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Features of mental disorders and their correction in patients with cardiac pathology

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Abstract

In everyday practice, the doctor rarely encounters only one specific disease, more often a patient with comorbid pathology comes to him. Such a group of concomitant diseases are mental disorders. Their prevalence in cardiology practice reaches 80%. Mood affective, anxiety and somatization disorders, as well as cognitive impairment are observed most often. The review looked at mental disorders that occur in cardiac diseases with the highest number of deaths, such as coronary heart disease, including myocardial infarction and cardiac arrhythmias, arterial hypertension and cerebrovascular diseases. Including attention is paid to the senile asthenia syndrome, which is accompanied by cognitive impairment, loss of previous vital interests and depression. The review highlights the questions of regular and adequate psychopharmacotherapy of cardiovascular diseases, which leads to a statistically significant decrease in the frequency of their exacerbations, which reduces the number of doctors who come to see for somatogenic symptoms, and also allows to improve the prognosis of the underlying disease and significantly reduce mortality. It was observed that the doctor should take into account the fact that modern cardiological preparations have effects that can cause side effects in the form of mental disorders when choosing a therapy. Understanding the processes of formation and occurrence of mental diseases in a patient with cardiovascular pathology, as well as methods for their correction, can increase the effectiveness of the therapy and improve the prognosis of the underlying disease.

Keywords: cardiovascular disease, mental illness, psychopharmacotherapy.

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It has become increasingly rare that doctors deal with only one specific disease as comorbid pathologies become more frequent in everyday practice [1]. Mental disorders constitute one of these groups of concomitant diseases. It is known that their prevalence is high in somatic patients, including patients with cardiovascular diseases (CVD), and, according to various sources, 1.5–5 times higher than in the general population [2]. This group of pathologies includes various types in clinical presentation; however, coronary heart disease (CHD), including myocardial infarction and cardiac arrhythmias; arterial hypertension (AH); and cerebrovascular diseases, including stroke, account for about 80% of lethal outcomes [3].

The prevalence of mental disorders at the clinical and subsyndromal levels in cardiology is more than 80%, among which affective, anxious, and somatic disorders are predominant [4]. Moreover, mental disorders can be due to organic brain damage leading to cognitive impairment and, as a result, dementia [5]. This is consistent with expert opinions provided in the recommendations for diagnostics and treatment of acute and chronic heart failure, where special attention is drawn to cognitive impairment, "senile asthenia," and acute delirium [6]. Senile asthenia syndrome ("fragile" patients) is a key concept in modern geriatrics, characterized by age-associated decline in the physiological reserve and functions in many of the body systems, accompanied with the development of cognitive disorders, loss of previous vital interests, and depression, in addition to physical involutive processes [7].

Mental disorders in CVD. The prevalence of AH among the adult population is 30–45% [8]. AH is an independent disease and its high prevalence and poor control make it an independent risk factor

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for the development of CVD [3]. It is one of the most significant risk factors for the development of CHD, and the issues on its therapeutic prophylaxis pose an urgent concern for modern cardiology [9, 10].

The mental status of AH patients has certain patterns. At disease onset, the anxious component predominates, followed by the neurotic, hypochondriacal, depressive, or hysterical components [11]. Many studies confirm a causal relationship between AH and affective disorders [12]. Anxiety and depression are independent risk factors involved in AH development, affecting CVD patient prognosis [13]. The prevalence of anxiety and depressive disorders in AH patients is higher than in other diseases [14, 15].

AH is an independent risk factor for cognitive impairment regardless of age [16]. This is because of both the high prevalence of the disease among middle-aged and elderly patients and the nature of damage to the cerebral vessels inherent only to this disease. Even in adolescence, high blood pressure (BP) causes damage to a number of cognitive functions, mathematical and creative ones in particular [17].

The role of AH in the development of dementia has been demonstrated in large-scale studies Framingham, EVA Gothenburg, and the Honolulu-Asia Aging Study [18–21]. These studies have shown the role of AH as the main eliminable risk factor for the development of cognitive impairment and also noted uncontrolled hypertension as a significant risk factor [17]. The development of cognitive disorders in AH patients can be caused by acute cerebral circulation disorders, damage to the white matter of the brain, and acceleration of degenerative processes in the cerebral cortex [22].

