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The place and role of psychopharmacology in oncological disorders.

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Abstract. At least 25-30% of cancer patients suffer from mental disorders, which is why psychotropic drugs have been successfully used in oncology for a long time. Psychopharmacological drugs are also used as the main or auxiliary treatment for symptoms associated with cancer itself and side effects of therapy (sleep disturbances, loss of appetite, pain, nausea, fatigue, etc.). The use of psychotropic drugs allows you to target symptoms that negatively affect the quality of life of patients. However, there are problems associated with the interaction of drugs and side effects when prescribing psychotropic drugs. The article states that the effect of drugs on the body depends on the type of personality. Anxiety-phobic disorders, depression, and in severe cases, the dependence of consciousness disorders on the nervous system has been studied.

Keywords:psychotropic, personality typology, anxiety, psychopathic depressive disorders, cancer, psychotherapy, nervous system.

Роль и место психофармакологии в онкологических заболеваниях.

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Аннотация. По меньшей мере 25-30% пациентов с раком страдают психическими расстройствами, поэтому психотропные препараты давно успешно применяются в онкологии. Психофармакологические препараты также используются в качестве основного или вспомогательного лечения симптомов, связанных с самим раком, и побочных эффектов терапии (нарушения сна, потеря аппетита, боль, тошнота, усталость и др.). Применение психотропных

препаратов позволяет воздействовать на симптомы, негативно влияющие на качество жизни пациентов. Однако при назначении психотропных препаратов существуют проблемы, связанные с лекарственными взаимодействиями и побочными эффектами. В статье указывается, что в зависимости от типа личности действие препарата на организм зависит от нервной системы.

Ключевые слова: психотропные препараты, типология личности, тревожность, психопатические депрессивные расстройства, рак, психотерапия, нервная система.

Relevance. Cancer remains one of the most complex problems not only in our republic, but also throughout the world. According to statistics, in recent years, the incidence of cancer has been increasing in many countries of the world. According to the World Health Organization, “by 2030, 15 million people worldwide may be diagnosed with cancer.” An oncological diagnosis leads to affective changes in patients. They analyze the meaning of their past and future lives, their ability to realize themselves, which in turn has been shown to lead to depression and anxiety in patients. Comprehensive treatment of oncological disorders should include not only specialized antitumor therapy, but also, if indicated, psychopharmacotherapy. At least 25-30% of patients with cancer meet the criteria for a mental disorder. The most common psychiatric disorders are depression, adjustment disorder, anxiety, sleep disorders, and delusional disorder[1, 2]. A meta-analysis found that one-third of cancer patients suffered from psychiatric disorders at diagnosis or during emergency department admission, requiring specific psychopharmacological treatment [3, 4]. Another large cohort study of 7298 cancer patients found that approximately 15.6% of patients met criteria for a psychiatric disorder, compared with 1.4% of healthy controls. Psychotropic medications were prescribed to 14.6% of patients within 6 months of newly diagnosed cancer [5]. In 2020, the results of the first population-based cohort study of cancer patients were published. Of the 142,270 patients, 46% had depressive symptoms according to the Edmonton Symptom Rating Scale. Factors such as younger age, higher comorbidity, receiving systemic

therapy as part of treatment, and oropharyngeal and respiratory cancers contribute to an increased risk of depressive symptoms [6]. Prescribing psychotropic medications may begin immediately after diagnosis, perhaps due to fear of the consequences of the disorder, but there is a tendency to increase towards the end of the disorder. A retrospective study of 113,887 cancer patients found that the use of psychotropic medications (antipsychotics, antidepressants, and benzodiazepines) was significantly higher in the last 3 months of life than in the first 3 months after diagnosis. The frequent use of antidepressants may reflect the high psychological stress in the late stages of cancer, while the increased use of antipsychotics in the late stages of cancer may be associated with the development of organic brain damage [7]. Given the high prevalence of psychiatric disorders in this group of patients,Psychotropic drugs have been successfully used in oncology for a long time, both in the complex treatment of mental disorders and as an adjuvant treatment of symptoms directly related to cancer (e.g., pain, fever). The relatively safe profile and minimal risk of serious side effects contribute to the widespread use of these drugs. A population-based study in the United States showed that more than half of elderly patients with bladder cancer received psychotropic drugs within 2 years of diagnosis. The most commonly prescribed drugs were GABA stimulants/modulators and selective serotonin reuptake inhibitors [8]. Another study by Japanese scientists showed that psychotropic drugs are most often used for lung cancer, and less often for prostate cancer: 62.6% and 35.1%, respectively [9]. Due to the high importance of this problem, it is urgent to study and systematize the literature on the use of psychotropic drugs in oncology. Due to the widespread prevalence of mental disorders in this group of patients, psychotropic drugs have been successfully used in oncology for a long time, both in the complex treatment of mental disorders and in the adjuvant treatment of symptoms directly related to cancer (for example, pain, fever).

