Review article

Hypertension in Association With Anxiety and Depression – A Narrative Review

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Abstract

Hypertension is recognized as a multifactorial disorder. Anxiety disorders, depressive disorder, psychosocial stress and certain individual psychological characteristics can influence the development and course of hypertension. Likewise, certain antidepressants can impact blood pressure. Association of anxiety disorders and depression with hypertension is bidirectional, so hypertensive patients are at risk of anxiety or depression. Monitoring the blood pressure of patients with anxiety disorders and depression, screening for anxiety and depression in patients with arterial hypertension and understanding pathophysiological mechanisms is important for future prevention and treatment strategies. This narrative review will briefly summarize current knowledge about the association of anxiety and depression with the risk of development of hypertension. Likewise, certain psychological factors and pathophysiological mechanisms in stress that are of importance for the association of hypertension with anxiety and depression are pointed out in this review, and effects of commonly used antidepressants are also considered.

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Introduction

Hypertension is a common chronic disorder in the general population and is itself an important risk factor for cardiovascular disease (1). According to WHO reports, in 2015, about ¼ of the world's adult population suffered from hypertension and about 40% of cardiovascular deaths were connected to hypertension (2). Blacher et al. showed that each increase of blood pressure by 10 mmHg raises the risk of severe cardiovascular disease complications and death by almost 20% (2).

Multifactorial aetiology of hypertension includes genetic predisposition as an unmodifiable factor and several potential modifiable factors. The risk of development of hypertension increases with age, especially in women, who are under lower risk in the reproductive period than men. The most important risk factors are smoking, sedentary lifestyle, excessive salt intake and high-calorie food intake, adiposity, as well as stress, anxiety and depression (3). Although the association of hypertension with stress, anxiety and depression has been studied for decades, study data are controversial and the underlying pathophysiological mechanisms have not been completely understood. However, it is known that hypertension is understood as a psychosomatic disorder, where psychological factors can play an important role in its development and can have an impact on its course and treatment. There is an impact of psychological factors, psychosocial stressors and mental disorders on the cardiovascular system (4). Type A personality, emotional distress, anxiety and depression have the greatest impact on blood pressure (4).

Recommendations for management of hypertension published in 2018 by the European Society of Cardiology/European Society of Hypertension (ESC/ESH) include psychosocial factors as risk factors for hypertension, while the British National Institute for Health and Clinical Excellence (NICE) recommended that management of hypertension in adults in primary healthcare settings include interventions for reducing stress and achieving relaxation (5).

The aim of this review is to summarize current knowledge about the association of anxiety and depression with the risk of development of hypertension. Likewise, certain psychological factors and pathophysiological mechanisms in stress that are of importance for the association of hypertension with anxiety and depression are pointed out in this review. Effects of commonly used antidepressants are also considered.

Methods

In order to summarize current knowledge about the association of anxiety and depression with the development of hypertension, we searched for relevant literature using PubMed, ScienceDirect, SpringerLink, PsycNet and Elsevier until February 2022. Keywords included were blood pressure, hypertension, anxiety, depression and stress.

Blood pressure control

The physiological process of blood pressure control is complex and involves regulation of volume and natriuresis, as proposed by Guyton, with rapid control (within seconds or minutes) of vessel resistance by the central nervous system (CNS) and the sympathetic nervous system (SNS), with circadian control (within hours) mostly dependent on activity of the renin-angiotensin-aldosterone-system (RAAS) and with long-term control (within days) mostly reflecting salt intake and activity of RAAS (6).

