occurrence and development of depression are associated with the levels of inflammatory factors. Indeed, preclinical, pharmacoepidemiologic, and pilot clinical trial data suggest that aspirin may have clinical potential in psychiatric use based on its anti-inflammatory properties.[51,52]

However, whether aspirin has an antidepressant effect is still controversial. Some studies show no significant association between aspirin and depression. A prospective cohort study including 1631 subjects (43.6% women, mean age 51.7 years), randomly selected from the general population of an urban area reported that, after a mean duration of 5.2 years follow-up, and adjusted for a wide array of potential confounders, data did not support large-scale preventive treatment of depression using aspirin or statins in subjects aged between 35 and 66.[16] To determine whether low-dose aspirin reduces the risk of depression in healthy older adults, Berk *et al*[53] observed 199,114 participants in whom 9525 received aspirin and 9589 received a placebo with a median follow-up of 4.7 (3.5–5.6) years, and a rate of depression of 70.4 events per 1000 person-years in the aspirin group and 69.1 in the placebo group; there were no significant differences at annual visits in the proportion of depression reports between the two groups. The result may be connected to an apparent increase in the risk of bleeding events on aspirin treatment. These negative results may be related to the dose of aspirin used in the trial. It is not clear whether low-dose aspirin reduces inflammatory cytokines. Studies found that aspirin reduced the risk of schizophrenia at doses ranging from 1 g/day to 45 g/day.[11] At the same time, aspirin can increase the risk of bleeding, which increases the economic and mental burden on patients to a certain extent and may also affect the experimental results.

Clopidogrel is another widely used antiplatelet drug in cardiovascular disease. It can significantly improve primary cardiovascular outcomes in patients following percutaneous coronary intervention. An antidepressant effect of clopidogrel has been reported in a few cases, but there is still a lack of robust clinical and animal experiments to confirm this.

The role of CCBs in depression

CCBs are a heterogeneous group of structurally unrelated compounds that are widely used today in the treatment of cardiovascular disease. CNS effects of verapamil and diltiazem have been described previously. Studies have confirmed that drugs with antagonistic effects on cellular calcium also possess psychotropic properties, an action which is associated with CCBs' has an influence on intracellular calcium homeostasis.[54] Cellular calcium homeostasis not only plays a crucial role in neuronal cell signal processing but also has an impact on both synthesis and release of neurotransmitters. In a rat model, CCBs can competitively combine with neurotransmitter receptors and induce psychotic symptoms.[55] It has been suggested that receptors interact with a neurotransmitter or neuromodulator in somewhat the same way that receptors for gamma-aminobutyric acid and benzodiazepines interact in the regulation of chloride-ion channels. Following observations that verapamil could improve response to antidepressants, an animal study sought to investigate whether this was the result of verapamil effects on the P-glycoprotein transporter in the BBB. Administered by mouth or intravenously, verapamil crossed the BBB, and verapamil pre-treatment significantly elevated concentrations of antidepressant imipramine in all brain regions studied; the effect was most pronounced in the brainstem and frontal cortex with about a doubling of brain region to serum concentration ratios being observed by Clarke *et al*[56] Further studies have confirmed that CCBs could be used alongside antidepressants to treat models of depression: Aburawi *et al*[57] found that combining nifedipine with alprazolam produced additional antidepressant effects in animal trials, indicating that they exert antidepressant effects through different mechanisms. However, some clinical trials have shown no correlation between depression and CCBs. In a multicenter randomized, double-blind, two-way, crossover study design, used to compare the antidepressant effect of bisoprolol and nifedipine in hypertension, there was no noticeable change in the depression scores observed in the 4 to 6 weeks follow-up.[58] Weir *et al*[59] also reported that there was no clear evidence of a link between depression and CCBs.