The purpose of the study. To summarize existing knowledge on the use of psychotropic drugs (antidepressants, antipsychotics, anxiolytics, and hypnotics) in

oncology for the treatment of psychiatric disorders and the relief of cancer-related symptoms.

Research materials and methods. To address these issues, a search was conducted using the keywords “psycho-oncology”, “psychopharmacotherapy” (“psychooncology”, “psychopharmacotherapy”) in the eLibrary, PubMed and Google Scholar databases. The primary search results were 622 articles, of which 93 were selected as the most complete publications that, in the opinion of the authors, reflect relevant scientific information on the topic under consideration (Figure 2).

Results and discussion Antidepressants. Over the past few decades, the use of this class of drugs in cancer disorders has become widespread, mainly due to the emergence of new classes of antidepressants that are better tolerated and have fewer side effects. First, antidepressants have been shown to be effective in treating depression, anxiety, and stress-related disorders in cancer disorders [10, 11]. Second, antidepressants are used as adjunctive therapy for non-cancer-related symptoms, such as hot flashes, neuropathic pain, nausea, vomiting, fatigue, and others [12]. The efficacy of antidepressants in cancer has been demonstrated in numerous randomized controlled trials [13-16]. Of all classes of antidepressants, selective serotonin reuptake inhibitors (SSRIs) are the most widely used in clinical practice due to their relatively simple dosing regimen and the optimal balance between potential benefits and the risk of side effects. SSRIs have also been shown to have anti-inflammatory properties against microglia, the main cells of the central nervous system that regulate and respond to inflammatory factors [17]. Since inflammatory mechanisms are involved in the biology and physiology of cancer, SSRIs are a reasonable option for the treatment of depression in these clinical situations. SSRIs may improve the immunity of cancer cells and have antitumor properties, including apoptotic properties in hepatocellular carcinoma cells [18]. Use of antidepressants in the treatment of comorbid psychiatric disorders. Depression is one of the most common disorders in cancer. Studies have confirmed the increased frequency of antidepressants prescribed to cancer patients to treat depressive symptoms [7, 11]. Systematic reviews and meta-analyses have shown that antidepressants, regardless of their class (e.g., SSRIs or

