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REVIEW ARTICLE

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Cardiovascular therapeutics: A new potential for anxiety treatment?

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Abstract

Besides the well-recognized risk factors, novel conditions increasing cardiovascular morbidity and mortality are emerging. Undesirable emotions and behavior such as anxiety and depression, appear to participate in worsening cardiovascular pathologies. On the other hand, deteriorating conditions of the heart and vasculature result in disturbed mental and emotional health. The pathophysiological background of this bidirectional

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT_{1A} receptor, serotonin 1 A receptor; ACE, angiotensin-converting enzyme; ACTH, adrenocorticotropic hormone; ADHD, attention deficit hyperactivity disorder; Ang, angiotensin; ANP, atrial natriuretic peptide; ARBs, angiotensin II receptor blockers; ARDS, acute respiratory distress syndrome; ARNI, angiotensin receptor-neprilysin inhibitor; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; AT1A receptor, angiotensin II type 1A receptor; AT1 receptor, angiotensin II type 1 receptor; AT2 receptor, angiotensin II type 2 receptor; BAI, Beck Anxiety Inventory; BDNF, brain-derived neurotrophic factor; beta-blockers, beta-adrenergic receptor blockers; BNP, brain natriuretic peptide; BSTvl, ventrolateral bed nucleus of the stria terminalis; CAD, coronary artery disease; CHARM, Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity; CNS, central nervous system; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; CoQ-10, coenzyme Q-10; COVID-19, Coronavirus disease 2019; CRH, corticotropin-releasing hormone; CSF, cerebrospinal fluid; CVD, cardiovascular disease; DOCA, deoxycorticosterone acetate; EPM, elevated plus maze; EUROPA, European trial on Reduction Of cardiac events with Perindopril among patients with stable coronary Artery disease; GABA, gamma-aminobutyric acid; GAD, generalized anxiety disorder; GPCRs, G-protein-coupled receptors; HAM-A, Hamilton Anxiety Rating Scale; HF, heart failure; HMG-CoA, 3-hydroxy-3-methyl-glutaryl -coenzyme ACoA; HOPE, Heart Outcomes Prevention Evaluation; HPA axis, hypothalamic-pituitary-adrenal axis; HSCL, Hopkins Symptom Checklist; HSD2, hydroxysteroid dehydrogenase-2; ICD, implantable cardioverter defibrillator; IL, interleukin; i.p., intraperitoneal; LDB, light-dark box; LDL, low-density lipoprotein; LIFE study, Losartan Intervention For Endpoint reduction in hypertension study; L-NAME, NG-nitro-L-arginine methyl ester; LPS, lipopolysaccharide; LV, left ventricle; MAPK, p38mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MI, myocardial infarction; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NADPH, nicotinamide adenine dinucleotide phosphate; NEP, neutral-endopeptidase; NF-κB, nuclear factor kappa B; NK-1, neurokinin type 1; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase; NYHA, New York Heart Association; OFT, open field test; PARADIGM HF, Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; PEACE, Prevention of Events with ACE inhibition; PPARα, peroxisome proliferator activated receptor alpha; PTSD, posttraumatic stress disorder; PVN, paraventricular nucleus; QOL, quality of life; RALES, Randomized Aldactone Evaluation Study; RAS, renin-angiotensin system; RHR, renal hypertensive rats; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAVE, Survival and Ventricular Enlargement trial; SD rat, Sprague–Dawley rat; SERT, serotonin reuptake transporter; SF-36, 36-Item Short Form questionnaire; SHIFT, Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial; SHRs, spontaneously hypertensive rats; SNS, sympathetic nervous system; SOLVD, Studies of Left Ventricular Dysfunction; SP, substance P; STAI, State-Trait Anxiety Inventory; TBI, traumatic brain injury; TNF-α, tumor necrosis factor alpha; TRACE, Trandolapril Cardiac Evaluation study; V-HeFT II, Veterans Administration Cooperative Vasodilator–Heart Failure Trial II; WAG/Rij rats, Wistar-Albino-Glaxo from Rijswijk rats.

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interplay could reside in an inappropriate activation of vegetative neurohormonal and other humoral systems in both cardiovascular and psychological disturbances. This results in circulus vitiosus potentiating mental and circulatory disorders. Thus, it appears to be of utmost importance to examine the alteration of emotions, cognition, and behavior in cardiovascular patients. In terms of this consideration, recognizing the potential of principal cardiovascular drugs to interact with the mental state in patients with heart or vasculature disturbances is unavoidable, to optimize their therapeutic benefit. In general, beta-blockers, central sympatholytics, ACE inhibitors, ARBs, aldosterone receptor blockers, sacubitril/valsartan, and fibrates are considered to exert anxiolytic effect in animal experiments and clinical settings. Statins and some beta-blockers appear to have an equivocal impact on mood and anxiety and ivabradine expressed neutral psychological impact. It seems reasonable to suppose that the knowledge of a patient's mood, cognition, and behavior, along with applying careful consideration of the choice of the particular cardiovascular drug and respecting its potential psychological benefit or harm might improve the individualized approach to the treatment of cardiovascular disorders.

KEYWORDS
aldosterone antagonists, angiotensin II type 1 receptor blockers, angiotensin-converting enzyme inhibitors, anxiety, beta-blockers, ivabradine, sacubitril/valsartan, statins

1 | INTRODUCTION

The most frequent cardiovascular disorders, hypertension and coronary artery disease, and the most common mental disturbances, such as anxiety and depressive disorders, dramatically increase morbidity and health care financial burden. Depressive disorders were the third leading cause of disability, after back pain and headache in 2017.[1] The link between cardiovascular and mental disorders has been discussed for decades. Obviously, psychosocial stressors such as anxiety disorder, type A behavior, hostility, stress, or conflict situations stimulate autonomic nervous system and neurohumoral cascade in varying degrees. Activation of neural and humoral mechanisms supports the development of hypertension, endothelial dysfunction, and atherosclerotic vascular changes. A meta-analysis focused on anxiety as a risk factor of cardiovascular diseases (CVDs) revealed that anxiety patients have increased risk of coronary artery disease, stroke, heart failure, and cardiovascular death.[2] Vice versa, the neurohumoral activation is accompanied by the formation of anxiety disorders such as generalized anxiety disorder (GAD), panic disorder, posttraumatic stress disorder

(PTSD), obsessive-compulsive disorder, as well as conditions arising during the therapy of accompanying mental conditions such as depression (Figure 1).[3–5]

There seems to be a bidirectional relationship between negative emotions and mental disturbances in the form of distress, anxiety, or depression and increased risk of CVDs. CVDs coincide with anxiety development,[8–10] whilst patients with anxiety are more prone to CVD[11–14] (Figure 1). Cardiac patients and patients with anxiety were observed to manifest similar symptoms such as nervousness, palpitations, apprehension, fatigue, breathlessness, headache, sweating, dizziness, or insomnia.[15] Both anxiety and hypertension or coronary artery disease are common occurrences in primary medical practice, and a diagnosis of anxiety can even predict future adverse cardiovascular events. Thus, a knowledge of mutual interference and causal relationship between anxiety and CVD could be of value for the early detection and treatment of these pathologies.[16]

Several review articles have examined the effects of only selected groups of cardiovascular drugs on emotions, cognition, and behavior. In contrast, this review provides data on the relationship between anxiety and the most commonly used groups of cardiovascular drugs in current cardiovascular practice. Two other specifics of this review may be of value. First, each presented drug group is introduced by a brief overview of its cardiovascular indications based on the evidence-based approach. Second, the interactions of cardiovascular drugs with symptoms of anxiety tend to be presented from the experimental level to clinical implications. The presentation of the mutual interactions of pathophysiological, psychological, and cardiovascular alterations provides a comprehensive view of this multidisciplinary medicinal problem.

2 | METHODS

The electronic database PubMed/MEDLINE was used to search for the following terms: *CVDs*, *anxiety*, *RAS (renin-angiotensin system) in brain* and cardiovascular drugs *beta-blockers*, *central sympatholytic drugs*, *angiotensin-converting enzyme inhibitors*, *angiotensin II type 1 receptor blockers*, *angiotensin (1–7)*, *aldosterone antagonists*, *angiotensin II type 1 receptor inhibitors*, *neprilysin inhibitors*, *statins*, *fibrates*, *ivabradine*, *calcium channel blockers*, *diuretics*, *vasodilators*, *antihypertensives* and *antiarrhythmics* in association with *anxiety*. The experimental studies, clinical studies, clinical guidelines, reviews, and meta-analyses in the full text and in English were included. Articles without a direct correlation between particular drugs and anxiety were excluded. Finally, 323 records from 1951 to 2021 were used.

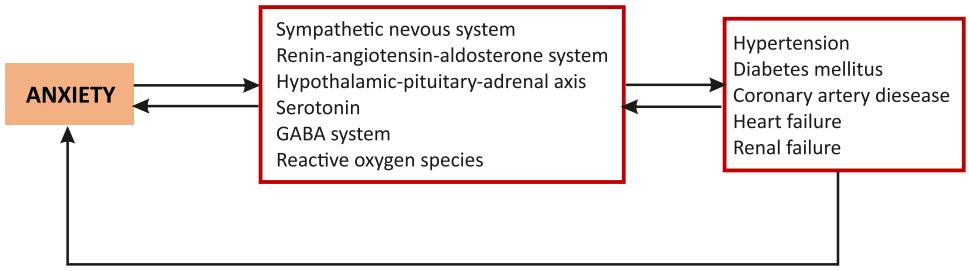

FIGURE 1 The potential link between anxiety and cardiovascular pathologies. Anxiety disorder activates stress, neurohumoral cascade, serotonergic and gamma-aminobutyric acid (GABA) pathways and increases free radical burden.[6,7] The activation of neural and humoral mechanisms supports the development of endothelial dysfunction, hypertension, diabetes mellitus, and target organ damage. Conversely, the cardiovascular pathologies associated with neurohumoral imbalance result in the formation of various anxiety disorders.[8–10] [Color figure can be viewed at wileyonlinelibrary.com]

3 | ANXIETY

Stress is considered one of the principal factors in the development of anxiety and depression.[17,18] These mental disturbances are the result of an inappropriate adaptation to stress, with a causal role of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathoadrenal medullary system releasing corticosteroids and catecholamines, respectively. However, in contrast to acute and chronic stress, anxiety disorders are considered diagnosable mental illnesses.[6,19]

3.1 | Pathophysiological background

It is widely accepted that an interplay of genetic, ontogenetic, and environmental factors plays a role in the pathogenesis of anxiety, while several systems seem to participate in its development, such as gamma-aminobutyric acid (GABA) system, sympathetic nervous system (SNS), HPA axis, oxidative metabolism, nitric oxide and serotonergic system.[6,7]

3.1.1 | Sympathetic nervous system

The excessive sympathetic response to stressors may be an important link between anxiety and development of cardiovascular events. The somatic symptoms of anxiety such as tachycardia, palpitations, hyperventilation, headache, diarrhea, and tremulousness are associated with autonomic nervous system hyperactivity.[20] The chronically enhanced sympathetic drive results in increased systemic vascular resistance and contractility contributing to increased arterial blood pressure. Moreover, increased levels of catecholamines induce myocardial damage including coronary spasms, coronary ischemia, and arrhythmias.[21] Taken together, the overactivity of sympathetic outflow in anxiety could increase the risk of CVD.

