Correction of Psychoemotional Disorders and Short-Term Prognosis in Patients with COVID-19

V. N. Shishkova, K. E. Imamgayazova, and L. A. Kapustina

This review discusses the importance of the main psychoemotional risk factors for the development of chronic noncommunicable diseases. Current data on the prevalence of anxiety and depressive disorders in patients with cardiovascular disease (CVD) are presented. Data on the relationship between the development of psychoemotional disorders and CVD are summarized and the prospects for managing such patients within the framework of interdisciplinary cooperation are discussed. The main pathogenetic mechanisms for the development of complications, including CNS damage in COVID-19, are considered. The significance of the selection of pathogenetic therapy for patients with comorbid somatic and mental diseases in the context of the COVID-19 pandemic is discussed. Results from multicenter placebo-controlled studies of the use of fluvoxamine in patients with COVID-19 of varying severity are addressed.

Keywords: psychoemotional disorders, cardiovascular disease, new coronavirus infection, depression, anxiety, fluvoxamine.

The Relationship between Psychoemotional and Cardiovascular Diseases. The relevance of studies of psychosocial risk factors (PSRF) for chronic noncommunicable diseases (CNCD) in the modern world is increasing [1]. Taking account of the fact that PSRF, along with traditional risk factors, play an important role in the development of cardiovascular (CVD) and cerebrovascular (CerVD) diseases, type 2 diabetes mellitus (DM2), obesity, respiratory diseases, and mental illness, the close interaction of doctors of various specialties, primarily neurologists, psychiatrists, therapists, and cardiologists, with the aim of improving provision of medical care to patients with comorbid diseases is important. The need for correcting PSRF has also increased in the context of the COVID-19 pandemic, which was a stimulus for further increases in the prevalences of CVD, CerVD, DM2, and mental disorders [2, 3].

The main PSRF include factors of various natures: from the negative impact of low socioeconomic status to individual character traits (Fig. 1); some PSRF are significantly associated with a 1.5-fold increase in the risk of de-

veloping CVD resulting in disability and death [4, 5]. PSRF are known to produce significant reductions in motivation to utilize any therapy; they minimize adherence to a healthy lifestyle, i.e., are associated with malnutrition, low physical activity, alcohol abuse, smoking, etc., which affect patients' health status and quality of life [1, 4]. Not all PSRF have an equal impact on health status and prognoses; depression and anxiety make the greatest contributions to the development of CNCD. These are the PSRF most commonly encountered in the clinical practice of primary care physicians – neurologists, internists, and cardiologists [6]. Significant increases in the prevalences of depressive and anxiety disorders, which are among the top three causes of loss of work capacity, has been demonstrated [7].

Depression and anxiety increase the risk of both CVD and adverse cardiovascular outcomes, including rehospitalization and death, independently of traditional risk factors [8–10]. A prospective study (involving about 2 million initially healthy individuals) showed that the appearance of symptoms of depression is associated with an increase in the risk of developing chronic heart failure (CHF) by almost 20%, while the effect of depression persisted even after adjusting for all traditional CVD risk factors [11]. Another prospective study of more than 80,000 respondents who

National Medical Research Center for Therapeutic and Preventive Medicine, Russian Ministry of Health, Moscow, Russia; e-mail: veronika-1306@mail.ru.
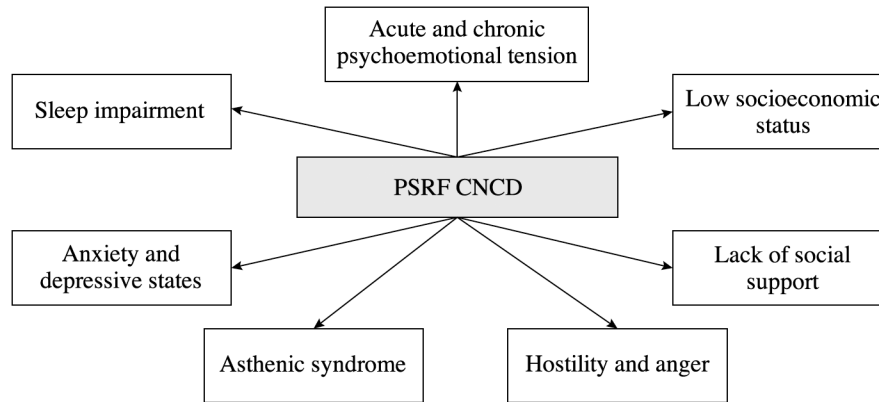
Fig 1. Main PSRF for chronic noncommunicable diseases.