Antihypertensive drugs act through sodium/volume regulation, renin-angiotensin system and the sympathetic nervous system. Antihypertensive drugs that act through sodium/volume regulation (diuretics and calcium-channels blockers) or through the renin-angiotensin system (angiotensin converting-enzyme inhibitors and angiotensin receptor blockers) manage to control

hypertension in at least 75% or more cases (7). 76% of adult patients diagnosed with hypertension in the USA have suboptimally regulated blood pressure (BP) despite appropriate medication and changes in lifestyle (8). In a minority of hypertensive patients, drugs that act through SNS manage to control hypertension better than the drugs mentioned above, so the sympathetic nervous system seems to have a key role (known as neurogenic hypertension in earlier literature) (7). Severe hypertension of non-secondary origin, treatment-resistant hypertension (failure of drug combinations that affect sodium/volume and RAAS) and paroxysmal hypertension (unprovoked severe BP elevation in patients without pheochromocytoma) are considered to be associated with psychological factors (7). Certain studies revealed high levels of anxiety among patients with treatment-resistant hypertension (8). Paroxysmal episodes of high BP have been observed in patients with unusually severe trauma who deny any emotions and in patients that minimize emotional distress (7). Paroxysmal hypertension is often managed acutely with anxiolytics and/or alfa/beta-blockers, and these drugs are also effective in long-term treatment by reducing the magnitude of BP elevation attacks (7). Likewise, antidepressants are shown to be successful in preventing paroxysmal BP elevation (7). Patients who complain of frequent variations in BP, with particularly high levels accompanied by rapid heartbeat, may also benefit from SNS-targeting medications (7).

In the 1930s, Franz Alexander considered the importance of psychological variables in hypertension and he pointed out the relationship of hypertension with repressed hostility (9). Expressing anger was shown to be inversely related to blood pressure (9). Likewise, reporting less emotional distress and less anxiety negatively affects the blood pressure (9). Individuals who are defensive also tend to have higher blood pressure (7).

Psychosocial stress is thought to be involved in the development of hypertension (10, 11). The risk of developing hypertension is associated with chronic stress, where the intensity of stress is more important than the specific type of stress (10). Higher levels of perceived chronic stress, rather than low intensity and short-term stress, are more likely to be accompanied by psychological and behavioural changes that increase the risk of hypertension (10). Stronger effects of chronic stress on blood pressure and incident hypertension are seen in women than in men (10). These effects are possibly linked to women being more exposed to psychosocial stressors and having more intense and prolonged emotional and physiological reactions (10).

In the Jackson Heart Study, a community-based cohort of black people, moderate and high perceived stress over time were associated with a significantly higher risk (15% and 22%, respectively) of incident hypertension over a median of seven years, compared to sustained low perceived stress (10). Consistent results were demonstrated in the Coronary Artery Risk Development in Young Adults study (CARDIA). The CARDIA study among black and white participants showed that increasing or sustained levels of stress are associated with incident hypertension among young adults (10). Therefore, evaluating prolonged and repeated stress over time can be an important part of primary prevention of hypertension and subsequent risk of cardiovascular disease (10).

Psychological stressors, according to Lazarus, are defined as perceived threats to a person's well-being that tax or exceed own coping capacity (12). Individual differences in coping resources are based on appraisal processes in forebrain neural circuits, where information is assessed in terms of personal relevance and potential threat, after which peripheral physiological reactions are initiated (12). The main response to stressors are immediate changes in the sympathetic and parasympathetic nervous system and hypothalamic-pituitary-adrenal axis, which then influence cardiac output and peripheral vascular resistance to redirect blood flow in peripheral tissue according to behavioural needs (12). Cortical and subcortical circuits, according to appraised stressors, generate anticipatory visceromotor commands to change

cardiovascular reactions in order to prepare individuals for a behavioural response, and those reactions can be exaggerated in the form of excessive increase of heart rate or blood pressure (12). Such exaggerated cardiovascular reactions, when repeated, can have cumulative consequences for cardiovascular disease and cardiovascular incidents among vulnerable individuals (12). Brain-imaging studies show that individuals with excessive increase of heart rate and blood pressure in stressful situations exhibit higher activity in the anterior cingulate cortex, medial prefrontal cortex, insula, hippocampus, basal ganglia, periaqueductal grey matter, pons and amygdala (12).