3.1.2 | Hypothalamic-pituitary-adrenal axis

The paraventricular nucleus (PVN) of the hypothalamus is a central point of the HPA stress response that contributes to anxiety.[22] In anxiety disorders, the corticotropin-releasing hormone (CRH) is released from the hypothalamus and stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH) into the circulation and finally, corticosterone from the adrenal gland.[6] Glucocorticoids contribute to cardiac dysfunction by prolonging the action duration, increasing the sensitivity of catecholamines to the myocardium, and promoting contractility, arrhythmias, and apoptosis leading to increased arterial blood pressure, tachycardia, and myocardial damage.[21] Cortisol also increases the level of angiotensinogen, the pressor responsiveness to angiotensin II (Ang II), thus contributing to hypertension development. Cortisol excess also leads to metabolic changes such as obesity, increased levels of fasting plasma glucose, or insulin resistance.[23] Since anxiety activates the HPA axis and promotes the corticosterone release from adrenal glands, it eventually results in hypertension development and metabolic disorders.[24,25]

3.1.3 | Nitric oxide pathway

Nitric oxide (NO) is a gaseous free radical synthesized by nitric oxide synthase (NOS) in the presence of oxygen.[26] It has been demonstrated that neurons expressing neuronal NOS (nNOS) are located in brain areas involved in

anxiety.[27] It appears that activation of nNOS may play an ambivalent, sex-dependent role in anxiety development.[28] Moreover, stress-induced increase of NO production in PVN activates the release of CRH and ACTH and thus, the HPA axis.[29]

3.1.4 | Serotonergic system

The serotonergic system is implicated in the regulation of emotion and anxiety. The stimulation of serotonin 1A (5-HT_{1A}) receptors produced anxiolytic effects in both humans and animals.[30] Moreover, serotonin activates the HPA axis and contributes to anxiety.[31]

3.1.5 | Gamma-aminobutyric acid system

Anxiety is related to GABA-ergic modulation in various areas of the brain. In general, the GABA receptor antagonists induce anxiogenic effects, while GABA receptor agonists reduce anxiety and stress responses.[32] It has been found that systemic, intracerebral, or intracerebroventricular injections of GABA-antagonists induce hypertension and tachycardia probably due to an increased sympathetic outflow to the cardiovascular system[33] which exerts deleterious effects on the cardiovascular system.

3.1.6 | Oxidative stress

The HPA axis activation and the release of corticosterone and Ang II along with the SNS activation induce oxidative stress in specific brain regions controlling anxiety and depression. The damage via free radicals found in experimental animals with anxiety-like behavior may result in neuroinflammation and neurodegeneration.[34]

3.2 | Methodological approaches to quantification of the anxiety level

For the purpose of the current review, the methods related to anxiety determination in experimental (rodents) and clinical (humans) settings are to be elucidated.

3.2.1 | Anxiety indices in rodents

Anxiety symptoms in humans and rodents are difficult to compare, although both groups share some common or similar behavioral responses such as freezing, hypoactivity, increased attention, or tachycardia.[35] In animals, the term "anxiety-like behavior" is used to describe the manifestation of experiencing anxiety rather than a statement indicating that an animal is anxious. Therefore, a variety of anxiety behavioral assays have been developed. For the needs of this review, only some of them are presented; however, extensive reviews are available.[36,37] Naturally, rodents prefer dark and closed spaces, which decrease the risk of potential threat. The excessive avoidance of light, open space, and novel objects is considered as a sign of anxiety-like behavior in rodents. In the light-dark box (LDB) the latency to enter and the shorter time spent in the light part indicates anxiety-like behavior. In the elevated plus maze (EPM) the latency to enter, the shorter time spent in, and the decreased number of entries in the open arms are used as anxiety indices. Regarding the open field test (OFT), the anxiety indices include the latency to enter and the shorter time spent in the center of the arena.[37]

3.2.2 | Anxiety measures in clinical conditions

In clinical practice, various measures indicating anxiety symptoms and their severity in patients have been developed. The State-Trait Anxiety Inventory (STAI) measures the presence and severity of anxiety symptoms via self-reporting.[38] The Beck Anxiety Inventory (BAI) is used as an indicator of anxiety focused on somatic symptoms.[38] The Hamilton Anxiety Rating Scale (HAM-A) reflects the severity of perceived anxiety symptoms.[39] The Hopkins Symptom Checklist (HSCL) is a self-report symptom inventory including anxiety.[40]

4 | RENIN-ANGIOTENSIN SYSTEM IN THE BRAIN AND ITS INTERACTION WITH CENTRAL NERVOUS SYSTEM

The RAS regulates not only the function of the cardiovascular system but also plays an important role in the regulation of the central nervous system (CNS). Circulating Ang II does not penetrate the blood–brain barrier.[41] It has been proposed that Ang II is synthesized by the local RAS in the brain.[42] However, van Thiel and colleagues showed that there was no local Ang I generation in the brain, therefore, the brain Ang II might represent Ang II originating from the blood that accumulates in the brain through damaged blood–brain barrier, rather than locally synthesized Ang II.[43] Regardless of its origin, the brain Ang II participates in the regulation of blood pressure and body fluid volume (sodium appetite, vasopressin, ACTH, and aldosterone release). Moreover, brain Ang II interacts as a neurotransmitter with catecholamines, serotonin or prostaglandins,[44] regulates the cerebral blood flow, blood–brain barrier, brain development, stress response[45] and is involved in sensory perception and emotional behavior (Figure 2).[42]

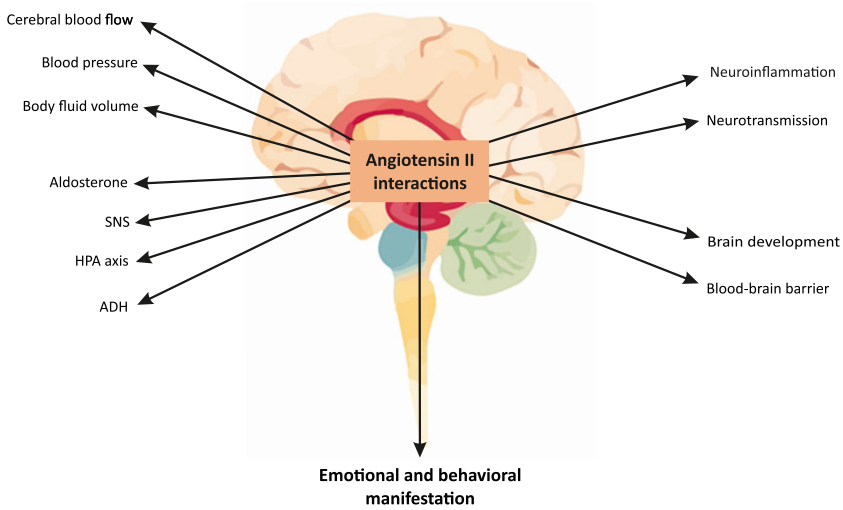

FIGURE 2 The role of brain angiotensin II. Angiotensin II in the brain modifies stress hormonal pathways, hemodynamic status in systemic and brain circulation, and structural and functional characteristics in the central nervous system.[44,45] All of these issues, individually or in concert, modulate the emotional and behavioral manifestation.[42] ADH, antidiuretic hormone; HPA axis, hypothalamic-pituitary-adrenal axis; SNS, sympathetic nervous system [Color figure can be viewed at wileyonlinelibrary.com]

Besides its regulatory role, brain Ang II may induce cerebrotoxicity via the enhancement of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase activity, leading to the intracellular generation of reactive oxygen species activating redox-sensitive signaling molecules, such as MAPKs (p38mitogen-activated protein kinases), NH2-terminal kinases, and extracellular signal-regulated kinases 1 and 2.[19] In addition, Ang II-induced enhancement of cellular and mitochondrial oxidative stress activates transcription factor nuclear factor kappa B (NF-κB), promoting the production of inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor alpha (TNF-α) along with chemokines such as monocyte chemoattractant protein-1 (MCP-1). The result is the activation of an inflammatory response and apoptosis (Figure 2).[46]

Psychological disorders are based on functional and structural disorders of neurons. Cerebral circulatory disorders due to cerebrovascular vasoconstriction and vessel remodeling, loss of vascular elasticity, impairment of autoregulatory mechanisms, or disorders of the blood–brain barrier are frequent causes of neuronal damage and dysfunction.[47,48] Another damaging factor is inflammation of the brain parenchyma due to the accumulation of inflammatory cytokines and hormones, activation of the microglia, as well as stress with consequent increased peripheral and cerebral sympathetic activity.[49] Structural and functional neuronal disorders lead to dual neuropsychiatric disorders:

1. Affective, psychotic, or stress-induced disorders being represented by somatic stress disorders, anxiety, PTSD, and depression, or autism and schizophrenia.
2. Circulatory, traumatic, and neurodegenerative diseases in the form of vascular stroke, cognitive disability, Alzheimer's disease, Parkinson's disease, and others.[50]

Because of the specific interaction of genetic equipment and the environment, there is an allostatic burden with consequent neuronal dysfunction and neuropsychiatric disorders. RAS appears to play a significant role in the pathogenesis and treatment of these disorders.[45]

4.1 | The brain angiotensin II in association with stress and anxiety

Overactivation of the brain pressor axis of the RAS has been implicated in the etiology of stress-associated anxiety disorders.[19] Stressors activate renin release, increasing the production of β-adrenergic receptors with enhanced peripheral RAS activity and increased production and release of Ang II in both the circulation and the brain.[51] The stimulation of angiotensin II type 1A (AT1A) receptors in the PVN of the hypothalamus leads to the release of CRH with the activation of HPA axis, resulting in stress-associated anxiety.[51] However, it has been shown that low doses of Ang II injected bilaterally into the hippocampal CA1 area of male Sprague–Dawley (SD) rats[52] or intracerebroventricularly in male Wistar rats[53,54] attenuated anxiety, while higher acute intracerebroventricular doses in male Wistar rats[55] or chronic subcutaneous administration in C57BL6 mice[56] induced anxiety-like behavior. Thus, the neuropsychiatric effect of Ang II is obviously dose-dependent.

5 | CARDIOVASCULAR DRUGS AND ANXIETY

A number of experimental and clinical evidence indicates that cardiovascular drugs interfering with the autonomic nervous system or the renin-angiotensin-aldosterone system along with several other groups of cardiovascular drugs such as statins or fibrates modulate the level of anxiety and related behavior in both experimental animals and humans.

