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Psychotropic drugs in clinical cardiology

Trofimov D.N.[1], **Khidirova L.D.**[1,2], **Madonov P.G.**[1,3]

[1] Novosibirsk State Medical University, Novosibirsk, Russia.
[2] Novosibirsk Regional Clinical Cardiology Dispensary, Novosibirsk, Russia.
[3] Research Institute of Clinical and Experimental Lymphology — Branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Novosibirsk, Russia.

AUTHORS

Daniil N. Trofimov, medical student, Novosibirsk State Medical University, Novosibirsk, Russia. ORCID: 0009-0009-3361-4969

Lyudmila D. Khidirova, MD, PhD, Professor of the Department of Pharmacology, Clinical Pharmacology and Evidence-Based Medicine, Novosibirsk State Medical University, Novosibirsk, Russia; cardiologist, Novosibirsk Regional Clinical Cardiology Dispensary, Novosibirsk, Russia. ORCID: 0000-0002-1250-8798

Pavel G. Madonov, MD, PhD, Professor of the Department of Pharmacology, Clinical Pharmacology and Evidence-Based Medicine, Novosibirsk State Medical University, Novosibirsk, Russia; Head of Experimental Pharmacology Department, Research Institute of Clinical and Experimental Lymphology — Branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Novosibirsk, Russia. ORCID: 0000-0002-1093-8938

This review article notes that the new generation of antidepressants — selective serotonin reuptake inhibitors and melatonin derivatives — do not have the side effects characteristic of tricyclic antidepressants and can be used in the treatment of patients with cardiovascular pathology in combination with depression. The causes and incidence of QT interval prolongation associated with the use of antidepressants are described. Numerous somatotropic and behavioral effects of tricyclic antidepressants have been demonstrated due to their effects on several receptor groups: α1-adrenoceptors, serotonin, muscarinic, and histamine H1 receptors. We searched PubMed, Embase, Web of Science, eLIBRARY and Google Scholar databases for the use of psychotropic drugs in cardiology practice, giving priority to systematic reviews, randomized clinical trials, supplemented by several cohort studies and the descriptions of some experiments. The data of comparative evaluation of modern antidepressants depending on pharmacological effects and development of adverse events are presented. The above-mentioned drugs, unlike traditional antidepressants, are acceptable for treatment of comorbid depressive disorders in patients with cardiovascular diseases. Proven efficacy among antidepressants are escitalopram, paroxetine, which have a strong cardiotropic effect, and agomelatine, which has proven efficacy in myocardial ischaemia–reperfusion injury.

* Corresponding author. Tel. +7 (923) 112-92-18. E-mail: h_ludmila73@mail.ru

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Introduction

In the clinical practice of a cardiologist, it is not uncommon to encounter depressive disorders as concomitant pathologies of the underlying cardiac disease, the correction of which requires the use of special drugs (antidepressants, sedatives, nootropics). Depression and cardiovascular diseases are related. In recent years, evidence has emerged that depression is an independent risk factor for coronary heart disease (CHD) [1-3]. The results of studies in recent years indicate that depression is present in 10–65% of patients hospitalized for acute coronary syndrome (ACS). Of these, 22% have depressive episodes of moderate to severe degree [4]. In general, most researchers agree that the presence of anxiety-depressive disorders in ACS patients is associated with higher rates of future cardiac complications. Several studies have shown that the risk of a new cardiovascular event or death in these patients is 1.36 times higher than in patients with myocardial infarction (MI) without depression [5].

According to the currently accepted concept, mild to moderate depression in cardiac patients can be treated by a cardiologist or general practitioner [6]. This has become possible due to the emergence in recent years of a number of new highly effective antidepressants that, unlike the classical tricyclic antidepressants (amitriptyline, etc.), do not have pronounced behavioral toxicity and negative side effects on the cardiovascular system.

