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THE ROLE OF ANTIDEPRESSANTS IN CARDIOLOGY PRACTICE

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Annotation: Amitriptyline was for a long time the sole medication for the management of depression in cardiological patients despite a large number of side effects. It was substituted by the safe and cardiologically neutral sertraline, a selective serotonin re-uptake inhibitor. Presently, the results of agomelatine therapy of cardiovascular diseases and accompanying depressions arise great interest.

Keywords: cardiovascular diseases, depression, antidepressants.

Cardiovascular diseases (CVD) are one of the most common diseases that reduce the ability to work and lead to disability . At the same time, their frequent combination with depressive disorders was noted, and this fact was confirmed by numerous studies. It is known that the prevalence of depression in patients with CVD ranges from 18 to 60% [1]. According to the World Health Organization, if existing demographic trends continue, by 2020 coronary heart disease (CHD) and depression will take the 1st and 2nd places, respectively, among all diseases in terms of the number of years of reduction in full-fledged life due to disability [2].

CVD can lead to depressive disorders or exacerbate their course, increasing the risk of suicide [3]. The relationship between CVD and mood disorders is multifactorial and complex. It can be assumed that there are at least three categories of causal relationships: depression is a direct consequence of CVD; depression is a psychological reaction to an illness; depression is a consequence of side effects of therapy for the underlying disease (for example, taking β- blockers). It has long been known that in patients with coronary artery disease, even without clinical manifestations of depression, the use of antidepressants improves prognosis and survival [4], which may be due to both its somatized nature and the effect of drugs on the pathogenesis of CVD [5].

Perhaps there are common genetic mechanisms that predetermine the development of depression and major CVD, leading to the development of chronic heart failure (CHF), and the same genes are involved in the development of each of these nosological forms. Polymorphism of the angiotensin - converting enzyme (ACE) gene, which is one of the important links in the formation of CHF, is associated not only with ACE activity, but also with hypercortisolemia , which is an important link in the neuroendocrine component of depression, and as a result with the development of an affective disorder proper. The main effector in the renin- angiotensin - aldosterone mechanism underlying the development of CHF, angiotensin II, has a direct stimulating effect on the secretion of corticotropin-releasing factor, which in turn is the leading trigger of the hypothalamic-pituitary-adrenal axis, which dominates in the formation of depression. . Finally, excessive production of aldosterone by the adrenal cortex, which plays an important pathophysiological role in the development of arterial hypertension, coronary artery disease and CHF, is a characteristic feature of depression, its "calling card", since patients with depression, even without CVD, have a significantly increased level of this mineralocorticoid . This made it possible to call hyperaldosteronism a marker of depression.

Thus, we can conclude that the development of CVD and depression is based on pathophysiological processes similar in mechanisms, which allows us to assume a possible relationship between these conditions and their mutual potentiating effect. Moreover, recent studies have shown that ACE

inhibitors, which are a key class of drugs in the treatment of arterial hypertension and coronary artery disease, can have antidepressant and anti-anxiety effects, which indirectly confirms the common pathogenetic mechanisms underlying CHF and depression [6].

History of development of antidepressants, main mechanisms of action, side effects. From the very beginning of the development of psychopharmacology, antidepressants have occupied one of the leading places in the practice of treating patients. They affect the central and peripheral regulatory mechanisms of organs and systems. This versatility of action of antidepressants allowed them to be effectively used in vegetative-vascular dystonia, bronchial asthma, neurological diseases (in particular, chronic pain), irritable bowel syndrome, peptic ulcer, anorexia nervosa and bulimia, and enuresis [7]. However, their widespread use in cardiological practice was preceded by a long and dramatic period of trial and error.

The founder of the group of tricyclic antidepressants (TCAs), imipramine , was synthesized in 1948 in the laboratories of Geigy (Switzerland). Later, he became the main representative of a large class of TCAs, which increase the content of neurotransmitters in the brain - serotonin, norepinephrine, dopamine, phenylethylamine and other neurotransmitters (approximately evenly). TCAs also slow down their reuptake into neurons, as a result of which the concentration of neurotransmitters in the synaptic gap between neurons increases and the transmission of impulses from one neuron to another is accelerated. These biochemical processes determine the clinical improvement of the mental state [8].