5.1 | Sympathetic nervous system and anxiety

5.1.1 | Beta-adrenergic receptor blockers

Beta-adrenergic receptor blockers (beta-blockers), which compete at the receptor level with catecholamines and attenuate the impact of the SNS, are used in a number of cardiovascular pathologies. Beta-blockers (along with diuretics) were the first drugs supplying the evidence that reduction of hypertension reduces cardiovascular events and mortality.[57,58] In the secondary prevention of coronary artery disease (CAD), beta-blockers reduce morbidity and mortality in patients with a recent myocardial infarction (MI)[59] or after percutaneous revascularization.[60] In the primary prevention within stable CAD, beta-blockers remain the principal treatment for symptomatic relief.[61] Some beta-blockers (carvedilol, metoprolol, bisoprolol, and nebivolol) are a cornerstone treatment in heart failure patients with systolic dysfunction.[61–64] Beta-blockers are indicated also in various dysrhythmias.[65,66]

Clinical studies

The idea of using beta-blockers in the treatment of mental disorders began in the 1960s, when propranolol, a $\beta_{1,2}$-antagonist, seemed to be beneficial in managing the physical symptoms of anxiety, especially cardiovascular complaints[67] with tachycardia, palpitations, chest pain, physiological tremor, and a compulsion to over breathe under stress.[68] The anxiolytic effect of beta-blockers has been studied in panic disorders,[69,70] specific phobias,[71,72] social phobias,[73] or PTSDs.[74–78] The use of propranolol after experiencing[79] or recalling[80] traumatic events reduced the symptoms of anxiety and PTSD. Metoprolol lowered the anxiety score in chronic heart failure patients[81] and atenolol reduced PTSD and anxiety symptoms in patients with mental health problems.[82] There is even some evidence of an anxiolytic effect of beta-blockers in healthy individuals[83] (Table 1).

Experimental studies

SD rats pretreated with propranolol or nadolol spent more time in the lit area of the LDB and in the open arms of the EPM after social defeat, suggesting anxiolytic-like behavior.[84] The pretreatment of mice with propranolol before social defeat reduced anxiety-like behavior with increased time to enter the dark zone and decreased total time spent in the dark zone in the LDB.[85] However, the results of these studies are not equivocal and vary from hopeful to negative. According to a meta-analysis performed by Steenen et al.,[86] there is a lack of evidence that could confirm or exclude the beneficial impact of beta-blockers in the treatment of anxiety disorders[86] (Table 1).

5.1.2 | Alpha antagonists

Prazosin, an alpha-1 antagonist, reduces blood pressure by direct dilation of the peripheral arteries.[167]

Experimental studies

Prazosin increased the time spent in the open arms of the EPM after alcohol deprivation in alcohol-naïve P rats.[87] In a rat model of PTSD induced by the predator scent test, prazosin promoted anxiolytic-like behavior measured as decreased anxiety indices in the EPM.[88,89] On the contrary, in non-stressed rats, prazosin decreased open arm entry in the EPM, suggesting anxiety-like behavior in non-traumatized individuals[88] (Table 1).

Clinical studies

The beneficial effect of prazosin in the treatment of PTSD and related sleep disorders, including nightmares, has been acknowledged.[90–92] Prazosin reduced subjective anxiety to high-threat stimulus in patients with alcohol use disorder[93] and reduced stress- and alcohol cue—provoked anxiety in abstinent patients accompanied with decreased cortisol after stress cue[94] (Table 1).

TABLE 1 The effects of cardiovascular drugs on anxiety

Drug	Model	Test	Effect	Refs.
Beta-blockers				
Experimental studies				
Propranolol, nadolol, bisoprolol	Sprague–Dawley rats, social defeat	LDT, EPM	Anxiolytic (propranolol and nadolol, not bisoprolol)	Zaidi et al.[84]
Propranolol	ArcCreER^{T2} × eYFP mice, 129S6/SvEv mice, 4-shock contextual fear conditioning followed by immediate or delayed context re-exposures	Contextual Fear Conditioning, Cued Fear Conditioning, Context Fear Discrimination, EPM, OFT	Reduced fear, traumatic memory	Leal Santos et al.[78]
Propranolol	Male C57BL/6 mice, repeated social defeat	LDT	Anxiolytic	Wohleb et al.[85]
Clinical studies				
Propranolol	Patients with anxiety	Interview on a Five-Point Scale	Anxiolytic	Granville-Grossman and Turner[67]; Kelly[68]
Propranolol	Patients with panic disorders	Panic and Anxiety Attack Scale, Marks-Sheehan Phobia Scale, HAM-A, Symptom Checklist Scale	Anxiolytic	Ravaris et al.[69]
Propranolol	Patients with specific phobias	Autonomic Perception Questionnaire, Self-Reported Anxiety	Anxiolytic	Fagerström et al.[71]; Liu et al.[72]
Propranolol	Patients with social phobias	Measures of specific fears, generalized social anxiety, self-image, and global tension and anxiety	Anxiolytic	Falloon et al.[73]
Propranolol	Patients with PTSD	Script-Driven Mental Imagery of Traumatic Event, Revised Children's Manifest Anxiety Scale	Anxiolytic	AlOkda et al.[74]; Brunet et al.[75]; Giustino et al.[76]; Rosenberg et al.[77]
Propranolol	Healthy humans	Differential Fear-Conditioning Procedure	Anxiolytic	Kindt et al.[83]

TABLE 1 (Continued)

Drug	Model	Test	Effect	Refs.
Propranolol	Subclinical population	Patient Health Questionnaire, Personal Report of Public Speaking Anxiety, Structured Clinical Interview for DSM-5 social anxiety disorder	Public speaking anxiety decreased in questionnaire measures	Elsey et al.[79]
Propranolol	Children with PTSD symptoms	Child PTSD symptom scale, Children's Depression Inventory	PTSD symptoms decreased	Thierrée et al.[80]
Celiprolol	Patients with mitral valve prolapse syndrome	HADS	Anxiolytic	Bachmann et al.[70]
Metoprolol	Patients with chronic heart failure	HADS	Anxiolytic, increase in depression score	Wu et al.[81]
Atenolol	Patients with PTSD symptoms	Researcher's questionnaire	PTSD symptoms decreased	Armstrong and Kapolowicz[82]
Alpha antagonists				
Experimental studies				
Prazosin	Alcohol-naïve male P rats, restraint stress	Social Approach/Avoidance Test, EPM	Suppression of stress-induced anxiety during subsequent alcohol deprivation	Rasmussen et al.[87]
Prazosin	Sprague–Dawley rats, predator scent stress	EPM	Anxiolytic in traumatized rats, anxiogenic in controls	Ketenci et al.[88]
Prazosin, clonidine, yohimbine	Wistar rats, predator scent stress	OFT, EPM	Anxiolytic (prazosin and clonidine, not yohimbine)	Aykac et al.[89]
Clinical studies				
Prazosin	Active-duty soldiers with PTSD	DSM-IV criteria for PTSD	Reduced PTSD symptoms	Hendrickson et al.[90]
Prazosin	Inpatient children and adolescents with PTSD nightmares	Chart review and ICD code	Nightmare resolution	Hudson et al.[91]
Prazosin	Oncological patient	Self-report for nightmares	Nightmare resolution	Santivasi et al.[92]

(Continues)

TABLE 1 (Continued)

Drug	Model	Test	Effect	Refs.
Prazosin	Patients with alcohol use disorder	PROMIS Anxiety, Depression and Anger T scores, STAI, BDI	Anxiolytic	Wilcox et al.[93]
Prazosin	Patients with alcohol use disorder	10-point visual analog scale, psychophysiological correlation of anxiety	Anxiolytic in alcohol que-induced anxiety	Milivojevic et al.[94]
Central sympatholytic drugs				
Experimental studies				
Methyldopa	Wistar rats, Koletsky SHR	EPM	Anxiolytic in hypertensive rats	Golda and Petr[95]
Clonidine	Sprague–Dawley rats	Fear conditioning, Fear-potentiated startle test, Sensitization by foot shocks, Light-enhanced startle	Anxiolytic	Schweimer et al.[96]
Guanfacine	C57BL/6J mice	LDT, TST, FST, Locomotor activity	Anxiolytic	Mineur et al.[97]
Clinical studies				
Clonidine	Patients with anxiety	HAM-A, Global Rating of Neurotic Symptoms, Global Rating of Somatic Symptoms, Global Rating of Persistent Anxiety, Global Rating of Anxiety Attacks, STAI, Somatic Symptoms Scale, Affects Balance Scale	Anxiolytic	Hoehn-Saric et al.[98]
Guanfacine	Critically ill postoperative patient	Richmond Agitation Scale Score	Anxiolytic	Srour et al.[99]
Guanfacine	Children and adolescents with ADHD and PTSD	UCLA PTSD Reaction Index, GAD scale of Screen for Childhood Anxiety and Related Disorders, Columbia Impairment Scale, ADHD Rating Scale-IV, clinician-completed Clinical Global Impressions Severity Scale	Anxiolytic	Connor et al.[100]

TABLE 1 (Continued)

Drug	Model	Test	Effect	Refs.
Guanfacine	Children and adolescents with GAD, separation anxiety disorder, and/or social anxiety disorder	Dimensional anxiety scales: Pediatric Anxiety Rating Scale and Screen for Child Anxiety Related Emotional Disorders; Clinical Global Impression-Improvement (CGI-I) scale	Improvement in CGI-I	Strawn et al.[101]
Clonidine, guanfacine	Patients with PTSD	NA	Anxiolytic, attenuated agitation, and hyperarousal	Belkin and Schwartz[102]
Angiotensin-converting enzyme inhibitors				
Experimental studies				
Captopril	Doxorubicin-treated Wistar rats	OF, EPM, LDB	Anxiolytic	Aziriova et al.[103]
Lisinopril	SHR	OF	Anxiolytic	Repova et al.[104]
Enalapril, losartan	RHR	OF	Anxiolytic, reduced hyperactivity	Srinivasan et al.[105]
Electroacupuncture, candesartan, perindopril	SHR with chronic cerebral hypoperfusion	OFT, NOR, MWM	Anxiolytic, improved memory	Feng et al.[106]
Egg white-derived peptides TNGIIR and RVPSL	SHR	EPM	Anxiolytic	Yu et al.[107]
Clinical studies				
Captopril	Patients with CVD	NA	Elevated mood	Zubenko and Nixon[108]
Enalapril, captopril	Hypertensive patients	BDI, HSCL	Reversed depression and anxiety	Braszko et al.[109]
Angiotensin II type 1 receptor blockers				
Experimental studies				
Losartan	Bilaterally olfactory bulbectomized rats	EPM	Anxiolytic	Tashev and Ivanova[110]

(Continues)

TABLE 1 (Continued)