Neuroleptics

The use of neuroleptics in cardiology is not fully studied, but individual trials have reported their cardiotropic effects. A meta-analysis of clinical trials of 20 antipsychotics showed that lurazidone and partial dopamine agonists (brexpiprazole and aripiprazole) were less likely to cause QT prolongation, whereas

Table 1. **Causes and frequency of the QT prolongation**

Mechanisms of action	Frequency of QT interval prolongation (absolute number of reports)	
Neuroleptics		
Direct and indirect antagonistic effect on IKr, inhibitory effect on cytochrome P450 system (CYP 1A2, CYP 2D6, CYP 3A4).	Haloperidol	16
	Ziprasidone	11
	Quetiapine	30
	Clozapine	12
	Olanzapine	22
	Risperidone	17
	Sertindole	1
	Sulpiride	13
	Thioridazine	2
	Chlorpromazine	3
Antidepressants		
Direct antagonistic effect on IKr, inhibitory effect on cytochrome P450 system (CYP 1A2, CYP 2C9, CYP 2C19, CYP 2D6, CYP 3A4).	Amitriptyline	8
	Doxepin	2
	Desipramine	—
	Imipramine	3
	Clomipramine	5
	Fluoxetine	16
	Sertraline	18
	Paroxetine	5

sertindole, amisulpride, and ziprasidone were more frequently associated with this adverse effect [7]. A positive correlation was also found between the risk of reporting QT prolongation and hERG channel affinity. According to the new clinical guidelines of 2021, neuroleptics, especially the group of atypical antipsychotics, are widely used in the treatment of depressive disorders and schizophrenia as long-term antidepressant therapy. In a recent publication Ostroumova O.D. presents a systematized psychotropic drugs according to their effect on the QT interval (Table 1) [8].

Improvement of autonomic function in response to antipsychotic pharmacotherapy in patients with schizophrenia, psychosis and additional cardiovascular risk has been demonstrated [9]. Cardiorespiratory coupling was observed to strengthen with antipsychotic administration, and the effect of heart rate on respiratory rate increased from day 1 to day 3 of the study.

Antidepressants

This type of drugs is much more widespread in clinical practice and has a greater impact on the cardiovascular system among other neurotropic drugs. Most of the research works mention the significant advantage of antidepressants from the group of selective serotonin reuptake inhibitors (SSRIs) over tricyclic antidepressants. A summary table of the pharmacodynamics and pharmacokinetics of modern antidepressants with side effects (Table 2) is presented below [10–13].

Many somatotropic and behavioral effects of tricyclic antidepressants are related to their non-selectivity — their influence on several groups of CNS receptors (α1-adrenergic receptors, serotonin, muscarinic, and histamine H1-receptors) (Table 3) [14–20].

Tricyclic antidepressants have a pronounced effect on prolongation of PQ, QT intervals, atrial-ventricular QRS complex, especially in patients with initial arrhythmia. Reflectory tachycardia is also one of the side effects that limits the use of tricyclic antidepressants in cardiological practice. Many somatotropic and behavioral effects of tricyclic antidepressants are related to their non-selectivity — their influence on several groups of CNS receptors (α1-adrenergic receptors, serotonin, muscarinic and histamine H1-receptors). SSRIs are selective and lack the side effects of tricyclic antidepressants (Table 4) [21].

One of the retrospective studies on the use of modern antidepressants in cardiological practice found that SSRI antidepressants were used for more than 3 days when treating main cardiovascular diseases [22]. The safe use of antidepressants was proved by their effect on the cardiac conduction system, which

Table 2. **Pharmacodynamics, pharmacokinetics and side effects of modern antidepressants**