Anxiety, depression, and stress are independent risk factors for the development of atherosclerosis and CHD, which determine the significance of changes in mental status [23]. The social functioning of patients is worsened by the combination of CHD and depression more than by each of these diseases separately [24].

The prevalence of depressive disorders in CVD patients reaches to 60% [25]. According to the World Health Organization (WHO), while maintaining current demographic trends, by 2020, CHD and depression will occupy a leading position among all diseases by the number of lost years of working life due to disability [26]. There are three main factors that can lead to disease onset, i.e., depression as a psychopathological reaction to the disease, depression as a direct consequence of CVD, and depression as a result of side effects of treatment for the underlying disease (e.g., intake of β-adrenoceptor blocking agents) [27].

A number of general genetic mechanisms determine the development of depression and major CVDs leading to chronic heart failure (CHF) [28]. One of them is the polymorphism in the angiotensin-converting enzyme (ACE) gene, associated not only with ACE activity but also with hypercortisolemia, which is a significant neuroendocrine component of depression [29].

Angiotensin II serves as the major effector of the renin-angiotensin-aldosterone system. It has a direct stimulating effect on the corticotropin-releasing hormone expression, which in turn activates the hypothalamic-pituitary-adrenal axis, which precedes depression onset [30]. In patients with depression, even without CVD, aldosterone level is noticeably increased; hence overproduction of aldosterone by the adrenal cortex not only plays an important pathophysiological role in the development of AH, CHD, and CHF but is also a characteristic feature of depressive disorder [31].

CHD, CHF, and AH are etiological factors for the development of atrial fibrillation, as they contribute to both increased atrial ectopic activity and impaired cardiac conduction, leading to the progression of atrial structural remodeling [32]. In patients with atrial fibrillation, anxiety and hypochondriacal disorders are often noted [33] and subsequently depressive disorders, due to the severe course of CVD that can develop to CHF [34].

Acute myocardial infarction (AMI) and its complications pose a serious problem to modern medicine due to its high mortality rate [35]. Mental disorders in AMI patients are recorded in 30–50% of cases [36], which is primarily due to the patient's emotional and personal response (fear of sudden death, repeated AMI, job loss, possible disability) to such life-threatening condition. External social factors, such as the significant others' response to a serious illness and the quality of care from medical personnel, have a certain influence on the patient's mental status [37].

It is important to note that anxiety and depressive disorders constitute the majority of all mental changes in a patient with this condition [38]. Clinically, this is manifested by increased irritability, the onset or frequency of pain symptoms, diminished physical load tolerance, sleep disturbances, palpitations, and arrhythmias, leading to a more severe course of the disease, which in turn significantly lengthens the duration of therapy and subsequent rehabilitation [39].

According to the INTERHEART Study, depression is one of the three leading causes of death from cardiovascular events [40]. The analysis of the mortality data of AMI patients with and without depression showed that AMI patients with depression

had 5 times higher risk of mortality than in patients without depression [41]. Treatment of depression in AMI patients can significantly reduce risk of death, repeat revascularization, and the number of hospitalizations [42].

It is important to note the prognostic siginificance of delirium among AMI complications. It represents a variety of conditions accompanied by both qualitative (delirium, amentia, and oneiroid) and quantitative (obtundation, stupor, and coma) disorders of consciousness, as well as impairment of associated cognitive and other mental functions [43]. Delirium can lead to the aggravation of somatic pathology due to the complexity of its diagnostics and treatment. It is considered as a significant unfavorable factor in the clinical prognosis of the underlying disease, which is determined by a clearly established relationship between the development of this condition in the early period of AMI and mortality in this group of patients [44].

The factors that determine the development of delirium in AMI include the prevalence of myocardial damage, the state of myocardial contractility, deterioration of rheological properties, and changes in the gas composition of the blood due to a decrease or absence of cerebrovascular reserve, as well as a patient's awareness of his illness, a sharp limitation of physical activity, a psychologically stressful atmosphere in the intensive care unit, and polypharmacotherapy [45]. The available data on the prevalence of delirium in AMI patients, obtained from Russian studies [46–48], are significantly lower than the level established by international experts [49, 50], which may be due to a more thorough diagnostic search and the inclusion of this complication in the diagnosis structure of the underlying disease. A group of patients with delirium is characterized by old age, the presence of a burdened neurological history, and a high risk of TIMI [51] of mortality in the next 30 days [45].