Drug	Model	Test	Effect	Refs.
Losartan	Female Long Evans rats, ovariectomy	EPM, OFT, NOR	Anxiolytic, improved memory	Campos et al.[111]
Losartan	Male BALB/c mice, LPS inflammation	MWM, NOR, passive avoidance, FST, EPM, marble burying task	Anxiolytic, improved learning and memory	Salmani et al.[112]
Candesartan	Wistar rats	EPM	Anxiolytic	Saavedra et al.[113]
Candesartan	SHR, LPS inflammation	MWM	Reduced memory impairment	Goel et al.[114]
Candesartan	Wistar Hannover rats, SHR, LPS inflammation	In vitro studies	Reduced brain inflammation	Benicky et al.[115]
Candesartan	Wistar Hannover rats, LPS inflammation, restraint stress	In vitro studies	Prevented LPS and restraint stress impact on CNS	Sánchez-Lemus et al.[116]
Candesartan	Sprague–Dawley rats, transient focal cerebral ischemia	In vitro studies	Protection from brain ischemia	Singh et al.[117]
Candesartan	Sprague–Dawley rats	EPM, FST, novelty-suppressed feeding test	Anxiolytic, antidepressant	Gong et al.[118]
Electroacupuncture, candesartan, perindopril	SHR, chronic cerebral hypoperfusion	OFT, NOR, MWM	Anxiolytic, improved memory	Feng et al.[106]
Irbesartan	Swiss albino mice, unpredictable chronic mild stress	Modified FST, TST, OFT	Anxiolytic, antidepressant	Ayyub et al.[119]
Telmisartan	C57BL/6N mice, C57BL/6J DIO mice, high fat diet	OFT, EPM	Anxiolytic	Huber et al.[120]
Clinical studies				
Valsartan	Anxiety-naïve patient	Subjective anxiety symptoms of generalized type	Anxiolytic	Shad[121]
ARBs	Highly traumatized civilian medical population	PTSD Symptom Scale, Clinician-Administered PTSD Scale	Decreased PTSD symptoms	Khoury et al.[122]

TABLE 1 (Continued)

Drug	Model	Test	Effect	Refs.
ARBs	Hypertensive patients	WMS-R Logical Memory II subtest, Rey Auditory Verbal Learning Test, Wechsler Adult Intelligence Scale, Trail Making Tests A and B, Animal Fluency, Vegetable Fluency, Boston Naming Test	Improved memory	Ho et al.[123]
Angiotensin-(1–7)				
Experimental studies				
i.c.v. Ang-(1–7)	(mRen2)27 hypertensive rats	EPM	Anxiolytic	Almeida-Santos et al.[124]
i.c.v. Ang-(1–7)	Wistar rats	EPM	Anxiolytic	Bild and Ciobica[125]
i.v./i.c. Ang-(1–7)	Wistar rats exposed to air-jet stress		Blocked tachycardia and pressor response	Martins Lima et al.[126]; Oscar et al.[127]
NA	ACE2 knock-in mice	EPM	Anxiolytic	Wang et al.[128]
NA	Transgenic rats TGR(A1–7)3292 overexpressing Ang-(1–7)	EPM	Anxiolytic	Kangussu et al.[129]; Moura Santos et al.[130]
NA	Transgenic rats TGR(A1–7)3292 overexpressing Ang-(1–7) exposed to air-jet stress		Reduced HR, reduced basal activity in renal sympathetic outflow	Moura Santos et al.[130]
Aldosterone antagonists				
Experimental studies				
Spironolactone	Streptozotocin-induced diabetic rats	Burying behavior test	Anxiolytic	López-Rubalcava et al.[131]
Spironolactone	Sprague–Dawley rats, social defeat stress and mild traumatic brain injury	EPM	Anxiolytic	Fox et al.[132]
Eplerenone	Wistar rats	OF, EPM	Anxiolytic	Hlavacova and Jezova[133]

(Continues)

TABLE 1 (Continued)

Drug	Model	Test	Effect	Refs.
Clinical studies				
Spironolactone	Patients with primary hyperaldosteronism	SF-36 questionnaire	Improved quality of life	Ahmed et al.[134]
ARNI				
Clinical studies				
Sacubitril/valsartan	HFrEF patients	Association between NYHA functional class and endorphin peptides	Improvement of patients' symptoms	Revuelta-López et al.[135]
Sacubitril/valsartan	HFrEF patients	BDI-II, BAI	Relief of depression and anxiety symptoms	Dereli et al.[136]
Statins				
Experimental studies				
Simvastatin	C57BL/6J mice	MWM, NOR, OFT, rotarod test, EPM	No effect on anxiety, impaired recognition, and spatial memory	Guo et al.[137]
Simvastatin	Sprague–Dawley rats	FST, EPM	Anxiolytic, antidepressant	Kilic et al.[138]
Atorvastatin	MPTP-lesioned C57BL/6 mouse model of Parkinson's disease	TST, EPM	Anxiolytic, antidepressant	Yan et al.[139]
Atorvastatin, simvastatin	Wistar albino rats, methionine-enriched diet with restricted vitamins B intake	OFT, EPM	Anxiolytic	Mijailovic et al.[140]
Atorvastatin, simvastatin, pravastatin	Wistar Albino Glaxo/Rijswijk rats, model of absence-type epilepsy, epileptogenesis and low-grade depression	FST, OF	Anxiolytic, antidepressant	Citraro et al.[141]
Rosuvastatin	Female Balb/c mice, chronic *Toxoplasma gondii* infection	OFT, NOR	Anxiolytic, improved memory	Evangelista et al.[142]

TABLE 1 (Continued)

Drug	Model	Test	Effect	Refs.
Simvastatin, rosuvastatin	Wistar rats	OF, EPM, MWM	Increased anxiety, impaired learning, and memory	Okudan and Belviranli[143]
Clinical studies				
Simvastatin	Patients with GAD	HAM-A	No support for efficacy in GAD	Mirzaei et al.[144]
Statins	Humans	Adverse drug reaction reporting, nonadherence	Anxiety, depression, aggression, suicidal tendency	Tatley a Savage[145]; Cham et al.[146]; Golomb et al.[147]; Duits a Bos[148]; Korhonen et al.[149]
Statins	Swedish population aged 15 years or older	Neuropsychiatric outcomes: self-injurious behavior or suicide attempt, death from suicide, depressive disorders, anxiety disorders, seizures	Reduced risk of depression, no effect on anxiety disorder	Molero et al.[150]
Fibrates				
Experimental studies				
Fenofibrate	NMRI mice, pentylenetetrazole-induced kindling seizure	EPM	Anxiolytic	Sarahian et al.[151]
Fenofibrate	Wistar rats, propionic acid-induced autism spectrum disorder	EPM	Anxiolytic	Mirza and Sharma[152]
Fenofibrate	Wistar rats, valproic acid-induced autism spectrum disorder	EPM	Anxiolytic	Mirza and Sharma[153]
Endocannabinoid congener N-palmitoylethanolamide	Swiss-Webster mice, social isolation, contextual fear conditioning	EPM, OF, FST, TST	Anxiolytic, antidepressant	Locci and Pinna[154]

(Continues)

TABLE 1 (Continued)

Drug	Model	Test	Effect	Refs.
Ivabradine				
Experimental studies				
Ivabradine	Wistar rats	Phenotyper, OF, EPM, LDB, NOR	No disturbing effects on anxiety, locomotion, or learning	Aziriova et al.[155]; Krajcirovicova et al.[156]
Ivabradine	Wistar rats, L-NAME-induced hypertension	Phenotyper	No disturbing effects on anxiety, locomotion, or learning	Aziriova et al.[155]
Clinical studies				
Ivabradine	CHF patients	SF-36 questionnaire, European quality of life-5 dimensions	Improved quality of life	Riccioni et al.[157]; Zugck et al.[158]
Ivabradine	Patients with chronic stable angina	SF-36 questionnaire	Improved quality of life	Riccioni et al.[159]
Calcium channel blockers				
Experimental studies				
Nifedipine, verapamil	Mice	Conditioned suppression of the motility test, the black and white box test	Anxiolytic (nifedipine in low dose), anxiogenic (nifedipine, verapamil in high dose)	Fulga and Stroescu[160]
Amlodipine	ICR mice, social defeat stress	EPM, TST	Anxiolytic, antidepressant	Joseph et al.[161]
Clinical studies				
Nifedipine	Phobic patients	Baseline anxiety ratings	No anxiolytic effect	Klein et al.[162]

TABLE 1 (Continued)

Drug	Model	Test	Effect	Refs.
Diuretics				
Experimental studies				
Furosemide, bumetanide	Long-Evans rats	Contextual fear conditioning, fear-potentiated startle, EPM, OFT	Anxiolytic effect on conditioned anxiety, no anxiolytic effect on unconditioned anxiety	Krystal et al.[163]
Vasodilators				
Experimental studies				
Nitroglycerin	Wistar rats, nitroglycerin-induced migraine	Modified EPM, LDB	Anxiogenic	Farajdokht et al.[164]
Nitroglycerin	Wistar rats, nitroglycerin-induced migraine	EPM, OFT, NOR	Anxiogenic, decreased locomotion, impaired spatial learning, and memory	Taheri et al.[165]
ICD				
Clinical studies				
ICD	Adults with an ICD		Depressive and anxiety disorders	Magyar-Russell et al.[166]

Abbreviations: ACE2, angiotensin-converting enzyme 2; Ang-(1–7), angiotensin-(1–7); ARNI, angiotensin receptor-neprilysin inhibitor; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CGI-I, Clinical Global Impression-Improvement; CHF, chronic heart failure; CVD, cardiovascular disease; EPM, elevated plus maze; FST, forced swim test; GAD, generalized anxiety disorder; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Rating Scale; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; HSCL, Hopkins Symptom Checklist; i.c.v., intracerebroventricular; ICD, implantable cardioverter-defibrillator; LDB, light-dark box test; LDT, light/dark test; L-NAME, L-NG-Nitro arginine methyl ester; LPS, lipopolysaccharides; MWM, Morris water maze; NA, not applicable; NOR, novel object recognition test; NYHA, New York Heart Association; OF, open field test; PTSD, posttraumatic stress disorder; RHR, renal hypertensive rats; SF-36 questionnaire, 36-Item Short Form Survey; SHR, spontaneously hypertensive rats; STAI, State-Trait Anxiety Index; TG, transgenic. TST, tail suspension test; UCLA, University of California at Los Angeles.

5.1.3 | Central sympatholytic drugs

Methyldopa, clonidine, and guanfacine are alpha-2 agonists that decrease sympathetic outflow on the level of the CNS. Their original indication was the treatment of hypertension,[168–170] however, currently these drugs are being tested and starting to be used in different indications.

Methyldopa

The experimental and clinical data regarding the effect of methyldopa on anxiety are sparse.

Experimental study

Methyldopa administration in normotensive rats reduced the number of entries to the center and time spent in the open arms of the EPM, suggesting anxiety-like behavior, while in hypertensive rats, methyldopa had the opposite effect.[95] There is a possibility, that like prazosin, methyldopa has different effects on anxiety in health and disease[95] (Table 1).

Clonidine

Clonidine is now being used for severe pain relief[171] and attention deficit hyperactivity disorder (ADHD) treatment.[172]

Experimental study

Clonidine injections in the bed nucleus of the stria terminalis decreased learned and unlearned (anxiety) fear in rats[96] (Table 1).