Rathmann *et al*[60] reported that the use of CCBs is associated with increased risk of depression. A trial that enrolled 972 diabetic patients indicated that, among diabetic patients, new prescriptions of calcium channel and β-blockers were associated with an estimated two- to three-fold increased risk of subsequently diagnosed depression. Although there are shreds of evidence that CCBs can interfere with nervous system activity, a qualitative association between depression and CCBs still lacks evidence derived from clinical trials; this may relate to the type and dosage of CCBs used. It has been suggested that fat-soluble CCBs are more strongly associated with depression than non-fat-soluble CCBs, which may reflect the ease of entry of fat-soluble drugs into the and across the BBB.[61]

The role of ACEIs/ARBs in depression

ACEIs/ARBs play a pivotal role in regulating the RAS by adjusting the synthesis and release of angiotensins in order to regulate blood pressure. In recent years, multiple studies found that ACEIs/ARBs can also delay and reverse ventricular remodeling, prevent further development of myocardial hypertrophy, improve endothelial function and heart function, and reduce the incidence of arrhythmia, and effectively improve healing in cardiovascular diseases and improve survival rate.[62] In addition to the regulation of blood pressure, the RAS is also a vital regulator of the inflammatory state of the nervous system. Several studies have shown that depression is closely related to the occurrence of inflammation in the brain.[63-65] Therefore, in recent years, many studies have proposed that ACEI/ARB drugs can reduce the risk of depression. Several observations have linked angiotensin-converting enzyme polymorphisms with depression and the serotonin and dopamine neurotransmitter systems. In a clinical trial that enrolled 625 Caucasian men with mild hypertension, the results suggested use of ACE inhibitors was associated with a reduced likelihood of risk of depression.[66] Prospective trials were initiated to compare the relative efficacy and influence on the quality of life of angiotensin converting enzyme inhibitors, and the results confirmed that ACEI captopril was associated with a more significant reduction in complaint rate as an index of life quality ($P < 0.05$) compared with methyldopa and showed a tendency to produce fewer symptoms of depression compared with other cardiovascular drugs.[67] However, there are few randomized clinical trials on ACEI and ARB targeting drugs and depression, which indicates the need to undertake future clinical studies.

The role of diuretics in depression

Diuretics are the most commonly chosen treatment for mild to moderate hypertension and are among the most commonly prescribed medications.[68] There is little evidence that these medications have effects on the CNS. Okada *et al*[69] reported eight cases (five men, three women; ages ranging from 44 years to 69 years) of depression induced by antihypertensive diuretics, but there is still no substantial further evidence. It is unclear whether the depression was caused by the drug directly or by lowered blood pressure. Some clinical studies have looked at the relationship between diuretics and depression, but the results have not shown any significant correlation. A nationwide population-based study investigated whether four antihypertensive drugs, angiotensin agents, calcium antagonists, β-blockers, and diuretics can decrease the risk of depression. They observed participants in the Danish population beginning January 2005 with follow up until December 2015. The results showed "Continued use of classes of angiotensin agents, calcium antagonists, and β-blockers was associated with significantly decreased rates of depression." [70] In a case-control study which enrolled 41 patients, Potempa *et al*[71] found there were no significant within or between subject effects for drug group or drug treatment effects with hydrochlorothiazide. Another multicenter randomized placebo-controlled trial of the treatment of isolated systolic hypertension in elderly subjects used chlorthalidone as the step one treatment. At the 5-year follow-up, no meaningful changes in mood were found in this population.[72] Although no meaningful results were observed, this study may serve as substantial evidence of no association between depression and diuretics due to the study's large sample size. Up to now, the majority view has been that diuretic's effects on depression or CNS behavior occur only when electrolyte disturbances develop. Otherwise, it appears that these medications have little or no effect on mood.