initially did not have CVD found that the appearance of depressive symptoms increased the risk of developing CHF by 21% over the next six years [12]. An increase in depressive symptoms or the establishment of a diagnosis of depression in patients with atrial fibrillation and CHF was associated with increases in the numbers of hospitalizations and recurrent cardiovascular events, as well as mortality [13]. A meta-analysis of a series of studies investigating the association between depression and CHF outcomes showed that the presence of depressive symptoms or the diagnosis of depression led to a two-fold increase in the risk of death or a non-fatal cardiovascular event [14]. It should be emphasized that CVD is most commonly associated with depression both in clinical studies and in real medical practice [11]. One patient in five with ischemic heart disease (IHD) or CHF suffers from depression; patients with CVD and concomitant depression have increased risks of recurrent cardiovascular events and death [15]. Clinical observations indicate that depression is more likely to develop in men who have had a stroke and in women with more than three chronic diseases [16].

The development of depression has been shown to produce a near doubling of the risk of IHD, a 1.4-fold increase in the risk of stroke, and a 1.2-fold increase in overall mortality [16, 17]. The ESSE-RF study shows that women with subclinical and clinical depression have an almost 2.4-fold increase in mortality, while men with subclinical and clinical depression have a 1.5-fold increase as compared with people without symptoms of depression [18]. Depression increases the risk of death from CVD by a factor of 1.6 and the risk of death from all causes by a factor of 1.8, especially in elderly patients [19].

Taking data from the ESSE-RF study on the prevalence of anxiety states into account, it is clear that these are common in the population, at a rate of more than 18% [16]. It should be noted that anxiety disorders develop during life in more than a quarter of the population and that symptoms of severe anxiety are detected in 40% of patients seen by primary care physicians, i.e., general practitioners, neurologists, and cardiologists [15]. Anxiety states, like depression,

are also independent risk factors for the development of coronary artery disease, cardiovascular events, and cardiac death [20]. Although the specific mechanisms by which depression and anxiety lead to the development of CVD or worsening of its course have not been established, they have potentially negative impacts on behavioral factors (smoking, excessive alcohol consumption, physical inactivity, malnutrition) and treatment compliance and operate in combination with the adverse effects of stress on the central nervous system (CNS) [8–10, 15]. Such relationships are often underestimated by primary care physicians in clinical practice [15]. In the context of the COVID-19 pandemic, which also leads to affective and psychoemotional disorders, the association of depressive and anxiety disorders with somatic diseases becomes more significant [2, 3, 21].

It should be noted that the frequency and severity of various long-term effects of COVID-19 do not always depend on its initial severity, existing comorbid diseases, or the patient's age, so even mild or asymptomatic COVID-19 may cause a long-term decline in quality of life. So-called post-COVID syndrome (PCS), which is a period of at least 12 weeks of various of the sequelae of COVID-19, determines the further strategy for managing patients [22]. The clinical manifestations of PCS cannot be ignored, given their impact on the quality of life and work capacity of those who have been ill [23].

The pathogenesis of the main PCS disorders is currently being studied. The virus itself is assumed to have significant damaging effects in the development of complications affecting the respiratory, excretory, cardiovascular, and central nervous systems. SARS-CoV-2 virus has been shown to be able to damage the cells that make up neurovascular units in the CNS, leading to the development of cognitive and psychoemotional disorders [24]. The processes of systemic inflammation, as well as the triggering of cytokine storms, are of key importance in the development of most of the complications of infection caused by SARS-CoV-2, including CVD and depressive and anxiety disorders [25]. The occurrence of microcirculatory and thrombotic disorders is an important element in the pathogenesis of many
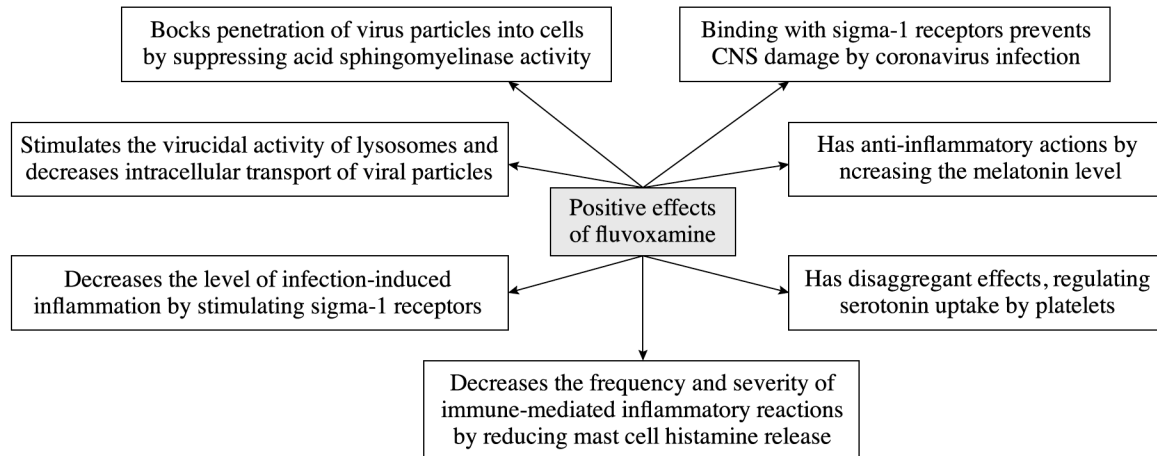
Fig. 2. Positive effects of fluvoxamine in COVID-19.