Clinical studies

In patients with GAD and panic disorder, clonidine decreased the frequency of anxiety attacks and mental symptoms.[98] In patients with PTSD, clonidine relieved symptoms of agitation and hyperarousal[102] (Table 1).

Guanfacine

Guanfacine is currently indicated for ADHD treatment.[173]

Experimental study

Guanfacine increased the time spent in the light compartment of the LDB which is a sign of anxiolytic-like behavior in mice. Its possible mechanism includes activation of alpha2-adrenergic receptors that decrease neuronal activity in amygdala[97] (Table 1).

Clinical studies

In a patient after cardiac surgery, guanfacine therapy effectively attenuated agitation and anxiety that was uncontrollable by conventional therapies.[99] In pediatric patients suffering from PTSD,[100] GAD, separation anxiety disorder, and social anxiety disorder, guanfacine extended-release, was well-tolerated and lead to global improvements[101] (Table 1).

5.2 | Modification of renin-angiotensin-aldosterone system and anxiety

Recently, attention has been focused on the role of brain RAS and on the potential therapeutic benefit of blocking this neurohumoral system. In animal models, inhibition of the angiotensin II type 1 (AT1) receptor in the brain by angiotensin II receptor blockers (ARBs) or inhibition of Ang II formation by angiotensin-converting enzyme (ACE)

inhibitors exhibits neuroprotective effects, reduces stress response acceleration and anxiety, alleviates chronic cerebrovascular inflammation and reduces acute inflammatory response.[174] The ultimate consequence is the protection of neurons from structural damage, which may be responsible for improving cognitive functions in the brain and alleviating anxiety.[110,114] The meta-analysis by Brownstein et al.[175] showed that the subjects receiving ACE inhibitors or ARBs presented better scores in the positive well-being, mental, and anxiety domains of the Quality of Life Questionnaire.

5.2.1 | Angiotensin-converting enzyme inhibitors

ACE inhibitors reduce the level of Ang II by the blockade of ACE converting Ang I to Ang II. Thus, reduction of preload, afterload, and growth-promoting and proliferating effect of angiotensin II is attenuated, resulting in hypotensive and anti-remodeling effects in the heart and vascular wall.[176-183] Indeed, ACE inhibitors not only reduce blood pressure, hospitalizations, cardiovascular events, and death in hypertensive patients when compared with diuretics and/or beta-blockers.[184,185] In the 90s, ACE inhibitors become a principal treatment of systolic heart failure (HF) with (SAVE, Survival and Ventricular Enlargement trial[186]; TRACE, Trandolapril Cardiac Evaluation study[187]) or without (CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study[188]; V-HeFT II, Veterans Administration Cooperative Vasodilator–Heart Failure Trial II[189]; SOLVD, Studies of Left Ventricular Dysfunction[190,191]) previous MI, improving survival. About 10 years later, ACE inhibitors were introduced in high-risk patients to reduce complications of atherosclerosis and mortality (HOPE, Heart Outcomes Prevention Evaluation; EUROPA, European trial on Reduction Of cardiac events with Perindopril among patients with stable coronary Artery disease; PEACE, Prevention of Events with ACE inhibition).[192] Besides cardiovascular protection, ACE inhibitors were shown to reduce anxiety-related behavior in rodent models and anxiety in clinical conditions (Figure 3).

Experimental studies

ACE inhibitor captopril exerted anxiolytic-like effect in doxorubicin-treated rats in a preventive experiment[103] and lisinopril reversed the alterations in terms of anxiety-like behavior in spontaneously hypertensive rats (SHRs).[104] Analogically, egg white-derived peptides TNGIIR and RVPSL that have ACE inhibitory activity, exerted an anxiolytic-like effect in SHRs in the EPM.[107] Renal hypertensive rats (RHR) showed hyperactivity in OFT, and anxiety-like behavior in the EPM. Treatment with enalapril and losartan significantly decreased the observed hyperactivity and anxiogenicity in RHR.[105] Perindopril increased the time spent in the central zone in the OFT, suggesting anxiolytic-like behavior and improved scores in the novel object recognition test, thus representing improved memory and learning in SHR with chronic cerebral hypoperfusion[106] (Table 1).

Clinical studies

The mood-modulating effect of captopril in humans has been described in 1984 by Zubenko and Nixon. They observed that captopril treatment due to another CVD elevated mood in patients with depressive symptoms.[108] In hypertensive patients, enalapril and captopril reversed depression and anxiety assessed by the Beck Depression Inventory and the Hopkins Symptom Checklist.[109] In another study of patients with anxiety or panic with stress-induced hypertension, the anti-anxiety effect of sublingual captopril was similar to diazepam[199] (Table 1).

5.2.2 | Angiotensin II type 1 receptor blockers

ARBs reduce the effect of Ang II by blockade of AT1 receptors. Differently to ACE inhibitors, ARBs do not stimulate bradykinin production, thus partly avoiding side effects such as cough or angioedema. Similarly to ACE inhibitors,

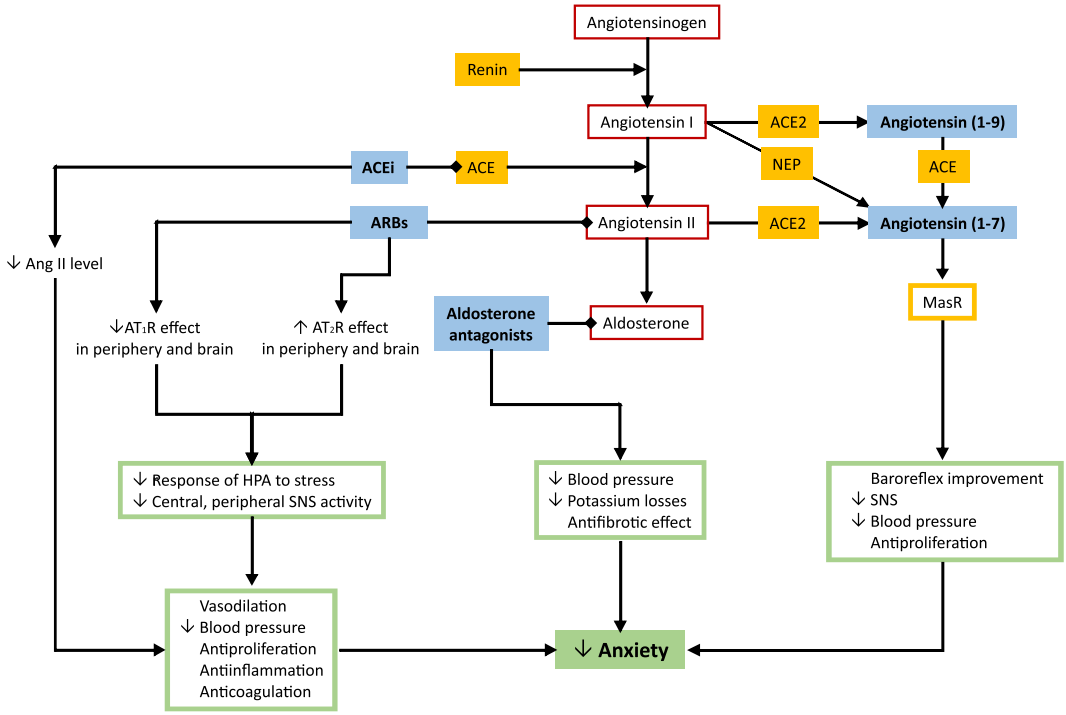

FIGURE 3 Modification of the renin-angiotensin-aldosterone system and its effect on anxiety. The inhibition of the renin-angiotensin system in the brain by angiotensin II type 1 receptor blockers (ARBs) or attenuating angiotensin II (Ang II) formation via angiotensin-converting enzyme inhibitors (ACEi) exhibits neuroprotective effects and reduces the level of the stress response and anxiety.[103,104,109,192] The possible mechanisms underlying the anxiolytic effect of ARBs and ACEi include the upregulation of the Ang II type 2 receptor (AT_2R) in the brain, and the enhancement of angiotensin (1–7) production acting on Mas receptors (MasR).[193] The stimulation of both AT_2R by Ang II and MasR by angiotensin (1–7) is considered to protect the cardiovascular system via vasodilation and antiproliferative effects[194,195] while exerting anxiolytic effects. Similarly, aldosterone antagonists reduce hemodynamic burden, potassium losses, profibrotic effects,[196,197] and anxiety level.[132,133] ACE, angiotensin-converting enzyme; AT_1R, angiotensin II type 1 receptor; HPA, hypothalamic-pituitary-adrenal axis; NEP, neutral-endopeptidase; SNS, sympathetic nervous system [Color figure can be viewed at wileyonlinelibrary.com]

ARBs reduce hemodynamic burden and exert antiremodeling effect.[181,200,201] In the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study with hypertensive patients, losartan exerted regression of left ventricular (LV) hypertrophy and reduction of cardiovascular events.[202] In heart failure CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) study, candesartan improved survival compared to placebo and co-treatment with candesartan and ACE inhibitors dominated over ACE inhibitors alone.[203] Moreover, in several heart failure trials, ARBs were equally effective compared to ACE inhibitors with fewer side effects.[204]

Analogically to ACE inhibitors, the pleiotropic nature of ARBs is projected into neuroprotective and mood modifying effects (Figure 3). Some preclinical and clinical studies with ARBs indicated the reduction of stress and anxiety in both rodents and humans.[193]

Experimental studies

Losartan showed anxiolytic-like behavior by increasing the number and time of open arms entries, the ratio of open/total entries and open/total time and decreasing the number and time of closed arm entries of the EPM in olfactory bulbectomized rats[110] and by the increased number of entries and percentage of time spent in the open arms of the EPM and increased time spent in the center of the OFT in ovariectomized Long Evans rats.[111] After i.p. lipopolysaccharide (LPS) injection in mice, losartan pretreatment improved memory impairment, increased the number of entries and time spent in open arms of the EPM, and decreased marble-burying.[112] Irbesartan increased time spent in the center of the OFT after unpredictable mild stress in mice.[119] Candesartan reduced anxiety represented by increased time spent in and the number of entries to the open arm of the EPM in rats,[113] increased time spent in the central zone of the OFT in SHR with chronic cerebral hypoperfusion and[106] increased time spent in and entries to the open arm of the EPM in LPS-induced neuroinflammation in SD rats.[118] Candesartan reduced memory impairment induced by LPS in SHRs[114] and in SHR with chronic cerebral hypoperfusion,[106] improved LPS-induced brain inflammation in Wistar Hannover rats and SHRs[115] and also protected from ischemia in the SD rat's brain.[117] Telmisartan reduced anxiety-like behavior in diet-induced obesity in mice[120] (Table 1).