Short-term psychological stressors evoke cardiovascular reactions which are adaptive, providing hemodynamic and metabolic support for surviving behaviour (known as the fight or flight reaction) (12). However, cardiovascular reactions that are evoked by stressors for a long period of time or in a repeated manner initiate or exacerbate pathophysiological changes in the heart and vasculature (12). Blood pressure is controlled by baroreceptors mainly distributed in the bulbus of the carotid artery and the aortic arch (12). Increase of blood pressure causes stretching of the baroreceptors, followed by transmission of information through vagal and glossopharyngeal pathways toward nucleus tractus solitarius in the brainstem, which makes neural connections to pre-autonomic nuclei in the brainstem and to the forebrain, such as the ventromedial prefrontal cortex, anterior cingulate cortex, insula and amygdala, which are key regions in threat appraisal (12). These pathways enable modifications in the operating characteristics of the baroreflex through various behaviours, psychological stress, physical activity and particular stages of lifespan and can have a role in disease risk (12). Given these findings, it is necessary to study the potential genetic and developmental causes of individual differences in central control of cardiovascular reactions and to prevent psychological reactions and behaviours that increase the risk of cardiovascular disease in response to stress.

Changes of hypothalamic pituitary adrenal (HPA) axis functioning also underlie stress-induced cardiovascular reactions. Chronic psychosocial stress causes continuous secretion of HPA axis hormones, such as cortisol, which lead to resistance of glucocorticoid receptors and consequently reduce sensitivity of the immune system to anti-inflammatory action, thus promoting mild chronic pro-inflammatory state (11).

Hypertension then develops in the manner that high levels of cortisol inhibit the expression of nitric oxide synthase and thus decrease the availability of endothelial nitric oxide and increase regional vascular resistance (11). Chronic low-intensity inflammation also leads to the development of obesity, primarily with intra-abdominal accumulation of visceral fat, increased salt retention and insulin resistance (11). Increased levels of cortisol and catecholamines in blood, urine and saliva are considered markers of chronic psychosocial stress, but are influenced by physiological fluctuations in circadian rhythms and transient stressors, while hair cortisol concentration is probably a more reliable biological marker reflecting chronic psychosocial stress since cortisol accumulates in the hair for several months (11). In the study by Bautista, individuals with high hair cortisol concentrations were twice as likely to be hypertensive compared to those with low levels of cortisol in their hair (11). There exists also an association of alexithymia, which is characterized by an inability to recognize and express emotions, with hypertension (7).

Hostility, as a personality trait, is a long-term risk factor for hypertension in the general population (CARDIA study), which also negatively affects the prognosis of coronary heart disease (13). Hostile individuals have higher blood pressure and higher rates of cardiovascular morbidity and mortality (13). Hostile individuals are cynical and suspicious toward others, their emotions and behaviour cause interpersonal conflicts and lead to a possible lack of social support with perceived fewer coping resources, which can result in difficulties for managing chronic conditions like hypertension and encourage unhealthy habits such as tobacco or alcohol consumption (13). Type A personality, characterized by anger, hostility and impatience,

increases the risk of coronary heart disease and is a predictor of sudden cardiac death (4).