tricyclic antidepressants), are more effective than placebo in treating depressive symptoms [19]. However, antidepressants should generally be reserved for severe depression, and psychotherapy is optimal. Stress, stress-related disorders, and adjustment disorders are also common in cancer patients [1, 21]. Studies have shown that approximately 12–25% of cancer patients suffer from post-traumatic stress disorder, and 20% of patients suffer from adjustment disorders [22, 23]. According to the literature, antidepressants, especially SSRIs, are the first-line treatment for PTSD and adjustment disorders, but there are no specific data for cancer disorders [24]. For anxiety disorders (e.g., phobias, severe and persistent anticipatory anxiety, social anxiety), SSRIs, and mirtazapine are the drugs of choice in cancer disorders [25, 26]. Circadian rhythm disturbances in cancer patients are associated with depression, anxiety disorders, as well asmay be a complication of chemotherapy [27]. In this case, in addition to classic sleeping pills, antidepressants with sedative effects (e.g. mirtazapine and trazodone) may be prescribed. Use of antidepressants for cancer-related symptoms. Clinical practice, supported by scientific evidence, has shown that antidepressants can be used to improve cancer-related symptoms, such as loss of appetite, anorexia, sleep disorders, pain, and hot flashes, which significantly affect quality of life. First, antidepressants are used as adjuvant agents in the treatment of cancer pain [28, 29, 30]. Tricyclic antidepressants and SSRIs (primarily duloxetine) are effective in the treatment of neuropathic pain in cancer patients receiving chemotherapy [31, 32]. Some chemotherapy drugs can cause hot flashes, which can have a negative impact on patients' quality of life. Antidepressants, especially SSRIs and SSRIs, have been shown to be effective in treating hot flashes [33]. The most effective of these drugs were fluoxetine [34], sertraline [35], escitalopram duloxetine [36], and venlafaxine [37] (Table 1). However, caution should be exercised when using these drugs due to their potential inhibitory effects on the CYP2D6 enzyme [34, 36]. The antihistaminergic properties of mirtazapine may be aimed at combating nausea, anorexia/cachexia, and severe weight loss [38]. Phase II studies have confirmed its beneficial effects on appetite, sleep disturbances, anxiety, pain, as well as quality of life and depression in cancer patients [39]. Limitations of antidepressant

use in oncology, side effects and drug interactions. Other important issues related to the use of antidepressants in cancer include side effects and drug interactions [40, 41]. Commonly prescribed drugs for cancer patients, such as tramadol, procarbazine and linezolid, increase the risk of serotonin syndrome when combined with serotonergic antidepressants. These drugs may increase nausea and gastrointestinal symptoms and increase the risk of bleeding in patients with thrombocytopenia or taking anticoagulants. Hyponatremia, seizures and a lowered seizure threshold may occur. Fluoxetine, due to its long half-life and strong inhibitory effect on cytochrome CYP2D6, should be used with caution in cancer patients receiving chemotherapy to avoid possible drug interactions with antineoplastic agents metabolized by the CYP2D6 system. Similarly, paroxetine has a strong inhibitory effect on CYP2D6 and also has anticholinergic effects that require special attention from the treating physician. Sertraline, citalopram, and escitalopram have the least drug interactions and are the drugs of choice in this setting.Tamoxifen is a selective estrogen receptor modulator used to prevent relapse in patients with hormone receptor-negative breast cancer. The enzyme cytochrome 2D6 (CYP2D6) is the main enzyme that converts tamoxifen to its active metabolite endoxifen. Genetic variations in CYP2D6 affect the conversion of tamoxifen to its active form; approximately 7% of women have alleles that do not function in CYP2D6 and have low endoxifen levels. Three antidepressants—paroxetine, fluoxetine, and duloxetine—are potent inhibitors of CYP2D6; they may interfere with tamoxifen metabolism [42]. A retrospective study found that women taking combination therapy with tamoxifen and paroxetine had an increased risk of breast cancer death, which has led many physicians to change their prescribing of antidepressants. Subsequent large studies investigating the effects of different CYP2D6 metabolic phenotypes have found no association with disease control or relapse [43, 44]. Current clinical recommendations are to avoid strong CYP2D6 inhibitors (paroxetine) in favor of drugs that are either non-selective or weak inhibitors of this cytochrome (escitalopram, venlafaxine), but the treating physician should be aware of further studies on this issue. [45]. However, a 2022 review found no difference in treatment outcomes between patients who received antidepressants

(including paroxetine) in combination with tamoxifen and those who did not [46]. It should be noted that the Russian-language instructions in the "Drug Interactions" section indicate that the entire group of SSRIs is capable of reducing the active metabolite of tamoxifen. Therefore, such prescriptions should be carried out with great caution and carefully documented.but the treating physician should be aware of further studies on this issue. will be available [45]. However, a 2022 study found no difference in treatment outcomes between patients who took antidepressants (including paroxetine) in combination with tamoxifen and those who did not [46]. It should be noted that the Russian-language instructions in the "Drug Interactions" section indicate that the entire group of SSRIs is capable of reducing the active metabolite of tamoxifen. Therefore, such prescriptions should be carried out with great caution and carefully documented.but the treating physician should be aware of further studies on this issue. will be available [45]. However, a 2022 study found no difference in treatment outcomes between patients who took antidepressants (including paroxetine) in combination with tamoxifen and those who did not [46]. It should be noted that the Russian-language instructions in the "Drug Interactions" section indicate that the entire group of SSRIs is capable of reducing the active metabolite of tamoxifen. Therefore, such prescriptions should be carried out with great caution and carefully documented.