Clinical studies

ARBs have decreased PTSD symptoms in the highly traumatized civilian medical population[122] and may be associated with a decreased risk of mood disorders.[205] Hypertensive patients using ARBs were found to have better-preserved memory.[123] The repeated onset of anxiety has been described in a patient after the discontinuation of valsartan therapy, while restarted valsartan treatment relieved anxiety symptoms completely[121] (Table 1).

All these actions of ARBs on mood and cognition are unrelated to cardiovascular effects. The possible mechanisms underlying the anxiolytic effect of ARBs include presumably the upregulation of angiotensin II type 2 (AT2) receptors in the brain,[194] while AT2 receptors exert antiproliferative, antioxidative, and anti-inflammatory action.[195] Candesartan prevented alterations in cortical benzodiazepine 1 receptors that were under AT1 receptor control in stress.[116] Losartan reduced markers of brain inflammation and oxidative stress,[112] attenuated the response of the HPA axis to stress and prevented cortical alterations via corticotrophin-releasing factor receptor 1 and benzodiazepine binding.[7] Valsartan decreased the activity of HPA axis and central and peripheral SNS activity in rats subjected to a forced swim stress[206] and restored hippocampal neurogenesis by upregulating the level of brain-derived neurotrophic factor (BDNF) protein in the brain (Figure 3).[207]

5.2.3 | Angiotensin-(1–7)

Angiotensin-(1–7) is formed by hydrolysis of Ang II by ACE2, carboxypeptidases, and prolyl-endopeptidases and by hydrolysis of Ang I by neutral-endopeptidase (NEP), prolyl-endopeptidase, and tymeth-oligopeptidase. Mas receptors mediate the actions of Ang-(1–7) in the CNS and peripheral tissues.[208,209] In the CNS, Ang-(1–7) induces various cardiovascular, metabolic, and non-cardiovascular effects.[196,210] Chronic administration of Ang-(1–7) facilitated baroreflex bradycardia at the nucleus tractus solitarii in Wistar rats,[211] reduced cardiac sympathetic tone in fructose-fed rats[212] and attenuated hypertension in deoxycorticosterone acetate (DOCA)–salt rats,[213] hypertensive transgenic (mRen2)27 rats[214] or Ang II-induced hypertension in SD rats (Figure 3).[215]

Experimental studies

Non-cardiovascular effects of Ang-(1–7) include attenuation of anxiety-like behavior that has been demonstrated in several experimental studies. The activation of AT2 and Mas receptors in the medial amygdaloid nucleus indicates anxiolytic-like behavior in mice.[216] Intracerebroventricular injection of Ang-(1–7) in transgenic (mRen2)27 hypertensive rats increased the percentage of entries into the open arms of the EPM.[124] ACE2 knock-in mice explored the open arms of the EPM significantly more than the wild type,[128] and intracerebroventricular administration of

Ang-(1–7) to Wistar rats increased percentage of time spent and frequency of entries in the open arms of the EPM.[125] Transgenic rats over-expressing Ang-(1–7) showed a significantly higher percentage in the number of open arms entries in the EPM.[129] They were also found to spend more time and enter the open arms of the EPM more often than the control SD rats[130] (Table 1). All these findings indicate the anxiolytic-like effect of ACE2-Ang-(1–7) cascade.

Of note, Ang-(1–7) has also the potential to modulate the cardiovascular response to emotional stress. In air-jet stress, the transgenic rats over-expressing Ang-(1–7) attenuated elevated heart rate and expressed reduced basal activity in renal sympathetic outflow compared to SD rats.[130] In Wistar rats exposed to air-jet stress, intravenous or intracerebral application of Ang-(1–7) blocked tachycardia and the pressor response[126,127] (Table 1) and the bradycardic effect of Ang-(1–7) was observed also after treatment with beta-adrenergic agonist isoproterenol.[126] These results indicate that Ang-(1–7) reduces the cardiovascular response to acute emotional stress and involves the Mas receptors.[126,127,130]

5.2.4 | Aldosterone antagonists

Aldosterone is produced by the zona glomerulosa of the adrenal cortex[217] and acts via mineralocorticoid receptors.[218] The principal role of aldosterone is the regulation of salt and water homeostasis by sodium and water absorption in the distal renal tubule. More recently, it was disclosed that aldosterone acts as a transcriptional factor of the cellular growth and proliferation in the heart, vasculature, and kidney, inducing excessive fibrosis and cardiovascular remodeling.[219] Aldosterone antagonists were originally considered to be potassium-sparing diuretics, applied to prevent hypokalemia during the treatment with loop diuretics.[220] At present, aldosterone antagonists in combination therapy are considered to be the drug of choice in resistant hypertension (ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial).[221–223] Moreover, aldosterone antagonists spironolactone and eplerenone added to conventional treatment are established drugs in the reduction of morbidity and mortality in patients with severe (RALES, Randomized Aldactone Evaluation Study)[197] or with moderate heart failure.[198]

In the brain, aldosterone acts on the hydroxysteroid dehydrogenase-2 (HSD2) neurons that represent a major input to the ventrolateral bed nucleus of the stria terminalis (BSTvl), a key control point for generating negative affective state. Thus, aldosterone might influence behavioral arousal.[224] Indeed, the elevation of plasma aldosterone level resulted in increased anxiety-like behavior in rats.[225]

Experimental studies

The administration of spironolactone in streptozotocin-induced diabetic rats showing increased anxiety-like behavior in burying behavior test exerted an anxiolytic-like effect.[131] Single subcutaneous injection of eplerenone, a selective aldosterone receptor antagonist, reduced ethological indices of anxiety-like behavior related to exploration and risk assessment behavior in Wistar rats.[133] A single subcutaneous administration of either spironolactone or mifepristone (a glucocorticoid receptor antagonist) partially reduced anxiety-like behavior in the EPM following social defeat stress and mild traumatic brain injury (TBI) in SD rats[132] (Table 1).

Clinical studies

In humans, primary hyperaldosteronism is linked to an elevated rate of GAD[226] and depressive symptoms.[227,228] Although spironolactone treatment in primary hyperaldosteronism improved the quality of life (QOL) measured by the 36-Item Short Form (SF-36) questionnaire,[134] unilateral adrenalectomy demonstrated faster and more profound QOL improvement (Table 1).[229]

5.2.5 | Simultaneous blockade of angiotensin II type 1 receptor and neprilysin (ARNI)

An additional approach to the inhibition of the RAS and SNS systems to attenuate vasoconstrictor, pro-inflammatory and pro-proliferative actions in CVDs could be the stimulation of the counterbalancing pathways such as the atrial (ANP) and brain natriuretic peptides (BNP). These peptides exert natriuretic, diuretic, and vasodilative effects while also inhibiting tissue growth and fibrosis.[230,231] Direct administration of these peptides requires a parenteral approach, which is technically demanding and not suitable for chronic heart diseases.[230] A simpler and more effective approach seems to be the slowing down of the splitting rate of these hormones by the inhibition of neprilysin (endopeptidase, vasopeptidase, neutral peptidase; NEP), the enzyme located in the cell membrane of various tissues.[233] Since neprilysin substrates include both, ANP/BNP and Ang II, its inhibition will not only increase the level of beneficial ANP/BNP but also adverse Ang II concentration, potentially counterbalancing the desirable vasodilative and antiproliferative effects of ANP/BNP. Therefore, sacubitril, an inhibitor of neprilysin, was combined with AT1 receptor blocker valsartan, thus mitigating the Ang II effects.[230,231] The PARADIGM HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) study with HF patients of NYHA (New York Heart Association) II/III severity showed that sacubitril/valsartan reduced the composite primary endpoint of cardiovascular death or HF hospitalization by 20% and even general mortality by 16% compared with the ACE inhibitor enalapril.[234,235] Sacubitril/valsartan has not only become one of the cornerstones in the treatment of HF with reduced ejection fraction[234] but may be considered for organ protection in a range of other cardiovascular pathologies.

Based on the rather complex pathophysiological background of sacubitril/valsartan actions, their potential impact on the mental state in terms of stress, anxiety, and depression modulation is difficult to predict. In addition to splitting natriuretic peptides, neprilysin degrades several other peptides exerting vasodilation and anti-proliferation, such as bradykinin, substance P, and adrenomedullin[236]; thus, the concentration of these substances supposedly increases during sacubitril/valsartan treatment. Indeed, in a study with 73 HF patients, sacubitril/valsartan resulted in the attenuation of soluble NEP activity along with an increase of ANP, substance P, and a glucagon-like peptide 1.[237] Moreover, NEP seems to be the principle peptidase responsible for degrading enkephalins in the intercalated cells of the amygdala.[238] Furthermore, the limited cleavage of endorphin peptides by NEP inhibition was suggested to promote symptomatic improvement in HF.[135]

Since ANP is produced both in the heart and in the CNS, its pleiotropic effects are assumed to contribute to neuropsychiatric diseases and stress-related conditions such as anxiety, major depression, addictive behaviors, panic attacks, and PTSDs.[238,239] In 117 patients with diastolic heart failure and proven anxiety, the plasma concentration of pro-ANP was negatively related to clinical anxiety, thus suggesting the potential anxiolytic effect of a circulating natriuretic peptide[241]; this effect might be related to an ANP-induced attenuation of ACTH and cortisol secretion.[242] Accordingly, the anxiety-reducing effect of the exercise was correlated with increased plasmatic ANP concentrations.[243]

Increasing the level of substance P, adrenomedullin, bradykinin, and enkephalins/endorphins could also modulate anxiety, although the data are sparse. Substance P (SP), a neuropeptide acting via a neurokinin type 1 (NK-1) receptor, is elevated in stressed conditions,[244] while the amygdala was suggested as the primary region mediating the SP-NK1 system on anxiety.[245] The NK-1 receptor's pharmacological antagonism or genetic modulation resulted in an anxiolytic response.[244]

Adrenomedullin, a vasoactive protein and tissue growth modulating factor, is not only a biomarker that predicts later cardiovascular pathologies,[246] but it seems to be related to psychological disturbances in terms of anxiety, stress, and depression. Five weeks of yoga training combined with psychoeducation led to lowered adrenomedullin levels, reduced anxiety, and sleep improvement.[247] Increased plasma adrenomedullin levels were associated with the development of anxiety disorders and LV hypertrophy in hypertensive patients.[248] On the other hand, mid-regional proadrenomedullin concentrations were inversely associated with anxiety in patients with diastolic heart dysfunction,[241] and the lack of adrenomedullin in CNS in genetically modulated mice was linked with hyperactivity

and overanxiousness compared with wild-type animals.[249] It seems that adrenomedullin may have both beneficial and deleterious actions regarding anxiety depending on the particular model. Similarly, bradykinin via its B1 or B2 receptors is considered to exert either protective or deleterious effects on depression and anxiety,[250–252] while the impact of enkephalins/endorphins in anxiety modulation remains to be established.