Association of anxiety and hypertension

Anxiety disorders are the most common mental disorders today, with a lifetime risk of occurrence of about 13.5% (2). Likewise, according to data of the European Study of the Epidemiology of Mental Disorders, the most frequent disorder is the panic disorder – 12.8% will be diagnosed with it (2). Anxiety disorders seem to have a central role among all mental disorders associated with hypertension (1). Systematic review and meta-analysis of cross-sectional and prospective studies by Pan et al. supported the association between anxiety and increased risk of hypertension (3). Pan et al. conducted a meta-analysis and found significant correlation between anxiety and hypertension in cross-sectional studies and longitudinal association in prospective studies, supporting earlier findings of anxiety as an independent risk factor for incident hypertension (14). In the Mechanisms and Outcomes of Myocardial Silent Ischemia (MOMSI) Study, incident hypertension in the evaluated period of one year was highly associated with baseline anxiety in middle-aged women, even after adjusting for factors of age, sex, BMI, smoking and psychopharmacotherapy (15). Data from World Mental Health Surveys show that of all anxiety disorders, diagnoses of panic disorder, social phobia and specific phobia have been associated with developing hypertension in the period of 11.7 to 34.2 years (15). In the study by Wu et al., one year prevalence in 2005 and average annual incidence of hypertension in the period 2006–2010 in patients with anxiety disorders were higher than in the general population (37.9% vs. 12.4% and 3.63% vs. 1.95%), seen in all age and sex groups (16). In the National Health and Nutrition Examination and Epidemiologic Follow-up Study, in a cohort of initially normotensive men and women that were followed up for 7 to 16 years, anxiety and depression, especially high levels at baseline, were found to be predictive of later experience of hypertension (17). Among outpatients with anxiety in the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey, up to 32.5% had unrecognized elevated blood pressure (18).

According to O'Donovan et al., individuals that suffer from anxiety disorders show greater threat-related vigilance and sustained threat perception, followed by prolonged activation of the HPA axis and the autonomic nervous system (15). At first, anxiety increases blood pressure transiently; in the long term, it may cause persisting vascular resistance, higher levels of angiotensin II, sustained sympathetic nervous activity and HPA axis activity as the major stress response system (14). Sustained activation of SNS reduces renal blood flow, increases sodium and water retention and through abnormal hemodynamic and dysregulating lipid metabolism causes damage and dysfunction of the endothelium, with consequent increase of the risk of atherosclerosis (14). Prolonged activation of the neurobiological stress system in different anxiety disorders can potentiate chronic inflammation along with functional and structural damage and, finally, cardiovascular, autoimmune and neurodegenerative diseases can develop (19).

Anxiety disorders are recognized as associated with higher blood pressure variability (BPV) (15). Likewise, the relationship between anxiety and BPV is bidirectional (20). In the study by Zhou et al., predictive values of long-term BPV for incident anxiety were studied among patients in family medicine clinics (20). Incident anxiety was significantly predicted by higher BP and higher BPV in female and older patients (20). Higher BPV is connected to reduced baroreflex sensitivity and it shows sympathetic predominance over decreased parasympathetic activity, which is also found in patients with anxiety disorders (20). Higher BPV is a predictor of development, progression and severity of organ damage associated with hypertension (15). Small cross-sectional and other studies have shown greater BPV and lower heart rate variability (HRV) among adults with higher levels of anxiety (15).

Sinhba et al. reported that anxiety levels are negatively correlated with heart rate and HRV in the stress response, and Yu et al. found that anxiety may diminish the cardiovascular response to stress by desensitizing beta-adrenergic receptors (1). An ambulatory blood pressure monitoring study reported that anxiety disorders were associated with nocturnal and early morning hypertension in hypertensive outpatients (21). Numerous studies showed a higher prevalence of panic disorder in hypertensive patients than in the control groups, e.g. Davies et al. found that 13% of hypertensive patients in primary care, in contrast with 8% of normotensive patients, suffer from panic disorder, and another study reported that 12% of patients with resistant hypertension have the diagnosis of panic disorder, along with 14% of those without treatment resistance (2). Increased lifetime risk of development of hypertension in patients with the diagnosis of panic disorder was reported in prospective studies by Grimsrud et al., Chou et al. and Stein et al. (2). Patients with panic disorder show autonomic dysfunction with increased sympathetic and decreased parasympathetic activity, so that increased heart rate and blood pressure and decreased HRV are observed (2).