At the same time, in the early 50s of the 20th century, the drug iproniazid was created in the United States , which increases the effectiveness of antibiotic treatment of tuberculosis. As a side effect, hyperactivity and improved mood were observed in patients who took it . Studies have shown that iproniazid blocked the brain enzyme monoamine oxidase (MAO), which breaks down 3 neurotransmitters in synapses : norepinephrine, serotonin and dopamine. When taking the drug, neurotransmitters were not destroyed by MAO, and the content of these mediators in the brain increased. Thus, a new group of antidepressants appeared, which were called MAO inhibitors [9, 10]. In addition, in the United States, the drug reserpine was isolated from the serpentine rauwolfia plant, which was used to treat schizophrenia, as well as to lower blood pressure. Among the patients who received it, depression and suicide attempts were observed. An assumption was made about the depressogenic effect of reserpine, and later it was found that the drug reduces the content of the same three mediators in the brain - norepinephrine, serotonin and dopamine, which confirmed the theory that depression is associated with the suppression of the functions of certain brain synapses [11].

Since different antidepressants have a different chemical structure, as well as a mechanism of action, the side effects of drugs from different groups are different. Until recently, TCAs have been key drugs for the treatment of depression, but multiple side effects and the possibility of death in case of overdose make them inconvenient for cardiac patients. TCAs act on adrenergic and serotonergic neurons in the central nervous system (CNS), and in the periphery they exhibit anticholinergic activity, give effects similar to those of quinidine by blocking P-adrenergic receptors. The most common side effects of TCAs are dry mouth, constipation, urinary retention, orthostatic arterial hypotension, disturbance of accommodation, increased intraocular pressure, drowsiness and lethargy, palpitations, and in some cases, impaired consciousness with convulsive seizures. Antihistamine action is expressed in an increase in body weight, drowsiness, lowering blood pressure. Inhibition of the capture of norepinephrine is manifested by tachycardia, muscle twitches, sexual dysfunctions - erectile dysfunction and ejaculation. The consequence of dopamine uptake inhibition is motor excitation, exacerbation of psychopathological symptoms. Inhibition of serotonin uptake is manifested by decreased appetite, nausea, dyspepsia, erectile dysfunction and ejaculation [12].

III antiarrhythmic drugs , so they reduce intracardiac conduction, reduce ventricular excitability and inhibit ectopic activity [13], delay atrial and ventricular depolarization, increase QT, PQ, QRS intervals, and reduce T wave amplitude. In the absence of conduction abnormalities in therapeutic doses, these effects are insignificant, however, with atrioventricular blockade of the II degree, intraventricular conduction disturbances, an increase in the QT interval and the simultaneous

administration of antiarrhythmic drugs, the appointment of TCAs is contraindicated. Atrial and ventricular extrasystoles are the most common arrhythmias, but with overdose, electrical instability, and recent myocardial infarction (MI), severe arrhythmias can develop, more often in the form of ventricular tachycardia. TCAs increase the heart rate by 5–20 per minute due to the anticholinergic block, which can be significant in patients with ischemic cardiopathy , cause postural arterial hypotension in 20% of patients. In elderly patients, this can cause orthostatic arterial hypotension, cerebral hypoperfusion , provoke falls and fractures. It must also be remembered that in patients with low ejection fraction, TCAs reduce myocardial contractility.

On the ECG, an overdose of TCAs is often accompanied by a turn of the mean electrical axis of the heart to the right, which is due to a violation of intraventricular conduction [14].

With MAO inhibitors, the most important side effect is that they dramatically increase sensitivity to tyramine and tryptophan, substances found in many foods, such as beer, avocados, chocolate, soy sauce, aged chianti wines, ham, cheese, cream , smoked meats, legumes, coffee, yeast, beef and chicken liver, bananas. MAO inhibitors of the first generation completely destroyed MAO, and its natural recovery after 1 tablet required 2-3 weeks . If during this period patients consumed products containing tyramine , then the so-called cheese syndrome developed - an acute and prolonged hypertensive crisis. The combination of MAO inhibitors with other types of antidepressants and many other drugs is characterized by such complications as a sharp increase in blood pressure, convulsions, clouding of consciousness, hallucinations, renal failure, hyperthermia, shock, death. A large number of side effects have led to the fact that irreversible MAO inhibitors have practically disappeared from therapeutic and, in particular, cardiological practice.

When using reversible MAO inhibitors, side effects are also sometimes noted, including tachycardia and hemodynamic instability. Attempts to combine MAO inhibitors and a mediator reuptake inhibitor led to fatal cardiovascular complications due to the fact that both actions were potentiated [15].