Clinical study

Only one clinical study investigated the impact of sacubitril/valsartan on anxiety and depression. In 115 symptomatic patients with systolic HF, the switch from an ACE inhibitor or ARB to sacubitril/valsartan resulted in the significant improvement of heart function along with a reduction of both depression and anxiety symptoms (Table 1).[136]

5.3 | Lipid modifying agents

5.3.1 | Statins

Statins competitively inhibit 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, the key enzyme in cholesterol biosynthesis in the liver.[253] The primary effect resides in the reduction of low-density lipoproteins (LDL). Statins were shown to reduce morbidity and mortality in a number of secondary prevention trials and even in primary prevention in patients with increased LDL but without organ affliction.[254] Additionally, statins express a number of pleiotropic effects including antioxidant, anti-inflammatory, and antiapoptotic actions resulting in improvement of antiproliferative action, attenuation of endothelial dysfunction, and stabilization of atherosclerotic plaques.[179,255–258]

Undesirably, the non-adherence to statins due to a number of side effects limits their clinical benefit. Besides myopathy presumably determined by the reduced production of coenzyme Q-10 (CoQ-10; Figure 4),[259] a number of mood and behavior affections were observed during statin treatment.

Experimental study

A high dose of simvastatin and rosuvastatin in healthy Wistar rats decreased the time spent in the center zone in the OFT, as well as the number of entries in the open arms and time spent in the open arms of the EPM, suggesting anxiety-like behavior[143] (Table 1).

Clinical studies

Pharmacovigilance databases reported anxiety, depression, aggression, suicidal tendency, cognitive, sleep, and other disorders,[145] and case studies reported irritability, aggression,[146,147] depressive symptoms,[146,148] nightmares, suicide attempts,[146] and experience of the somatic symptoms of anxiety[149] associated with antihyperlipidemic drugs, including statins (Table 1).

These adverse manifestations are supposedly linked to low cholesterol levels in plasma and brain. It has been observed that a low level of cholesterol is associated with violence,[262] suicidal attempts in patients with major depressive disorder,[263] aggression and hostility in suicide attempters,[264] while lower plasma levels of essential fatty acids are associated with self-harm, impulsivity, and depression.[265]

The brain contains a high proportion of cholesterol, representing 23% of free cholesterol present in the whole body.[266] Cholesterol is essential for determining the biophysical properties of membranes. In the mature brain, cholesterol is a part of the exocytosis apparatus in presynaptic terminals and of the biogenesis and transport of synaptic vesicles, which mediates axonal transport along microtubules, promotes cell adhesion between postsynaptic and presynaptic ends, and induces synaptogenesis.[267] Brain cholesterol is synthesized in situ with no evidence of the transfer of plasma lipoproteins through an intact blood–brain barrier.[268] Cholesterol may modulate

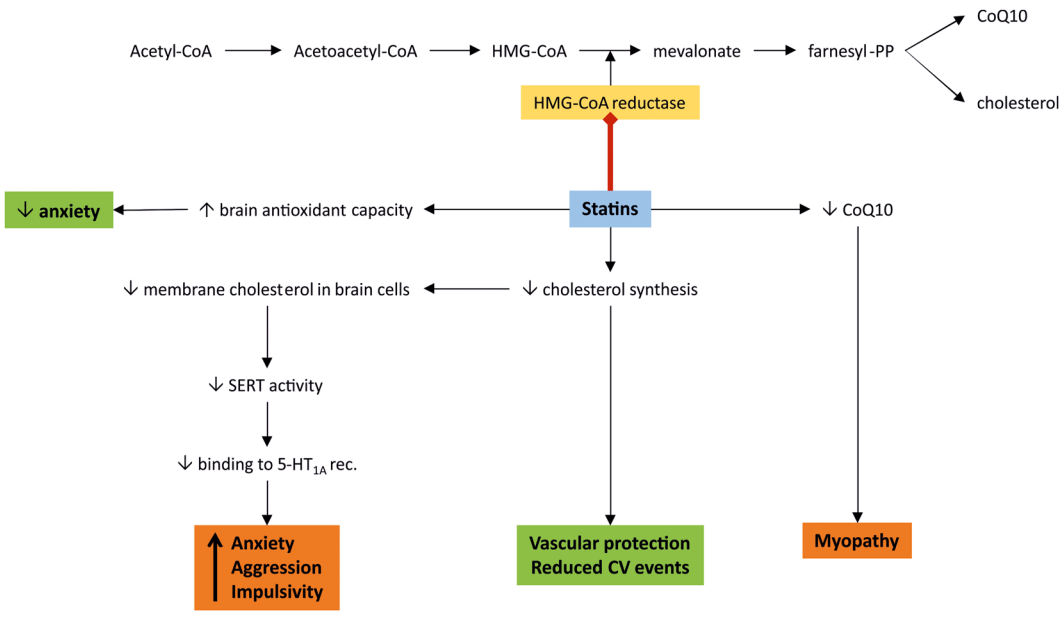

FIGURE 4 The role of statins on mood and behavior. Statins competitively inhibit 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, the key enzyme in cholesterol biosynthesis in the liver.[252] Reducing the cholesterol level is considered protective for the vasculature,[254] while the simultaneous reduction of the synthesis of coenzyme Q-10 (CoQ-10) could result in undesirable myopathy.[258] However, a reduction of membrane cholesterol in the brain neurons decreased serotonin reuptake transporter (SERT) activity and attenuated the level of ligand binding to the serotonin$_{1A}$ (5-HT$_{1A}$) receptor[259] that resulted in anxiety, aggressive and impulsive behavior.[260] On the other hand, enhanced antioxidant capacity in the brain after statin use mitigates anxiety.[139,140] CoA, coenzyme A; CV, cardiovascular; Farnesyl-PP, farnesyl pyrophosphate [Color figure can be viewed at wileyonlinelibrary.com]

the function of G-protein-coupled receptors (GPCRs) directly through a specific interaction with GPCRs with conformational change in the receptor, indirectly by altering the membrane physical properties or through a combination of both.[260] Upon statin treatment, a reduction of membrane cholesterol decreased the activity of serotonin reuptake transporter (SERT) and attenuated the level of ligand binding to 5HT$_{1A}$ receptor that belongs to the GPCRs family.[260] Indeed, there is an established relationship between depressed central serotonergic activity and aggressive and impulsive behavior (Figure 4).[261,269] In male cynomolgus monkeys, a low-fat and low-cholesterol diet decreased serotonergic activity within the hypothalamus[269] and led to aggressive behavior.[270] In human males, a correlation between low serum total cholesterol and low cerebrospinal fluid (CSF) levels of the main serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) has been found, which predisposes the males to violent and risky behavior.[271] Low levels of serotonin and 5-HIAA were found in post-mortem examinations of brain-stem tissues of suicide victims,[272] a low concentration of 5-HIAA in the CSF were detected in attempted suicides who have killed their children[273] and in murderers and suicide attempters.[274]

On the other hand, some experimental and clinical studies have not confirmed the link between statin use and suicide tendency, aggression, or anxiety.

Experimental studies

Simvastatin treatment in mice caused a deficiency in recognition and spatial memory but had no effect on motor ability or anxiety-like behavior.[137] Simvastatin administration to healthy SD rats increased the time spent in the open arms of the EPM[138]; atorvastatin increased the ratio time spent in the open arms of the EPM in 1-methyl-4-

phenyl-1,2,3,6-tetrahydropyridine (MPTP) mice[139]; atorvastatin and simvastatin in rats fed with a methionine-enriched diet improved exploratory and locomotor activity in the OFT and EPM[140]; atorvastatin, simvastatin and pravastatin treatment in Wistar-Albino-Glaxo from Rijswijk (WAG/Rij) rats increased the time spent in and number of entries to the center of the OFT[141]; and rosuvastatin increased the time spent in and locomotion in the central zone of the OFT in mice infected with the chronic ME-49 strain of *Toxoplasma gondii*.[142] All of these findings point to anxiolytic-like behavior after statin use in experimental animals. Possible mechanisms include decreased brain expression of NADPH oxidase 2,[139] lipid peroxidation and increased brain activity of the antioxidant enzymes, catalase, and superoxide dismutase after statin administration[140] (Table 1).

Clinical studies

Recent studies of Molero et al.[150] and Mirzaei et al.[144] have not found an association between statin treatment in patients and suicidality or anxiety disorders (Table 1).

5.3.2 | Fibrates

Fenofibrate activates the peroxisome proliferator-activated receptor alpha (PPARα) thus increasing lipolysis, activating lipoprotein lipase, and reducing apoprotein C-III. It is used to treat primary hypercholesterolemia, mixed dyslipidemia, and severe hypertriglyceridemia.[275]

Experimental studies

In the pentylenetetrazol-induced kindling seizure model in mice, the fenofibrate treatment increased the time spent in the open arms and the percentage of open arm entries in the EPM.[151] Fenofibrate in autism spectrum disorder in rats increased the percentage of time spent in and number of entries to the open arm in the EPM.[152,153] It seems that this anxiolytic property of fenofibrate includes antioxidative, anti-inflammatory,[153] and neurosteroidogenic effects through PPARα activation in the brain[154] (Table 1).

5.4 | Other cardiovascular drugs and anxiety

5.4.1 | Ivabradine

Increased heart rate is an independent risk factor of cardiovascular mortality. Ivabradine is a selective inhibitor of hyperpolarization-activated channel in the sinoatrial node responsible for pacemaker generation through the I_f (funny) current. It reduces the spontaneous pacemaker activity, leading to a slowing of the heart rate without inducing negative inotropy as beta-blockers do.[276] In the SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial), ivabradine decreased the composite end-point of mortality and hospitalizations for HF.[277] Moreover, a number of ivabradine pleiotropic effects have been described, including anti-inflammatory, anti-apoptotic, antiremodeling, oxidative stress-reducing, and hypotensive actions,[278–283] that may be potentially beneficial in several off-labeled indications.[284]

The potential effects of ivabradine on mood, cognition, and behavior in experimental animals and humans remain elusive.

Experimental studies

In our laboratory, no disturbing effects of ivabradine were observed on anxiety, locomotion, or learning in healthy and NG-nitro-L-arginine methyl ester (L-NAME)-induced hypertensive rats, while some of these parameters were

even improved.[155,156] Moreover, the survival of rats with isoproterenol-induced myocardial injury was significantly improved[285] (Table 1).

Clinical studies

Scarce clinical studies revealed that the administration of ivabradine in chronic heart failure patients[157,158] and patients with chronic stable angina pectoris[159] improved their quality of life (Table 1).

A recent study revealed that ivabradine may affect brain functions by its agonist activity in the $GABA_A$ channel in the brain, which is similar to diazepam. It was also demonstrated that ivabradine pretreatment attenuated pentylenetetrazol- and picrotoxin-induced epileptic seizures in mice that were accompanied by a decrease of lipid peroxidation in the prefrontal cortex, hippocampus, and striatum, as well as by a reduction of cleaved-caspase 3 expression, a marker of apoptosis, in various hippocampal regions.[286]

5.4.2 | Calcium channel blockers

Amlodipine, nifedipine, and verapamil are L-type calcium channel blockers used to treat hypertension,[287] angina,[288] and to control supraventricular tachyarrhythmias.[289]

Experimental studies

Amlodipine,[161] nifedipine, and verapamil[160] increased anxiety-like behavior in mice (Table 1).