There is a close relationship between the central nervous system and the immune system [52, 53]. Inflammation is known to play a significant role in the pathogenesis of atherosclerosis [54]. The role of inflammatory processes in the development of depression is a problem that probably gained the greatest attention [55]. There are theories which state that an increased level of pro-inflammatory markers, such as C-reactive protein [56], interleukin-6 [57], and tumor necrosis factor α [58], was detected in patients with depression to a greater extent than in healthy people, regardless of somatic diseases [59].

The principles of drug therapy of mental disorders in cardiology. In Russia, the procedure for the use of psychopharmacotherapy for the treatment and prevention of mental disorders in CVD patients was described for the first time in the Guide to Primary Health Care, which states that a general practitioner is able to correct and treat mild forms of depression [60]. Moreover, the duration of preventive psychopharmacotherapy in CVD patients is determined by the dynamics of psychopathological disorders [61].

The development of depression and CVD is based on pathophysiological processes that are close in mechanisms, which suggests a possible relationship between these conditions and their mutual potentiating effect. Thus, ACE inhibitors, which serve as the main class of drugs in the treatment of AH [62] and CHD [63], are capable of exerting an antidepressant and antianxiety effect, which indirectly confirms the common pathogenetic mechanisms underlying CVDs and depression [64]. In CHD patients, even in the absence of clinically pronounced symptoms of depression, the use of antidepressants improves the prognosis of the underlying disease and survival [65], which can be due to both the somatic nature and the effect of drugs on the CVD pathogenesis [66].

There is a well-known classification of applied groups of psychopharmacological drugs, such as antipsychotics (neuroleptics), anxiolytics (tranquilizers), antidepressants (thymoanaleptics), nootropics, and substances with a nootropic component of action, stimulants, and mood stabilizers [67].

A complex therapy of AH is of great importance, which includes the targeted effect on affective disorders and comorbid AH [68]. For this purpose, a group of antidepressants is used, and it is suggested that their effect is due to a decrease in the pathological activity of the sympathoadrenal system [69]. There are three classifications of antidepressant drugs [70]:

1) Drugs of nonselective action that block the neuronal reuptake of monoamines (tricyclic antidepressants [TCA]) and neuronal reuptake of serotonin and norepinephrine (amitriptyline, imipramine) and drugs of selective action that block the neuronal reuptake of serotonin (fluoxetine) and norepinephrine (maprotiline)

2) Inhibitors of monoamine oxidase (MAO) of nonselective action (nialamide, transamine), inhibiting MAO-A and MAO-B, and those of selective action, inhibiting MAO-A (moclobemide)

3) Monoamine receptor agonists, i.e., noradrenergic and specific serotonergic antidepressants (mirtazapine, mianserin), as well as specific serotonergic antidepressants (trazodone, nefazodone)

It should be noted that the use of TCAs in medium therapeutic doses can lengthen the QT, QRS, and PQ intervals on the patient's electrocardiogram

and can cause tachycardia, orthostatic hypotension (especially in elderly patients), increased drowsiness, decreased concentration and attention deficit, and intellectual activity, associated with their effect on central α-adrenergic receptors and serotonin, muscarinic, and histamine H_1 receptors [71].

A new generation of antidepressants includes the selective serotonin reuptake inhibitor (SSRI) sertraline which has a high antidepressant activity and does not have side effects characteristic of TCAs. This group of drugs rarely cause side effects and do not cause withdrawal symptoms [72–74]. SSRIs do not only have antidepressant but also antianxiety effects [71]. There is also evidence of the absence of a negative effect of sertraline on the cardiovascular system [75, 76].

In a study of the effect of complex therapy with antihypertensive drugs (captopril or metoprolol) and SSRI antidepressants on the clinical condition, BP, and myocardial functional state in patients with AH and concomitant affective disorders, positive dynamics was noted in patients taking antidepressants. Although the administration of antidepressants lasted for only 3 months, it persisted throughout the follow-up period [69]. A decrease in the index of relative wall thickness, in accordance with the literature [77], indicates left ventricle remodeling. In the study [69], the degree of decrease was noticeable in patients receiving antihypertensive drugs in combination with antidepressants, which was the result of a significant decrease in the activity of the renin-angiotensin and sympathoadrenal systems when using antidepressants in complex treatment.