The fight against side effects and the therapeutic power of drugs served as the main motive for the creation of new drugs for the treatment of depression in patients with a burdened somatic history.

One of the leading side effects of TCAs is their anticholinergic effect, due to the presence of two CH3 groups at the end of the structural formula of TCAs of the first generation [16]. After it was possible to get rid of these groups, the preparation petilil was obtained (deaminated melipramine). Thus, it was possible to get rid of the pronounced anticholinergic effect, but this led to a decrease in the antidepressant effect. The next step was drugs created, on the contrary, by attaching another benzene ring to the TCA, tetracyclic antidepressants - maprotiline (ludiamil), mianserin (le-rivon), mirtazapine (remeron). These drugs, also with fewer side effects, have taken their place in clinical practice, but are inferior to TCAs in their antidepressant effect.

A little later, drugs were synthesized that block one of the mediators, which is considered the main one in the development of depression - serotonin. Thus, antidepressants appeared - serotonin reuptake inhibitors. These drugs (fluoxetine , citalopram , sertraline) still have a slightly lesser antidepressant effect than typical TCAs, but due to their high selectivity, they have much fewer side effects. Side effects of selective serotonin reuptake inhibitors (SSRIs) include nausea, vomiting, dyspepsia, abdominal pain, diarrhea, constipation, insomnia, headache, tremors, sweating, decreased libido or potency, restlessness, increased or increased parkinsonism, trismus , acute dyskinesia. In addition, in cardiological practice, when prescribing antidepressants, irritability, aggressiveness, and dysphoria come to the fore. Rare side effects are bradycardia, bleeding, granulocytopenia , seizures, hyponatremia . Drugs with selective inhibition of reuptake of norepinephrine - reboxetine (edronax), atomoxetine (strattera), uptake of dopamine and norepinephrine - bupropion (wellbutrin , zyban), uptake of serotonin and norepinephrine - venlafaxine (velaxin , efevelon), milnacipran (ixel), etc. [17]. The nature and frequency of side effects of representatives of these groups differ, but are less pronounced. Currently, further development of antidepressants is underway, in which there will be even greater selectivity for the reuptake of serotonin and / or other neurotransmitters precisely in order to get rid of unnecessary side effects.

Efficiency and features of the use of antidepressants in cardiology practice . The most important conditions for the use of antidepressants in cardiac practice are their tolerability, the absence of side effects, safety in case of possible overdose, ease of use, minimal behavioral deviation, and minimal risk of unwanted interactions with other drugs [18].

Currently, for antidepressants used in cardiology practice, a classification based on the degree of risk of side effects and unwanted interactions has been proposed. For cardiac patients, this risk is minimal when using SSRIs, as well as reversible MAO inhibitors type A and selective serotonin reuptake stimulants. The average level of risk is determined by serotonin and norepinephrine reuptake inhibitors (SNRIs), selective norepinephrine reuptake inhibitors, atypical antidepressants, TCAs in doses up to 100 mg / day . A high level of risk may be caused by the use of TCAs in doses of more than 100 mg / day . Some antidepressants (nialamide) are excluded from the practice of pharmacotherapy due to high cardiotoxicity [19].

The main representatives of the SSRI class are sertraline , fluoxetine , paroxetine , fluvoxamine , citalopram , reversible MAO inhibitors - moclobemide , serotonin reuptake stimulants - tianeptin , SNRIs - venlafaxine and milnacipran , selective norepinephrine reuptake inhibitors - maprotiline , TCAs - amitriptyline .

SSRI antidepressants have outperformed TCAs as first-line drugs for the treatment of cardiac patients with depressive disorders. Approximately the same efficacy, but better tolerability and greater safety, especially in case of overdose, make them more attractive in the practice of a cardiologist [20]. SSRIs have minimal anticholinergic and antihistamine activity, have adrenergic properties and are presumably able to inhibit platelet aggregation, thereby prolonging bleeding time. They are easily dosed and do not affect the effectiveness of antianginal , antiarrhythmic and antihypertensive therapy, do not affect the contractility and conduction of the heart muscle, blood pressure, although occasionally they can reduce the heart rate. In addition, these drugs have not only antidepressant, but also anti-anxiety (anxiolytic) effects, and therefore they are effective in the presence of concomitant anxiety symptoms, panic attacks, and phobic syndromes in patients with depression [21]. In patients after myocardial infarction, drugs significantly reduce the risk of recurrent myocardial infarction, the risk of all-cause mortality and mortality from recurrent myocardial infarction compared with patients who did not receive SSRIs. SSRIs may have clinically significant interactions with some drugs used in cardiac practice [22].