However, some researchers have not found a link between anxiety and hypertension; this was reported in the Nord-Trøndelag Health Study (HUNT) in Norway (8). Patients who participated in the HUNT study from 1984 to 1986 were re-examined 11 years later and it was reported that high levels of anxiety and depression at baseline predicted low systolic blood pressure at follow-up (22). Researchers also found that increase in symptoms of anxiety and depression from baseline predicted a decrease in blood pressure in men and women of all adult age groups (22). It is important to note that those effects were not explained by the use of antidepressant or antihypertensive medication (22). Likewise, patients in the HUNT study were re-examined 22 years later and it was found that high levels of combined anxiety and depression at baseline were associated with lower mean systolic and diastolic blood pressure (22). It was reported that the risk of developing hypertension at year 22 was 20% lower and that both anxiety and depression separately contributed to the lowering of blood pressure (22). It is noteworthy that there was no evidence of mediating effects of heart rate changes and that the association of lower blood pressure with anxiety and depression persisted after excluding individuals who used antidepressants or antihypertensive medications (22).

It is known that individuals with anxiety disorders, compared to those without such diagnosis, are more likely to smoke, excessively consume alcohol and be obese, but there are studies that show the association of anxiety disorders and prevalent hypertension that is independent of unhealthy behaviour patterns as risk factors for hypertension (15). Likewise, patients with anxiety disorders may poorly adhere to medication treatment for hypertension, which makes blood pressure control difficult (11). However, numerous epidemiological studies concerning potential association of anxiety and hypertension have given inconsistent results. In addition to researchers that found that patients with anxiety are at higher risk of developing hypertension, others did not support the role of anxiety in development of hypertension and, finally, a few reported on lower blood pressure in patients with anxiety (14). The Australian Longitudinal Study of Women's Health (ALSWH) reported incident hypertension in 29.8% of women in 15 years of follow-up, but the association was not significant after adjusting for covariates (15). Similar findings of generalized anxiety disorder not being significantly correlated with incident hypertension in the elderly after adjusting for covariates were shown in the ESTHER study (15).

Association of depression and hypertension

Depressive disorders are the most widespread mental disorders (23). Depression is common among patients with cardiovascular diseases, with prevalence estimated between 15% and 50% (4). It is an important risk factor for coronary heart disease and is strongly associated with

angina pectoris, myocardial infarction and cardiac death (4). Depression leads to greater disability and lower quality of life in cardiovascular patients (23). Major depressive disorder is also associated with development of hypertension (1). There are reports of 1.4 times greater chance of having hypertension when depressed (8). The average annual incidence of hypertension in patients diagnosed with major depressive disorder was higher than in the general population (3.96% vs. 2.90%) when studied by Liang-Wu et al. in the period 2006–2008, and the 1-year prevalence was also shown to be higher than in the general population (21.21% vs. 13.28%); the results were comparable regardless of sex and age (16). One study conducted on women showed significant increases of systolic blood pressure in relation to increasing depressive symptoms, while increasing intensity of anger and anxiety and decreasing levels of social support showed a greater likelihood of developing hypertension in middle-aged women (24). A meta-analysis by Meng et al. showed an increased risk of hypertension incidence in depression, and it was significantly correlated with the baseline intensity of depressive symptoms and length of follow-up (9.6 years) (25). Depression is recognized as a significant and independent risk factor for hypertension, especially in younger people, and inducing lower heart rate variability is accompanied by greater mortality of cardiovascular disease (3). In the field of physiological research, a significant correlation has been found between depression, arterial stiffness and hypertension, with the intensity of depressive symptoms independently associated with arterial stiffness (8).

There is also growing interest about the role of intracellular calcium homeostasis dysregulation and calcium/cAMP signalling pathway in the pathogenesis of depression and hypertension (26). Calcium channel blockers are known as antihypertensives, but are also reported to have beneficial effects on certain symptoms of depression, such as cognitive dysfunction, and the possible link lies both in regulation of neurotransmitters such as serotonin and sympathetic outflow (26).