Antipsychotics. Antipsychotics are also drugs that have been used in oncology practice for a long time. They are used to treat mental disorders such as psychosis, depression, anxiety; psychotic disorders (delirium and/or psychotic symptoms caused by certain drugs), as well as side effects of chemotherapy. In many cases, individual antipsychotics are used to control the side effects of specific antipsychotics, such as nausea, vomiting, or decreased appetite. Use of antipsychotics in the treatment of comorbid mental disorders. For acute anxiety in cancer patients, antipsychotics may be preferable to benzodiazepines, as the latter increase the risk of mood changes and respiratory depression. For similar reasons, low-dose sedative atypical antipsychotics (quetiapine, olanzapine) are preferable to hypnosis for the treatment of insomnia [47, 48, 49]. Risperidone and olanzapine have been shown to be effective and well-

tolerated in reducing agitation and depressive symptoms in children with cancer [50]. Use of antipsychotics for cancer-related symptoms. Haloperidol, levomepromazine, and droperidol are not recommended for the control of nausea and vomiting in cancer patients due to insufficient data on their efficacy [51, 52, 53]. However, the atypical antipsychotic olanzapine has shown efficacy in the treatment of chemotherapy-induced nausea and vomiting [54]. Olanzapine 10 mg significantly reduced nausea, vomiting, and the use of palliative care compared with placebo in cancer patients undergoing chemotherapy and experiencing severe vomiting [55]. In pediatric oncology, olanzapine, at a mean dose of 0.1 mg/kg, reduced chemotherapy-associated vomiting. The mean age of the patients in the sample was 13 years [56]. Thus, the use of olanzapine as part of a comprehensive treatment for nausea and vomiting is justified in both children and adults with cancer. Studies have shown that olanzapine reduces weight loss by more than 10% and increases food intake in cancer patients [57, 58, 59]. This property may be useful in the treatment of anorexia nervosa caused by cancer. More than 90% of cancer patients experience antemortem delirium in the last days of life [60, 61]. In addition, 70% develop anxiety, agitation, or aggressive behavior [62]. Antipsychotics have long been used as first-line treatments for delirium and related agitation [63, 64]. Among the typical antipsychotics, haloperidol is one of the most commonly used [65].In a survey of 135 palliative care physicians in nine countries, haloperidol was considered one of the four essential drugs that should be available in all settings for the treatment of cancer [66]. In addition, the combination of lorazepam and haloperidol was shown to be superior to haloperidol monotherapy in terms of control of agitation and subjective assessment of patient comfort [63, 67]. In addition to haloperidol, chlorpromazine is also preferred for the treatment of antemortem delirium. It blocks alpha1-adrenergic receptors, which effectively reduces agitation [68]. However, haloperidol is not recommended for hypoactive delirium due to lack of efficacy or worsening of symptoms, possibly due to multi-organ failure [69]. In addition, the increased risk of neuroleptic malignant syndrome, which is common with haloperidol and other antipsychotics that are D2 receptor antagonists, should be considered [70]. A recent systematic review found that