There is evidence that some antidepressants have an antiarrhythmic effect [78, 79]. Thus, TCAs can reduce intracardiac conduction as well as ventricular excitability and inhibit ectopic activity and delay atrial and ventricular depolarization, thereby increasing the QT, PQ, and QRS intervals and decreasing the T wave amplitude [80]. In turn, SSRI drugs, which do not have such effect, can increase the blood levels of some antiarrhythmic drugs [81].

Currently, benzodiazepines and butyrophenone derivatives, individually or in combination, are the drugs of choice to treat delirium in patients in the acute period of myocardial infarction [45]. Continuous administration of sedatives leads to a more reliable and predictable anxiolysis with maximum benefit and minimal side effects in AMI patients [46, 49].

An important aspect in the prevention of cognitive impairment in hypertensive patients is adequate antihypertensive therapy, in addition to nonpharmacologic means [81]. Neuropsychological studies in AH patients demonstrate that BP normalization due to antihypertensive therapy leads to a marked improvement in cognitive functions even at short (3–6 months) treatment periods [82]. Olmesartan, an angiotensin II receptor blocker, is a highly efficient modern antihypertensive drug that is able to favorably affect target organs and slow the progression of cognitive impairment and the development of dementia, in addition to effective control of BP [83]. The ACE inhibitor perindopril in combination with indapamide also has a similar effect [84].

It is important to note that at the stage of pronounced cognitive impairment, psychosocial, and behavioral influences are necessary, which must be started as soon as possible after diagnosis [85]. To correct cognitive and behavioral disorders, acetylcholinesterase inhibitors (galantamine, rivastigmine, donepezil) can be used, which is a substitution therapy in the treatment of mild to moderate Alzheimer's disease, associated with the presence of cholinergic deficiency [86], and they help with mild to moderate vascular and mixed dementia to a lesser extent [87].

Another drug that can be used to correct such disorders is memantine, a noncompetitive N-methyl-D-aspartate receptor antagonist. Its effectiveness in correcting cognitive functions in patients with mild to moderate vascular dementia has been proven in two randomized placebo-controlled trials [88, 89]. For moderate and severe dementia, a combination of memantine and central acetylcholinesterase inhibitors can be used [90]. In a meta-analysis of the effectiveness of cerebrolysin, which included the results of six studies, it was found that the drug has a positive effect on cognitive functions in patients with vascular dementia [91]. Patients with senile asthenia are also recommended to use memantine or acetylcholinesterase inhibitors [92, 93].

The most important considerations for the use of antidepressants in cardiology include patient's tolerance, absence of side effects, safety in case of overdose, ease of use, minimal behavioral changes, and minimal risk of unwanted interactions with other drugs [94]. This risk is minimized with the use of SSRIs, as well as reversible MAO type A inhibitors and selective serotonin reuptake stimulants. Serotonin and norepinephrine reuptake inhibitors, selective norepinephrine reuptake inhibitors, atypical antidepressants, and TCAs in small doses cause a slightly higher level of risk. Antidepressants such as nialamide are withdrawn from psychopharmacotherapy practice due to their high cardiotoxicity [95].

SSRIs are superior to tricyclic antidepressants as first-line drugs for the treatment of heart disease patients with concomitant depressive disorders.

Although they have comparable equal efficacy, their better tolerability and greater safety make them more suitable in healthcare practice [96]. SSRIs have negligible antihistamine and anticholinergic activity, do not have adrenergic properties, and are supposedly capable to inhibit platelet aggregation, thereby increasing bleeding time. They are also dosed easily and do not affect the efficiency of antihypertensive, antianginal, and antiarrhythmic therapy, as well as contractility and conduction of the heart muscle and BP. However, they can occasionally reduce the heart rate. In addition, these drugs do not only have antidepressant but also antianxiety effects and therefore are successfully used in patients with depression with concomitant anxiety symptoms, anxiety attacks, and phobic syndromes [75]. In patients after AMI, they reduce the risk of recurrent infarction, overall mortality, and mortality from a recurring acute coronary event in comparison with patients not receiving SSRIs [97]. A positive effect of sertraline on the patient's cognitive status was noted, which makes it a drug of choice in the treatment of "vascular" depression with signs of cognitive impairment [26]. USA doctors most often prescribe sertraline for heart disease patients with depression [39].