The role of nitrate drugs in depression

Nitrate drugs are one of the oldest cardiovascular drugs in clinical practice. They were initially used to prevent and treat angina pectoris and gradually applied to the treatment of HF and hypertension.[73] The primary mechanism of action is that nitrate esters can be converted into NO by the action of a series of enzymes; this then activates intracellular signal transduction pathways, reducing the concentration of calcium ions in smooth muscle cells, and relaxing smooth muscle.[74] There are few studies on the correlation between nitrates and depression. However, some studies suggest that plasma NO concentration can be related to the functioning of nerve cells, and the increase of NO concentration can change the functional activities of nerve cells and induce depression, anxiety, and other mental-health conditions.[75,76] A case-control study in 50 treatment-naïve young adults with a first episode of major depression and 50 healthy control subjects was conducted. The authors reported that decreased plasma concentrations of nitric oxide metabolites was not associated with vascular endothelial dysfunction in these young subjects.[77] Reduced nitrate levels could reflect decreased nitric oxide production in the CNS of depressed subjects. Further studies are needed to confirm this hypothesis.

Discussion

There is a bidirectional association between depression and cardiovascular disease. Patients with depression are more likely to develop cardiovascular disease than healthy individuals and vice versa. Studies have confirmed that depression is an independent risk factor for predicting the prognosis of patients with cardiovascular disease.[78,79] Clinical trials have found that the depressive symptoms of

patients with cardiovascular depression often change during treatment, which may be due to the relationship between cardiovascular drugs and depression.

This article describes the relationship between seven common cardiovascular drugs and depression and their possible mechanisms. Statins can reduce the risk of depression by reducing inflammatory factors, while the antidepressant effect of aspirin is still controversial. There have been case reports on ACEI and ARB drugs' abilities to reduce the risk of depression, but there is less compelling data on their potential physiological benefits. β-blockers were previously thought to reduce the risk of depression, but recent studies have found no significant association between the two. CCBs affect nervous system activity by affecting calcium channels, but their role in depression remains undetermined. Some cases of depression induced by diuretic drugs have been reported, but it is believed that depression may be related to electrolyte disturbance. Finally, nitrate drugs were not significantly associated with depression.

The present study suggests the correlations between cardiovascular drugs and depression remain unclear; the reason for differences between research results, in addition to the human factor, may arise mainly from the following: First, the drug dose differs; in studies on statins, Berk *et al*[18] found that the use of statins can relieve the symptoms of depression. At the same time, Jun-Jun *et al*[27] believe that low doses of statins and depression show no significant correlation. Therefore, the relationship between a high dose and a low dose of drug administered and depression needs to be further studied. Moreover, the effect of different doses on the treatment outcome should not be ignored. Therefore, the relationship between high dose or low dose therapy and depression needs to be further studied. Second, there are different criteria for depression evaluation. At present, the main diagnostic methods for depression include Patient Health Questionnaire (PHQ-9), Beck Depression Questionnaire (BDI), Hamilton Depression Scale (HAMD), etc.[80] To eliminate this difference, large-scale clinical trials need to be implemented. Third, we may mention the influence of other drugs. Because clinical patients may have various diseases, it is inevitable that they may take different drugs, a variable which may not be controlled for. Although the association between cardiovascular medications, such as nitroglycerin and diuretics and depression, is unclear, several studies have found that cardiovascular medications can enhance the effectiveness of antidepressants.

Conclusion

In this literature review examining PubMed, EMBASE, and Web of Science from January 1990 through May 2021, we systematically investigated whether the seven most used antihypertensive drugs were associated with altered risk of incident depression. Statins have been proven to have antidepressant effects. Some studies believe ACEIs/ARBs can exert an antidepressant influence by acting on the RAS, but further clinical trials are needed to confirm this. β-blockers have previously been associated with depression, but the current survey found no significant association between β-blockers and the risk of depression. Aspirin may have antidepressant effects by suppressing the inflammatory response, but its role as an antidepressant remains controversial. CCBs can regulate nerve signal transduction by modulating calcium channels, but whether this effect is beneficial or harmful to depression remains unclear. Finally, some cases have reported that nitrates and diuretics are associated with depression, but the current clinical evidence is insufficient. However, the findings should be replicated in well-designed, more extensive randomized controlled trials using appropriate designs and statistical analyses to address selection and confounding factors. Further research is needed to determine whether common cardiovascular drugs reduce the risk of depression and to identify the factors that are associated with such a reduction.

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Conflicts of interest

None.

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