Mechanism of action, doses, toxicity, and effect on weight gain of modern antidepressants										
Drugs	Initial doses, (mg/day)	Standart doses, (mg/day)	Overdose lethality	Side effects						
				Insomnia and agitation	Sedation	Hypotension	Anticholinergic effects	Nausea and gastrointestinal disturbances	Sexual dysfunction	Weight gain
SSRIs										
Fluoxetine	20	20-40	Low	Moderate	No or mild	No or mild	No or mild	Moderate	Moderate	No
Paroxetine	20	20-40	Low	Moderate	No or mild	No or mild	Mild	Moderate	Moderate	Moderate
Sertraline	50	50-150	Low	Moderate	No or mild	No or mild	No or mild	Moderate	Moderate	Mild
Fluvoxamine	50	100-250	Low	Moderate	No or mild	No or mild	No or mild	Moderate	Moderate	Mild
Citalopram	20	20-40	Low	Moderate	No or mild	No or mild	No or mild	Moderate	Moderate	Mild
Escitalopram	10	10-20	Low	Moderate	No or mild	No or mild	No or mild	Moderate	Moderate	Mild
Reboxetine	4-8	8-12	Low	Mild	No or mild	No or mild	No or mild	Mild	Mild	No or mild
Venlafaxine	75	150	Moderate	Mild	No or mild	No orMild	No or mild	Moderate	Moderate	No or mild
Desvenlafaxine	50	100	Low	Mild	No or mild	No or mild	No or mild	Mild	Mild	No or mild
Duloxetine	30	60-120	Low	Mild	Mild	Moderate	No or mild	Mild	Mild	No or mild
NSSRIs	100	200	Low	Mild	Mild	No or mild	No or mild	No or mild	No or mild	No or mild
NSSRIs										
Desipramine	25-50	100-300	High	Mild	No or mild	Moderate	Mild	No or mild	Mild	Mild
Nortriptyline	25-50	75-200	High	Mild	Mild	Mild	Mild	No or mild	Mild	Mild
Maprotiline	75	75-200	High	Mild	No or mild	Mild	Mild	No or mild	Mild	Moderate

Table 3. **Extent of inhibition of monoamine receptors and transporters by antidepressants**

Drugs	Norepinephrine transporter	Serotonin transporter	A1-adrenoreceptor	H1-histamine receptor	Muscarinic receptor	Serotonin receptor (5-HT-2A)
TCAs						
Amitriptyline	++	+++	+++	+++	+++	+++
Clomipramine	++	+++	++	+++	++	+++
Doxepin	++	+	+++	+++	+++	++
Imipramine	++	+++	++	++	++	++
Nortriptyline	+++	+++	++	++	++	++
Opipramol	+	+	—	+++	—	+
Trimipramine	+	+	++	+++	+++	++
Mirtazapine	+	—	—	++	—	+++
SSRIs						
Duloxetine	++	++	—	—	—	—
Venlafaxine	++	++	—	—	—	—
Citalopram	—	+++	—	—	—	—
Sertraline	—	+++	—	—	—	—
Paroxetine	—	+++	—	—	+	—
Other antidepressants						
Agomelatine	—	—	—	—	—	—
Bupropion	++	—	—	—	—	—
Vortioxetine	—	+	—	—	—	+

Note. – — no inhibition; + — mild inhibition; ++ — moderate inhibition; +++ — strong inhibition.

Table 4. **Values of inhibition constant (Ki) (nmol/L) in TCAs and comparison of drugs by two criteria — inhibition of reuptake and antagonism toward postsynaptic receptors**

Drugs	Reuptake inhibition			Antagonism towards postsynaptic receptors		
	5-HT	NA	H1	A1	M2	5 HT-2A
Mirtazapine	>10000	4600	0.14	500	670	16
Mianserin	>4000	71	0,4	34	820	7
Doxepin	68	29,5	0,24	24	83	25
Amitriptyline	20	50	1	27	18	29
Imipramine	7	60	40	32	46	80
Clomipramine	0,14	54	15	32	25	35
Nortriptyline	100	10	6.3	55	37	44
Dothiepin	78	70	4	400	38	260
Desipramine	18	0,83	110	100	100	280
Reboxetine	58	7.2	310	>1000	>1000	>1000

was evaluated by the dynamics of the QT interval on the ECG, systolic and diastolic blood pressure (SBD and DBP), heart rate and hemorrhagic complications. Data obtained for periods of 3, 6 and 8 days were analyzed. The result confirmed the high cardiological safety of new generation antidepressants, no clinically significant changes of QT interval on ECG were detected during regular treatment. Analysis of the dynamics of blood pressure and heart rate in patients also revealed no significant differences in these parameters before, as well as 3, 6–8 days after the administration of these drugs. No cases of hemorrhagic complications were observed.