The prevalence of depression increases with age due to the fact that it often has a common pathogenetic relationship with senile asthenia [7]. Patients with suspected depression are recommended to use SSRIs or non-SSRIs as first-line drugs [98]. When choosing between two groups of antidepressants, SSRIs are preferred due to better tolerance [99].

The use of benzodiazepine tranquilizers helps to reduce somatovegetative disorders in patients with a paroxysmal form of atrial fibrillation and enables to achieve positive results in the prevention of rhythm disturbance attacks [100]. The presence of autonomic disorders in cardiac pathology serves as a pathogenetic basis for the use of complex therapy of drugs with combined anxiolytic and antianxiety properties and agents that normalize autonomic imbalance [101]. There are a large number of such drugs, but from the point of view of a medical practitioner as regards the use of the drug in a heart disease patient, tetramethyltetraazobicyclooctanedione has a competitive advantage, as it has pronounced anxiolytic, vegeto-stabilizing, stress-protective, and antioxidant properties, as well as high safety (it is a derivative of bicyclic bioureas and is close to natural purine metabolism products) [72, 102]. The combination of the drug with antiarrhythmic drugs helps to reduce autonomic imbalance, which reduces the arrhythmogenic readiness of the myocardium [103].

It is important to note that regular psychotherapy and adequate pharmacotherapy for prophylactic purposes in heart disease patients within 0.5–1.5 years significantly leads to a decrease in the frequency of CVD exacerbations, such as angina attacks, hypertensive crises, paroxysmal arrhythmias, and increased CHF symptoms, which significantly reduces the number of hospitals visits due to the somatogenic symptoms not subject to objective disease severity, according to laboratory, physical, and instrumental examinations (e.g., cenesthopathy, cardialgia, cephalalgia, anxiety attacks, precollaptoid states, hyperventilation syndrome, and asthenia) [104].

Negative psychotropic effects of certain heart disease drugs. All cases of mental side effects of drugs are registered in the WHO global database VigiBase [105]. This group of side effects also includes a large list of disorders. One of the most frequent side effects when prescribing certain heart disease drugs is a pro-depressive effect which causes the so-called "iatrogenic depression" [72]. The study of such side effects was started with antihypertensive drugs, such as the drug reserpine derived from the plant Rauwolfia (Laffer F., Esselier A., 1953), which marked the beginning of a number of publications about registering them for patients. However, as a result of subsequent controlled studies, it was revealed that the probability of depressive episodes does not exceed that with the use of other antihypertensive drugs [106].

Currently, β-adrenoceptor blocking agents are one of the first-line drugs for CHF treatment, which effectively slow down the disease progression, reduce the number of hospitalizations, and improve prognosis in serious patients [107]. A side effect of these drugs is depression. Research in this area shows contradicting results. The first message was made by H. J. Waal [108], who noted a high level of depression among the group of hypertensive patients taking propranolol. Subsequent studies revealed the pro-depressive effect of the only lipophilic blockers, i.e., propranolol [109] and timolol [110]. The following mechanisms that determine this kind of effect have been proposed:

1) A centrally mediated specific β-adrenergic mechanism, when β-adrenoceptor blocking agents that penetrate the brain in a sufficiently large amount (especially lipophilic ones) bind to adrenergic receptors [111].

2) A centrally mediated specific serotonergic mechanism, when β-adrenoceptor blocking agents that penetrate through the blood-brain barrier also (1) bind to non-adrenergic (e.g., serotonergic) receptors, (2) interfere with the signal passage to non-adrenergic pathways, and (3) disrupt activity and reactivity in controlled networks, thereby disrupting

behavioral/neuropsychological mechanisms [112].

3) A centrally mediated nonspecific mechanism, when β-adrenoceptor blocking agents that penetrate the brain through the blood-brain barrier inhibit the most sensitive neurons of the central nervous system due to their membrane-stabilizing properties (preventing the excitation of neurons).