complications, including cardiovascular and cerebrovascular complications [26, 27]. Also important are correct assessment of the impact of side effects of treatments provided for COVID-19 and the consequences of prolonged immobilization, the stress factor of hospitalization and, of course, social isolation [28]. Thus, the COVID-19 pandemic is characterized by additional impact on both the occurrence and exacerbation of pre-existing PSRF in many patients.

The Sigma-1 Receptor-Associated Anti-Inflammatory Effect of Fluvoxamine. Establishment of the mechanisms of action of the SARS-CoV-2 virus on the human body has led to studies of new properties of drugs that have not previously been used in viral infections, i.e., drugs of the antimalarial, antipsychotic, antihistamine, and antidepressant classes. Among the latter, fluvoxamine (Rokona) stands out; this has a wide range of positive effects, not only improving patient's psychoemotional state, but also resisting SARS-CoV-2 virus infection (Fig. 2). Fluvoxamine has been shown on the one hand to have an antiviral effect, disrupting the intracellular transport of viruses and preventing their exit from cells, while on the other hand it has significant anti-inflammatory effects mediated by sigma-1 receptor activation and a decrease in histamine release by mast cells; it weakens the negative consequences of systemic inflammation and reduces the severity of cytokine storm. Fluvoxamine also produces significant increases in melatonin levels which, in addition to the regulatory effect on the sleep–wake cycle, has anti-inflammatory effects. Given that serotonin is directly involved in the pathogenesis of microcirculatory disorders, the direct effect of fluvoxamine – it decreases serotonin reuptake by platelets – is associated with an antithrombocyte action, and this is an additional advantage of its use during the COVID-19 pandemic [29–31]. These effects of fluvoxamine appear not to apply to the entire class of antidepressants, as evidenced by results from a meta-analysis demonstrating an increased risk of death in COVID-19 patients associated with taking antipsychotics and antidepressants [32].

We will consider the anti-inflammatory effects of fluvoxamine separately; these are mediated by activation of sigma-1 receptors, which are chaperone proteins able to migrate within cells. Sigma-1 receptors are present in various tissues and are located mainly on the endoplasmic reticulum membrane, which is involved in lipid synthesis, calcium homeostasis, energy metabolism, autophagy, and apoptosis [33]. Experimental studies have shown that mice with inactivation of sigma-1 receptors had higher mortality from septic shock and higher levels of proinflammatory cytokines (interleukin-6 and tumor necrosis factor α) (Fig. 3). The levels of these cytokines correlate with poor survival prognosis in patients with sepsis. Decreases in cytokine contents increased survival in animals, while administration of fluvoxamine promoted survival in mice with preserved sigma-1 receptors, though administration to mice with inactivated sigma-1 receptors did not affect survival. The authors concluded that the anti-inflammatory effect of fluvoxamine is mediated by activation of sigma-1 receptors. It should be noted that the survival rate of mice with experimental septic shock and given fluvoxamine was comparable to the survival rate on the background of treatment with ceftriaxone; when the two drugs were combined, their positive effects were summed. The data obtained in these experiments were reproduced in human blood samples in vitro, when addition of fluvoxamine contributed to a manifold decrease in the level of proinflammatory cytokines, which had been increased by prior addition of bacterial lipopolysaccharide [34]. Thus, the greater affinity of fluvoxamine for sigma-1 receptors than other antidepressants may provide an indirect indication of its possible potential in the treatment of patients with COVID-19 [35, 36].