Gonzalez-Sanchez et al. reported about increased sympathetic vasomotor tone in patients with depression, association of depressive symptoms with an increase of SNS activity and/or decreased PNS, cardiac hyperactivity during SNS stimulation, morning SBP surge in positive correlation and nocturnal SBP dipping in negative correlation with depressive symptoms (1). The exact mechanism of hypertension development in depression, whether joint with anxiety or separate, still remains incompletely understood (1). The incidence of depression in hypertension patients is 27%, higher than in the general population (13). Depression increases the risk of hypertension complications (13). In hypertension patients that also suffer from depression, hypertensive crises are more common than in those without depression (23).

Villarreal-Zegarra showed that the association between hypertension and depression changes as time passes after diagnosing hypertension (27). Less than one year after hypertension diagnosis, patients were twice as likely to experience depression compared to individuals without hypertension, and as time passes, the risk of depression in patients with hypertension decreases, but it remains increased even in the period of five years or longer after hypertension is diagnosed (27). Possible explanations for this effect can be biological, such as chronic vascular and brain damage under high blood pressure during long periods, and/or psychological, mainly as emotional reactions to awareness of diagnosis and adaption difficulties to personal abilities and need for lifestyle changes. It is probable that patients with arterial hypertension adapt better after a longer period with the diagnosis and thus the risk of depression decreases (27).

In the study concerning the impact of anxiety and depression on quality of life among patients with arterial hypertension by Polishchuk et al., the majority of hypertensive patients and patients with nonpsychotic mental disorders had high levels of trait and state anxiety, and there was a direct correlation between trait anxiety and severity of depression. Levels of anxiety and depression were higher and quality of life was

lower in female patients with arterial hypertension, with significantly lower quality of life in patients with mixed anxiety and depressive disorder, as the most common diagnosis in the observed population (28).

Effects of antidepressants on blood pressure

In patients suffering from depressive disorders and anxiety disorders, blood pressure changes have to be considered in the context of taking antidepressants. The longitudinal National Study of Adolescent to Adult Health (ADD Health) that followed teenagers to adulthood concluded that taking antidepressants is an independent factor for development of hypertension in men, but not in women, with diastolic BP increased by an average of 1.6 mmHg (8). It has to be questioned whether elevations in blood pressure in patients taking antidepressants are a result of the medication or of the disorder (depression and anxiety disorder) itself.

Possible effects of antidepressants on blood pressure may be associated with their mechanism of action through serotoninergic, adrenergic, dopaminergic, histaminergic and cholinergic systems (29). Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) may lead to changes of blood pressure through basic mechanisms of inhibiting the serotonin transporter (SERT) and the norepinephrine transporter (NET). SSRIs are the most frequently used antidepressants in treatment of depression, but also of anxiety disorders. SSRIs selectively inhibit SERT, but also act through presynaptic serotonin (5-HT) receptor desensitization, mostly 5-HT1A, thus enhancing serotoninergic neurotransmission (29). SSRIs show limited effects on the autonomic nervous system, which is why they are considered to be a safe class of antidepressants, especially for patients with cardiovascular disorders and older patients; additionally, their long-term use is accompanied by an increase in HR variability, which results in reduced cardiac morbidity and mortality (29). However, Humbert et al. analysed the WHO pharmacovigilance database and showed that the use of SSRIs significantly increases the risk of hypertension (30). Humbert et al. suggested that hypertension can be a possible adverse effect explained by SERT inhibition and its vasoconstrictor effects and/or inhibited nitric oxidase vasodilatation effect, while the pharmacoepidemiological-pharmacodynamic study found a positive correlation of the NET/SERT pKi ratio with the occurrence of hypertension in patients treated with SSRIs, as well as SNRIs (31). One cohort study in primary care in London was conducted to assess the risk of incident hypertension over 10 years and it showed the correlation of antidepressant use with developing hypertension (and other cardiovascular risks such as DM and hyperlipidaemia), possibly regarding the use of SSRIs in anxiety treatment (14).