Clinical study

A single dose of nifedipine had no reducing effect on anxiety in phobic patients with generalized anxiety[162] (Table 1).

5.4.3 | Diuretics

Furosemide is a loop diuretic indicated for the treatment of volume overload and edema associated with congestive heart failure,[290] liver failure with cirrhosis,[291] and renal failure, including nephrotic syndrome.[292]

Experimental study

In conditioned models of anxiety in rats, furosemide decreased freezing in contextual fear-conditioning, thus indicating anxiolytic-like behavior[163] (Table 1).

5.4.4 | Vasodilators

Nitroglycerin is a nitrate vasodilator used for symptomatic relief in myocardial ischemia,[293] and the treatment of MI,[294] hypertensive emergencies[295] and heart failure[296] predominantly through the venodilatation-induced reduction of the hemodynamic burden.

Experimental studies

Chronic nitroglycerin administration in rats led to a decreased percentage of entries and time spent in the open arms of the EPM and reduced time to enter the dark part of the LDB with fewer transitions and decreased time spent in light part of the LDB, all indicating anxiety-like behavior[164,165] (Table 1).

6 | IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR AND ANXIETY

The implantable cardioverter-defibrillator (ICD) represents an important tool for modifying cardiovascular mortality in patients with electrical instability and potentially fatal dysrhythmia. The ICD is used to intervene in life-endangering ventricular dysrhythmias and prevent sudden cardiac death.[166] The ICD is an electronic device that continuously monitors heart rhythms and at the onset of an abnormal heart rhythm, it delivers energy in the form of pacing or shocks to restore sinus rhythm.[298] In the past, secondary prevention was administered to patients experiencing life-threatening arrhythmia, but at present, primary prevention is mainly used for patients with serious left ventricular dysfunction who have not experienced potentially fatal dysrhythmia.[299]

6.1 | Clinical studies

Some ICD patients suffer from mental alterations in terms of depression and anxiety, which in turn, may influence adherence to the device. A number of conditions are thought to underlie mental disturbances, such as the severity of the cardiac disorder, concerns regarding cardiovascular prognosis, fear of ICD tolerance, and the unpredictable nature of ICD shocks.[299,300] Several reviews on the prevalence of depression/anxiety in ICD patients revealed inhomogeneous data due to small patient samples, different testing modes, or variable indications to ICD.[301,302] A systematic review of forty-five studies including over 5000 patients concluded that based on the analyzed studies there is an approximately 20% prevalence rate for both anxiety and depression in patients with ICD, which is similar to other cardiovascular pathologies.[166] It has recently been revealed that patients with depression at the time of ICD implantation had a greater risk of mortality, while anxiety only showed a trend.[304] Moreover, in a large cohort of ICD recipients, the probability of anxiety and depression symptoms was associated with younger age, living alone, previous history of MI and heart failure, and female gender.[305] Suggestively, the patient's psychological characteristics are greater predictors of a poor quality of life than the actual shock experience.[306] A cognitive behavioral rehabilitation program for patients with ICD in terms of ICD shock and stress management seems to attenuate symptoms of depression and anxiety,[306,307] while specific factors should be addressed to improve outcomes (Table 1).[305]

7 | DISCUSSION

CVDs, anxiety, and depression are highly prevalent pathologies that deteriorate the quality of life and prognosis of patients.[309] Patients with current cardiovascular alterations such as hypertension-induced target organ damage, MI, cerebral ischemia, heart failure, or kidney dysfunction frequently experience mental disorders, including feelings of worry, anxiety or depression. These states may result from or be deteriorated by the primary cardiovascular pathology. Vice-versa, anxiety or depression may worsen the course of CVDs or trigger cardiac or vascular complications. Importantly, drugs used to treat cardiovascular disorders seem to affect the development and severity of anxiety or depression.[310]

A considerable number of experimental and clinical studies have strived to determine the impact of different cardiovascular drug groups on anxiety or depression. This review has focused on presenting the impact of currently used, well-established cardiovascular treatment for mental alterations regarding anxiety and related disorders and on delineating potential future clinical and research directions.

Beta-blockers and drugs interfering with the renin-angiotensin-aldosterone system seem to be of considerable importance. Propranolol, the nonselective beta-adrenergic receptor antagonist, exerted an anxiolytic effect in both experimental and clinical settings supposedly due to its sympatholytic action.[86] However, this drug is seldomly used in current clinical practice due to a number of novel beta-blockers with higher receptor selectivity and fewer side

effects. We assume that selective beta-blockers could not only improve energy metabolism and reduce hemodynamic alterations and proarrhythmogenic potential induced by excessive sympathetic excitation[311] but they might be more effective in alleviating mental stress and anxiety disorders. Indeed, selective beta-blockers decreased symptoms of anxiety in patients with chronic heart failure (metoprolol),[81] mitral valve prolapse syndrome (celiprolol)[70] and anxiety-related mental health problems (atenolol).[82]

Prazosin, the alpha-1 antagonist, is currently used more often for indications other than hypertension. Thanks to its anxiolytic effect, it is used in the treatment of PTSD with related sleep disorders and nightmares[90–92] and in the treatment of alcoholic use disorder.[93,94] Central sympatholytic drugs such as clonidine and guanfacine represent another group of antihypertensives that have demonstrated a positive effect on anxiety symptoms. Clonidine[96,98,102] as well as guanfacine[97,99–101] exerted an anxiolytic effect in experimental and clinical settings and may be useful in the treatment of PTSD and GAD.

Both ACE inhibitors[103–106,108,109,198] and ARBs[106,110–114,116–123,193–195,205–207] indicate well-established mental effects in reducing neuropsychological alterations, including stress and anxiety. The direct neurocellular protection on the level of the brain structure concerning their anti-inflammatory and antiproliferative action along with improving hemodynamics of the CNS[112,194,195,207] could prove to be the underlying pathomechanism. The nonclassical ACE2/Ang-(1–7)/Mas receptor pathway opposes the vasoconstriction, profibrotic and inflammatory action of the ACE/Ang II/AT1 receptor pathway protecting the cardiovascular system.[196,209,210] Its stimulation appears to be beneficial in terms of reducing undesirable stress response and anxiety[124–130] by exerting vasodilatation, antiproliferation, anti-inflammation and oxidative stress reduction in the cardiovascular system[209,210,311] and potentially in the CNS.[196] Aldosterone, another important player of RAAS, seems to induce anxiety,[225] while aldosterone receptor blockers were shown to attenuate this undesirable emotional disorder.[131–134] The data presenting effects of ARNI on anxiety are sparse. The dual AT1/neprilysin blockade not only reduces the effect of Ang II but enhances the level of various peptides (ANP, bradykinin, substance P, enkephalins), which are considered to exert cardiovascular protection,[230,231] while some are believed to interfere with stress-related conditions such as anxiety.[136,239,240] Well-controlled prospective studies with angiotensin II/neprilysin inhibition focused on anxiety and depression are warranted.

Statin's various neuropsychiatric adverse effects in terms of aggression, depression, or impulsivity[145–149] appear to be related to low cholesterol and omega-3 fatty acid levels[262–265] and correlate with decreased serotonergic activity in the brain.[260,261,269,271] Another potentially harmful condition could be statin-induced CoQ-10 depletion associated with anaerobic metabolism, mitochondrial bioenergetic impairment,[313] and increased oxidizability of LDL cholesterol,[314] which might induce ischemia and functional alterations in CNS. On the contrary, statin's pleiotropic effects including antiproliferation, antioxidation, and anti-inflammation[256] could underlie some protective findings in terms of anxiety mitigation demonstrated in experimental settings[138–142]; the same can be valid for fenofibrate's anxiolytic effects.[151–153]

Although ivabradine's protection in HF patients is restricted,[277] it could be beneficial in several off-labeled indications due to its various pleiotropic actions.[284] No disturbing effects of ivabradine on anxiety were observed in animal experiments,[155,156] while in patients with CVDs, ivabradine administration was even associated with improved quality of life.[157–159] The experimental and clinical studies regarding the effect of other cardiovascular drugs including antihypertensives, calcium channel blockers, diuretics, vasodilators, and antiarrhythmics regarding mood or behavior are sparse and not directly related to anxiety.

The coronavirus disease 2019 (COVID-19) pandemic has influenced all areas of medical practice. Although acute respiratory distress syndrome (ARDS) is the most challenging and harmful condition resulting in the serious course of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the affliction of the cardiovascular,[314,315] digestive,[317] and CNSs, among others,[318] are rather frequent complications. Moreover, stress and anxiety were disclosed in different groups of health care providers, such as dental practitioners,[319] other healthcare workers,[319,320] health profession students,[322] social workers[323] and in patients afflicted by COVID-19.[324] The underlying reasons for mental disturbances involve fear of exposure to infection, proximity to death generated by the pandemic, extreme

working demands, economic uncertainty, disruption of social life, insufficient knowledge of the disease and SARS-CoV-2-induced physical disturbances in terms of endothelial inflammation, microvascular thrombosis, ischemia from pulmonary damage and multiple organ dysfunctions.[318,319,321,323] In addition to professional psychological support for those groups with increased risk of stress, anxiety, and depression development, the consideration of the potential mental effects of the current medical treatment of cardiovascular, respiratory, and other system dysfunctions could offer significant benefits for anxiety-afflicted patients.

It is becoming obvious that health-related quality of life depends in substantial measure on the mutual interactions between CVDs and mental disorders including anxiety. In the near future, anxiety resulting from cardiovascular pathology or developed independently from heart disorder could rank among the targeted risk factors deteriorating cardiovascular prognosis. Thus, knowledge of the interference of cardiovascular drugs with the mental state of the patient will improve the approach to the choice of optimal treatment, in particular, of cardiovascular affliction.

8 | CONCLUSION

Negative emotions, mood and behavior alterations, and various cardiovascular pathologies are tightly bound, exerting a causal bidirectional relationship potentiating each other. The neurohumoral activation seems to underlie this cardiovascular-psychological interference. It is of utmost importance to reveal signs and symptoms of altered mood, cognition, and behavior in terms of distress and anxiety in cardiovascular patients to prevent worsening of their conditions. Moreover, various principal cardiovascular drugs can interplay with anxiety and depression symptoms. In general, beta-blockers, ACE inhibitors, ARBs, aldosterone receptor blockers, and sacubitril/valsartan are considered to exert an anxiolytic effect in animal experiments and clinical settings. Statins, fibrates, and central sympatholytic drugs exert a prevailingly protective impact on mood and anxiety, and ivabradine expressed a neutral mental and cognitive impact. Improving the level of knowledge of these therapeutics regarding their possible interference with mood, mind, and behavior could help manage both the cardiovascular and mental burden of the population with cardiovascular pathologies. It warrants future clinical trials focused not only on reducing cardiovascular morbidity and mortality but also on protecting patients' well-being by preserving the normal state of mood and mental integrity.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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