SSRIs inhibit cytochrome P-450 isoenzymes in the liver together with isoenzymes involved in the metabolism of many drugs, including lipophilic P - blockers (metoprolol , propranolol), calcium antagonists, group 1C antiarrhythmic drugs, ACE inhibitors, anticonvulsants, antihistamines, benzodiazepines , TCAs, codeine and warfarin . With the simultaneous appointment of SSRIs, they can increase the concentration of these drugs in the blood; particular caution should be exercised against warfarin [23].

Sertraline is the most studied member of the SSRI group in terms of its effect on the course of CVD and the treatment of depression in CVD. At the moment, there are data on several randomized placebo-controlled studies on the effect of sertraline in patients with depression who underwent myocardial infarction. Most patients received sertraline at an average dose of 50 mg/ day . The authors unanimously express the opinion that sertraline contributes to the restoration of cardiac function in depressed patients with depression after myocardial infarction. A positive effect of sertraline on cognitive status (cognitive disorders is the most common comorbid disorder in CVD and depression) has been noted: memory, orientation in space, learning, counting, etc. This allows us to consider it as the drug of choice for the treatment of "vascular" depression with impaired cognitive functions . In addition, taking sertraline in patients with CVD and concomitant depression is also justified from an economic point of view: it has been proven that such treatment within 6 months after MI reduces direct costs by 10–15%, despite the additional costs of purchasing this drug.

Based on a survey of US physicians, it was found that it is sertraline that they prescribe most often when diagnosing depression in cardiac patients [24]. Thus, SSRI drugs should be recognized as the

most suitable in most cases of treating depression in patients with CVD. Speaking of new antidepressants with other mechanisms of action, it should be noted that most of them also have a favorable cardiological profile due to selective selective action on mediators in the CNS. Bupropion , which acts on the dopamine and norepinephrine systems, is safe in overdose, causes a smaller decrease in blood pressure than TCAs, does not affect cardiac contractility and conduction, and helps to get rid of smoking. The drug increases the concentration of P - blockers and class 1C antiarrhythmic drugs prescribed at the same time. Venlafaxine acts on the reuptake of serotonin and norepinephrine, has minor cardiovascular side effects, increases heart rate in high doses, and increases blood pressure. Trazodone has little effect on the reuptake of dopamine and norepinephrine, mainly acting on the reuptake of serotonin, has anxiolytic , thymoleptic , muscle relaxant and sedative effects. In terms of effectiveness, this drug is comparable to TCAs, significantly surpassing them in terms of safety and less side effects; in cardiology is used in small doses as a hypnotic.

New generation of antidepressants: agomelatine , the first melatonergic antidepressant So far, we have discussed drugs with a traditional monoaminergic mechanism of action, which is the main one for the latest generation of antidepressants. Currently, there has been progress in the creation of fundamentally new antidepressants with an alternative mechanism of action. The new target is melatonergic receptors and melatonin, with its key role in synchronizing circadian cycles, which are disrupted in depression. Recently, other non- monoaminergic mechanisms for the creation of antidepressants have also been explored in programs that have focused on neurokinins (neurotransmitters that play a key role in pain transmission and emotion regulation), corticotropin- releasing factor receptors , etc., however, their results have not been impressive. .

The first non-monoaminergic antidepressant , valdoxan (timanax), was proposed in 2009. From the point of view of the mechanism of action, depression is associated with a change in the circadian rhythm of melatonin release. In depression, less melatonin is released, and an increase in circulating melatonin levels in the body correlates with effective treatment with certain antidepressants. By itself, melatonin administration is ineffective in major depression, although it can improve sleep; therefore, it is the effect on melatonergic mechanisms in general that is the therapeutic strategy for depression [25].