Citalopram and its enantiomer escitalopram, the most selective SSRIs, are considered among the safest SSRIs due to not changing either systolic or diastolic BP nor HR and QTc interval in studies conducted on the older population with or without coronary artery disease (29). Sertraline is one of the commonly used SSRIs and it has the ability to increase dopaminergic neurotransmission. Sertraline is also considered one of the safest SSRIs, even in patients with unstable angina pectoris or after myocardial infarction and among older hypertensive patients (29). Fluvoxamine is an SSRI with agonistic effect on the sigma-1 receptor. The sigma-1 receptor is believed to mediate vasodilatation and decrease systolic BP in the presence of nitric oxide; however, fluvoxamine is not associated with changes to blood pressure or other significant cardiac effects, although it can cause mild bradycardia and rarely QTc prolongation (29). Fluoxetine is an SSRI with antagonist effects on 5-HT2C receptors that could enhance noradrenergic and dopaminergic neurotransmission. With short-term use of fluoxetine (12 weeks), depressive patients, either hypertensive or normotensive, show a modest decrease of systolic and diastolic BP, although there are some reports about a larger BP decrease in hypertensive than normotensive

patients (29). Paroxetine is an SSRI that additionally inhibits norepinephrine reuptake and has anticholinergic properties. In patients with ischaemic heart disease and depression, paroxetine shows a significant increase of supine systolic BP after a period of six weeks of administration (29).

Depressive patients on SSRI therapy compared to those on placebo in a meta-analysis by Zhong et al. did not show significant changes in blood pressure, while patients on SNRIs compared to patients on SSRIs experienced a modest increase in systolic and diastolic BP in short-term and long-term treatment (less or more than eight weeks) (32). On the contrary, psychiatric evaluation and ambulatory blood pressure measurements taken in the Mayo Clinic in Florida in the period 2012–2016 showed that patients taking SSRIs or SNRIs had higher nocturnal systolic and diastolic BP compared to individuals without a diagnosis of mental disorder and without psychopharmacotherapy (33). A single-centre retrospective study among patients with mental disorders who were taking SSRIs or SNRIs, a group of patients with mental disorders who were not taking SSRIs or SNRIs and a group of individuals without a mental disorder diagnosis who were not taking psychopharmacotherapy used information obtained from 24-hour ambulatory blood pressure monitoring and showed that SSRIs and SNRIs were significantly associated with higher nocturnal systolic and diastolic BP (34). That finding is important because nocturnal BP is reported to be a value predictor of cardiovascular mortality regardless of sex and age (34). Among SNRIs, venlafaxine shows a significantly higher risk of hypertension in a dose of 150 mg per day, but the risk is reduced by its extended release (ER) form (31). It is recommended that venlafaxine users be screened and monitored for hypertension, while duloxetine users are advised to monitor their BP if they have a prior diagnosis of hypertension or CVD (35). In a meta-analysis of 17 randomized clinical trials, Park et al. showed that duloxetine does not increase HR and BP in short-term therapy (20). Other concerns regarding duloxetine and venlafaxine include their effects on HR and QTc interval because of their described effects on sodium or potassium channels (35), but SNRIs are generally considered safe.

Tricyclic antidepressants (TCAs), however, are connected with serious arrhythmias; they are considered more toxic for the cardiovascular system and should not be administered to cardiac patients (30). TCAs inhibit 5-HT reuptake (mainly amitriptyline, imipramine, clomipramine) and NE reuptake (mainly nortriptyline and desipramine), but are also antagonists on cholinergic M1 receptors, histaminergic H1 and adrenergic $\alpha 1$ receptors, and orthostatic hypotension is one of the common side effects. Randomized trials have shown that SSRIs and SNRIs have better safety profiles than TCAs, although some meta-analyses reported that citalopram prolonged the QTc interval (36). The use of TCAs was accompanied by increased systolic and diastolic BP and patients suffered from hypertension in the study by Licht et al., which is why it was concluded that there is an increased risk of hypertension (30). Patients with major depressive disorder had a significantly lower systolic BP and anxious patients had a significantly higher diastolic BP compared to healthy controls, while for patients taking TCAs, systolic and diastolic BP were significantly higher (37).