4) The peripheral mechanism implies changes by β-adrenoceptor blocking agents in autonomous activity on the periphery, which are then transmitted to the central nervous system to change the functioning of various central mechanisms (systems) [113].

The significance of these mechanisms depends on the drug pharmacological characteristics, in particular the degree of lipophilicity, affinity for non-adrenergic receptors, membrane-stabilizing properties, and the dose [114]. Due to the low methodological quality of the studies conducted in this field, new attempts were made to study this group of drugs, as a result of which, according to contemporary systematic studies and meta-analyzes, no significant increase in symptoms of depression was detected in such patients, regardless of the pharmacological characteristics of the drugs [114]. This is evidenced by the results of the last placebo-controlled study which clearly demonstrated that depression during the period of drug administration is more common in the placebo group than in the control group [115].

According to some authors, calcium channel blockers also have a pro-depressing effect [116]. Subsequent studies rejected this statement and demonstrated the opposite result [117] and also revealed that severity of such effects is significantly lower than that of β-adrenoceptor blocking agents [118]. Cases of depressive events are also reported in the adverse drug reaction base for ACE inhibitors. Attempts have been made to relate depression and the use of this group of drugs [119]. Long-term studies concluded that drug intake, on the contrary, corrects depressive symptoms and, improves mood and cognitive function [120].

There were also cases of statin therapy in patients with primary hypercholesterolemia that caused depressive symptoms, suicidal ideation, and compulsive thoughts [121]. The Centre for Adverse Reactions Monitoring in New Zealand has recorded 203 reports of psychiatric side effects associated with statin intake (20.5% of all reports are related to simvastatin, atorvastatin, fluvastatin, and pravastatin). The reports included mood disorders, cognitive impairment, sleep disturbances, perceptual disorders, and other reactions (asthenia, fatigue, lethargy, malaise, and drowsiness) [122].

The pathophysiological mechanism of the development of side effects in terms of the possibility of depression occurrence was due to a decrease in the level of serotonin, neurosteroids, and polyunsaturated fatty acids in the cerebral cortex as a result of decrease in cholesterol level [123–125]. Subsequently, after a deeper analysis of the side effects of statins, it was revealed that it has no significant risk for side effects compared with other drugs, but there is the possibility of insomnia development [126]. It is believed that statins have a positive effect on cognitive functions and reduce the risk of dementia [127], and due to their anti-inflammatory properties and in combination with SSRIs, they can have a certain antidepressant effect [128].

Considering other mental side effects, there are examples of cases of digitalis intoxication with the development of acute psychotic phenomena due to severe (60% or more) inhibition of Na^+/K^+-ATPase in cardiomyocytes and the central nervous system [129]. For antiarrhythmic drugs, cases of acute psychotic phenomena have been described for disopyramide [130] and lidocaine, which, in case of excess concentration in the blood, has led to side effects in the form of increasing anxiety, mood changes, and hallucinations [131].

J.K. Kahn described a case of developing acute psychosis while taking nifedipine in an 84-year-old man whose symptoms disappeared after drug discontinuation. The author associated this condition with a disorder of the synthesis of neurotransmitters (catecholamines in particular), excessive dopaminergic activity, and increased activity of tyrosine hydroxylase [132].

Among the latest drugs used in cardiology practice, there is the drug entresto (valsartan + sacubitril) which slows down the degradation of endogenous natriuretic peptides, thereby enhancing their beneficial cardiovascular effects. However, some studies in animal models [133, 134] revealed that sacubitril may contribute to neuronal dysfunction and cognitive impairment in CHF patients due to possible neprilysin inhibition at the level of the central nervous system. Large-scale studies, such as PARAGON [135] and PARADISE-MI [136], are currently studying this issue. The current results of one retrospective cohort study aimed at identifying the effects of sacubitril/valsartan on cognitive function in CHF patients who have been taking this drug for at least 3 months do not confirm the expected harmful effect [137].

Thus, it should be emphasized that understanding the processes of the formation and occurrence of mental disorders in patients with cardiovascular pathology, as well as methods for their correction, can increase therapy efficiency and improve prognosis of the underlying disease [138].

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