The pineal gland, which produces melatonin (a hormone also synthesized in all major organs: in the gastrointestinal tract, lungs, liver and gallbladder, kidneys and adrenal glands, in the thyroid gland), is phylogenetically an ancient structure. Melatonin was discovered in 1917 when McCord and Allen demonstrated how an extract from the pineal gland of a cow altered skin pigmentation in tadpoles. After 40 years, melatonin was isolated in its pure form and chemically identified (N-acetyl-5-methoxytriptamine), and until 1980 it was assigned a fundamental role in the control of reproduction. A more systematic study of melatonin began in 1988. It became clear that melatonin, coupled with light signals, controls circadian cycles. Of particular importance was the fact that the peak concentration of melatonin in the plasma of circadian periodicity in mammals occurs at night. Relationships have been established between melatonin, the suprachiasmatic nuclei of the CNS, and circadian rhythms. Further research has created melatonin derivatives that are more lipophilic for introduction into clinical trials , making them easier to penetrate into the brain, and have proven to be more effective in practice. Agomelatine (known as melatonin derivative S20098) has proven to be the most promising drug in this profile. Agomelatine synchronized circadian cycles in animals and volunteers blocked 5-HT2C receptors in the CNS (playing a leading role in mood control, sleep quality, and response to stress), and its antidepressant effect was maintained by activation of MT1 and/or MT2 receptors (also involved in mood control) in the hippocampus , nucleus accumbens (nucleus accumbens) and the frontal cortex [26]. It was especially effective when administered in the evening. In clinical trials, agomelatine at doses ranging from 5 to 800 mg was well tolerated and was not associated with significant side effects (only mild sedation and headache were observed). In the treatment of major depression, the 25 mg dose has been found to be the most effective [27]. When assessing the treatment of depression according to the Hamilton HAM-D scale, more than 50% reduction in the level of depression was demonstrated; in addition, agomelatine reduced anxiety [28]. Comparing agomelatine (25–50 mg) with venlafaxine (75–150 mg) and sertraline (50–100 mg),

agomelatine was more effective than the conventional drugs mentioned. In addition, an earlier therapeutic response to agomelatine than sertraline [29], better well-being and daytime activity of patients, improved sleep quality, and normalization of all phases [30, 31] compared with venlafaxine were revealed . Within a year of therapy, Valdoxan guarantees the absence of relapse in 8 out of every 10 patients, providing a powerful antidepressant efficacy in depression of any severity of non - psychotic level [32].

Cardiovascular and gastrointestinal complications, sexual dysfunction, excessive sedation , and weight gain can sometimes prompt early discontinuation of some antidepressants. The absence of cardiovascular and gastrointestinal complications, neutrality in relation to body weight, sexual function are the hallmarks of agomelatine [33, 34].

The total side effects of antidepressants are shown in the table.

Currently, the latest results of studies on the treatment of patients with CVD and concomitant depression with agomelatine are of increasing interest [35]. With the accumulation of sufficient positive experience, this drug can take its rightful place in the practice of treating depression in patients with CVD.

Table. Comparative side effects of drugs

A drug	Anticholine ergic	Cordially Vascular	Nausea	Sedation	Sexual disfunction
Valdoxan	*	*	*	*	*
Amitriptyline (TCA)	+++	+++	++	+++	++
Sertraline (SSRI)	*	*	++	*	++
Venlafaxine (SNRI)	*	++	++	+	++

Conclusion. Depressive disorders often accompany CVD and significantly aggravate their prognosis. Lifestyle changes in the development of CVD, prolonged (weeks and months) hospitalizations, constant fear and anxiety lead to depression and can provoke a deterioration in somatic status up to sudden death. The existence of a link between CVD and depression is explained by the action of complex pathophysiological mechanisms, often having a common basis, and is primarily due to an imbalance in neurohumoral systems. Effective therapy of depression in patients with CVD with modern antidepressants, elimination of its symptoms improves the clinical course of the underlying disease, and increases the effectiveness of complex therapy. Properly selected antidepressants are one of the important links in the treatment of depression in this category of patients in outpatient and hospital settings. When using antidepressants in cardiology practice, the most important conditions are good tolerability, absence of toxic effect, minimal interaction with other drugs, and relative safety in case of overdose. Knowledge of the risk factors, mechanisms of development and clinical manifestations of depression in patients with CVD and the use of modern antidepressants allow the cardiologist not only to effectively deal with depression, alleviate the suffering of the patient, prevent suicide, improve the prognosis of the underlying disease and reduce mortality, but also improve the quality of life, maintain full social adaptation of the patient after discharge. The introduction of modern antidepessants that meet these requirements into cardiology practice has provided physicians with a unique opportunity to treat depression in patients with various CVDs with minimal involvement of psychiatrists.

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