Mirtazapine, a noradrenergic and specific serotoninergic antidepressant (NaSSA), seems to have a significantly lower risk of adverse cardiovascular effects (36). Mirtazapine has antagonistic properties on adrenergic alpha2-autoreceptors and alpha2-heteroreceptors as well as 5-HT2 and 5-HT3 receptors, thus enhancing the release of norepinephrine and 5-HT1A-mediated serotonergic transmission. In a meta-analysis of 25 randomized and controlled trials by Wanabe at al., significantly lower risk of hypertension was shown for mirtazapine than for TCAs (30).

Trazodone is an antidepressant with partial agonistic activity at 5-HT1A receptor and antagonism at 5-HT2A, 5-HT2C, $\alpha 1$ and H1 receptors. Trazodone is described as safe for the cardiovascular system, although mild

orthostatic hypotension can occur, so the general recommendation is to take blood pressure before administration and to avoid getting up abruptly from a lying or seated position (38).

Vortioxetine is an antidepressant with multimodal activity; it has antagonistic properties on 5-HT3, 5-HT7 and 5-HT1D receptors, a partial agonistic effect on 5-HT1B and an agonistic effect on 5-HT1A receptors, as well as an inhibitory effect on SERT. According to Baldwin et al., vortioxetine has a favourable cardiovascular safety profile when compared to the placebo in acute randomized controlled trials (six to eight weeks in duration) and in long-term open-label treatment (52 weeks of duration) (39).

Agomelatine is an antidepressant with agonistic properties at melatonin (MT1 and MT2) receptors and antagonistic properties at 5-HT2B/5-HT2C receptors. In addition to the effect on the circadian rhythm, agomelatine can influence the autonomic output to the cardiovascular system; however, agomelatine seems to have a safe cardiovascular profile (29). Clinical studies suggest agomelatine as a safe option among antidepressants in patients with cardiovascular disease; additionally, its cardioprotective and anti-inflammatory effects are described (40).

Moclobemide is a reversible inhibitor of monoaminoxidase (MAOI) and through that mechanism, breakdown of monoamines is reduced. Earlier MAOIs were irreversible and had a greater risk of increasing blood pressure, even causing a hypertensive crisis, when taken together with tyramine-rich food and medications like phenylephrine and pseudoephedrine. The general recommendation is to avoid such food and medications when taking MAOIs (30). Further studies for the assessment of effects of commonly used antidepressant medications are needed – particularly an analysis of potential association of changes in blood pressure to the prescribed doses of antidepressants.

Conclusion

Aetiology of hypertension has been widely studied in the last few decades. It is known that hypertension is the result of complex interaction of genetic and environmental risk factors, especially lifestyle and psychosocial factors. Mental disorders, emotional distress and certain individual psychological characteristics have been associated with increased incidence of hypertension. Anxiety disorders and depression have been established as risk factors for hypertension. As hypertension is itself a major preventable factor for cardiovascular disease, cerebrovascular diseases and chronic kidney damage and is associated with earlier mortality, better understanding of the pathophysiological mechanisms underlying the association of anxiety and depression with hypertension could improve prevention and treatment of hypertension. Implementing systematic screening for hypertension among patients suffering from anxiety disorders or depression can be questioned. Because of the bidirectional relationship and possible negative effects of anxiety disorders and depression on hypertension, treatment and quality of life, patients should be screened for mental disorders and, if needed, referred to clinical psychological interventions and administered psychiatric medication, i.e. antidepressant therapy. Knowledge about the effects of antidepressants on blood pressure is of importance and enables the optimal selection of medications for patients with anxiety disorders or depression, especially those for whom other risks of development of hypertension are present or those that are already hypertensive.

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