Effects of Fluvoxamine on Patient Survival during the COVID-19 Pandemic. Results of studies using fluvoxamine in individuals infected with the SARS-CoV-2 virus are very interesting and important from the practical standpoint. Several randomized, double-blind, placebo-controlled studies have demonstrated the ability of fluvoxamine
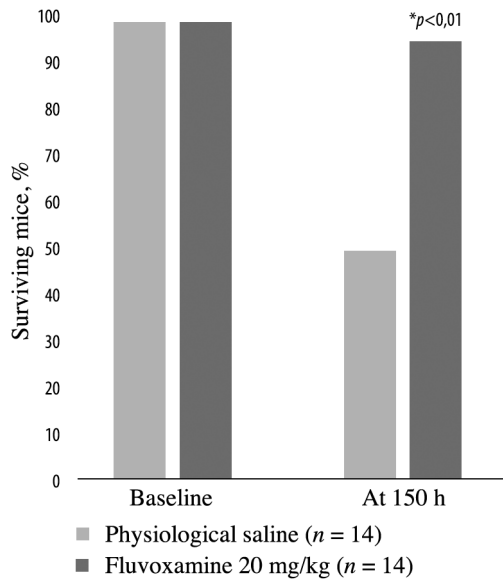
Fig. 3. Effects of fluvoxamine on survival in mice with septic shock.

to reduce the risks of hospitalization and mortality in patients with COVID-19 [37–40]. Of all the studies conducted to date addressing the effects of fluvoxamine on the course of COVID-19, the multicenter, randomized, double-blind, placebo-controlled TOGETHER study, the largest in terms of the number of participants, should be singled out [39]. This trial was conducted on unvaccinated outpatients with confirmed COVID-19 who had additional risk factors for the development of severe complications (CVD, CerVD, DM2, obesity, respiratory system diseases, immunodeficiency, cancer, chronic kidney disease, etc.). Disease duration at randomization was no greater than seven days; all patients received symptomatic therapy, and, depending on randomization, fluvoxamine 100 mg b.i.d. for 10 days or placebo. All side effects and unwanted effects, including those possibly associated with taking placebo or fluvoxamine, were thoroughly documented. The results exceeded expectations: for example, taking fluvoxamine at a dose of 200 mg/day for at least eight days prevented worsening of patients' condition and the progression of the disease with subsequent hospitalization in 99.8% of cases. The safety analysis demonstrated equal overall numbers of adverse events for placebo and fluvoxamine, though the number of serious adverse events was significantly higher in the placebo group. As regards the safety of fluvoxamine in patients, including the elderly, with COVID-19 and various comorbidities, other authors have also reported similar conclusions, emphasizing the lack of any effect of fluvoxamine on the QT interval, whereby it differs from many other antidepressants [37, 38]. Another important step in studying the efficacy and safety of fluvoxamine treatment was a case-control study in patients with severe COVID-19 treated in intensive care units [40]. This showed that fluvoxamine at a dose of 300 mg/day (100 mg t.i.d.) for 15 days in addition to basic therapy led to a significant reduction in mortality in hospitalized patients with severe COVID-19. These results led to the inclusion of fluvoxamine in clinical guidelines and protocols for the treatment of patients with COVID-19 in many countries, including Russia [41–44].

Conclusions. The impact of the COVID-19 pandemic in terms of an increase in the incidence of anxiety and depressive disorders in the population, including in the long-term period after the disease, affecting both prognosis and patients' quality of life, should be emphasized. Thus, the whole set of unfavorable aspects associated with the mutually potentiating effects of somatic diseases, particularly CVD, and mental disorders, in combination with the impact of the COVID-19 pandemic, is of particular importance today. We can be confident that further studies of the problem of managing comorbid patients on the backdrop of the COVID-19 pandemic will, in the future, reduce the number of complications and improve patients' quality of life. This will largely depend on the selection of therapies effectively able to influence the main manifestations of COVID-19 and provide good amelioration of mental or somatic pathologies. Fluvoxamine can be regarded as a promising drug in this direction, as it has not only high efficacy against anxiety and depressive symptoms and a good safety profile, including in patients with comorbid diseases, but also immunomodulatory and antiviral activity against the SARS-CoV-2 virus, as well as having positive effects on the prognosis of the progression of coronavirus infection – reducing the risk of hospitalization and death.

The authors declare no conflict of interest.

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