Hildebrandt V., Dumenil K. et al. conducted a study on BP changes after the administration of a new generation antidepressant in a psychiatric institution [23]. This is an observational single-center analytical retrospective cohort study with additional data collection on patient stays between 2013 and 2015. Patients were divided into two groups — antidepressant treatment (which they took during their hospitalization) and control (no antidepressant). Blood pressure measurements were taken over a 30-day period. Of the 1241 patients, 124 were in the treatment group and 1117 in the control group. The mean age was 56, 80 ± 0.54 years (37 to 79 years). Increased

SBP was associated with baseline SBP variability and BMI. Assessment of DBP showed an association with baseline elevated DBP, BMI, and the presence of a history of bipolar disorder. There was no significant difference in BP change over time between the treated and control groups at 30 days. This result is reassuring with regard to the early development of arterial hypertension after antidepressant administration. Among antidepressants, citalopram has been found to have a greater effect on QT interval prolongation than other SSRIs, although the clinical significance of this prolongation remains unclear [24]. In a recent study evaluating the effect of escitalopram, a less pronounced effect on the myocardial conduction system was found (with citalopram — QT reached up to +0.04 sec to baseline (QT — 0.35 sec), respectively up to 0.39 sec). And in patients who were older than 60 years and took citalopram in 20 mg dosage — QT prolongation was up to 0.42 sec. Escitalopram administration was associated with QT interval prolongation in average up to 0.35 sec, $p < 0.05$. In addition, this study proved that taking ziprasidone at a dose of 160 mg daily led to QT prolongation up to 0.46 sec in 188 patients. While aripiprazole, which is a representative of the same group, was the safest and practically did not lead to QT interval prolongation (0.35 sec, $p<0.05$.).

In an experimental study, paroxetine was shown to have a beneficial effect on myocardial remodeling by blocking the interaction of GRK2 and ADRB1 in AH [25]. The expression of GRK2 and ADRB1 in peripheral blood mononuclear cells was found to be positively associated with the blood pressure level in AH patients and with the expression of these genes in the myocardium. In vitro data showed their direct interaction, and genetic depletion of GRK2 blocks epinephrine-induced activation of hypertrophic and fibrotic genes in cardiomyocytes. In vivo treatment with paroxetine reduced AH-induced cardiac hypertrophy, dysfunction and fibrosis in animal models. This drug was found to suppress sympathetic overload and increase the sensitivity of adrenergic receptors to catecholamines. Concomitant administration of paroxetine with metoprolol enhances BP and HR reduction and activates reverse myocardial remodeling in the experiment with spontaneous hypertension.

A recent study describes the cardioprotective use of agomelatine in myocardial reperfusion injury [26, 27]. Agomelatine is a melatonin receptor agonist and a serotonin receptor antagonist. To study the effect of agomelatine on myocardial reperfusion injury, an experimental model was used that was subjected to 30 minutes of ischemia followed by 120 minutes of reperfusion; agomelatine (10, 20, or 40 mg/kg) was administered intraperitoneally 1 hour before cardiac isolation. Agomelatine (20 mg/kg and 40 mg/kg) significantly improved cardiac function, attenuated pathological changes in ischemic myocardium, reduced infarction size, and decreased creatine kinase-MB and lactate dehydrogenase release.

Conclusion

Thus, unlike traditional antidepressants, the presented drugs are acceptable for the treatment of comorbid depressive disorders in patients with cardiovascular diseases. Brexpiprazole and aripiprazole (drugs from the group of partial agonists of dopamine receptors) have proven efficacy in the treatment of depressive disorders in patients with remodeled myocardium due to significantly lower shortening of the QT interval. Escitalopram and paroxetine have a pronounced cardiotropic effect practically without significant side effects; Agomelatine, on the other hand, proved its efficacy in myocardial reperfusion damage by the experiment in which an inhibitory effect on the apoptosis rate was found.

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