olanzapine and quetiapine are suitable alternatives to haloperidol, especially in patients with severe extrapyramidal symptoms, who require sedation, or who are intolerant to haloperidol [71]. Risperidone is also used in the treatment of delirium, and its efficacy has been comparable to haloperidol and olanzapine [72, 73]. Cancer patients are at increased risk of adverse events due to their poor general health. For example, hypovolemia may increase the risk of orthostatic hypotension, which can lead to syncope and collapse. The intramuscular route of administration of antipsychotics is associated with an increased risk of hematomas in cancer patients with thrombocytopenia. The problem of neuroleptic hyperprolactinemia in patients with breast cancer is increasing. The lifetime prevalence of breast cancer in patients with schizophrenia is 25% higher than in the general population [74, 75]. Many intracranial tumors overexpress prolactin receptors and promote tumor growth regardless of prolactin receptor status. A recent study from Finland showed that long-term use of antipsychotics that increase prolactin levels (risperidone and haloperidol) increases the risk of breast cancer [76]. Of the antipsychotics most commonly used in oncology practice, risperidone and haloperidol often cause hyperprolactinemia, while aripiprazole, ziprasidone, and quetiapine cause minimal increases in prolactin [77]. Astasia may occur with other extrapyramidal symptoms, especially when antipsychotics are combined with antimimetics. Although extrapyramidal symptoms are usually associated with typical antipsychotics, they can also occur with atypical antipsychotics such as risperidone and olanzapine, especially at high doses [78]. Regular monitoring of the QT interval,This is particularly important in cancer patients with electrolyte abnormalities and in patients receiving drugs that prolong the QT interval, as QT prolongation may predispose to life-threatening ventricular arrhythmias [79]. This adverse effect is most pronounced with thioridazine, sertindole, ziprasidone, haloperidol, risperidone, and olanzapine, but regular QT interval monitoring is recommended for all patients taking antipsychotics [80]. A meta-analysis of antipsychotic use in schizophrenia found that aripiprazole, lurasidone, paliperidone, and asenapine were the least likely to prolong the QT interval [81]. Other serious adverse events associated with the use of atypical

antipsychotics in the elderly have been described [82]. Additional concerns with antipsychotic use include the risk of metabolic syndrome (i.e., insulin resistance, dyslipidemia, obesity) with long-term use, hyponatremia, decreased seizure threshold in the context of concurrent steroid use and QT, drug interactions, increased hepatic transaminases, and anticholinergic effects (e.g., constipation, dry mouth, urinary retention). There is a risk of falls and aspiration pneumonia when antipsychotics are prescribed to patients with delirium [83]. When prescribing antipsychotics, you should start with minimal doses and then titrate to achieve a more favorable effect [84]. The use of anxiolytics and hypnotics in the treatment of comorbid psychiatric disorders in patients with cancer. A meta-analysis of 70 studies found that the prevalence of adjustment disorders and anxiety disorders in cancer patients was 19.4% and 10.3%, respectively [1]. Although serotonergic antidepressants remain the mainstay of treatment for generalized anxiety and panic attacks in cancer patients, treatment often includes short- and long-term benzodiazepines. Benzodiazepines are often the drug of choice for acute anxiety and panic symptoms. Short-acting drugs such as alprazolam, lorazepam, and oxazepam may be useful for short-term procedures (fear of injections, closed MRI) or panic attacks [76]. Clonazepam and diazepam are longer-acting and may be useful for symptomatic anxiety and insomnia. Zolpidem, zopiclone, and zaleplon, also known as the “Z-drugs,” are nonbenzodiazepine drugs used to treat insomnia in cancer patients. This class of drugs has minimal anxiolytic effects and is associated with a lower risk of tolerance and adverse reactions [85, 86]. The antihistamine hydroxyzine may also be prescribed for panic symptoms when needed [24]. The main advantage of nonbenzodiazepine drugs is that they are not usually addictive.Lemborehant has previously been shown to be effective and well-tolerated in patients with insomnia who have difficulty falling asleep and frequently waking up [87]. A small pilot study evaluated lemborehant with similar results for sleep disorders in cancer patients, including delirium. Despite the limitations of the study (small sample, retrospective evaluation), the results are encouraging and suggest that the drug may be more widely used in the future [88]. Use of anxiolytics and hypnotics for cancer-related symptoms. Benzodiazepines are

often used to treat psychomotor agitation and seizures. If symptoms are refractory, they are used for palliative sedative therapy. The ideal benzodiazepine for use in palliative care is midazolam, due to its rapid onset of action, short duration of action, and lack of significant withdrawal symptoms. It is one of the four essential drugs for patients with end-stage disease [89-92]. In combination with antiemetics and behavioral therapies, benzodiazepines may also be effective in chemotherapy-induced nausea [83]. Aquagenic pruritus (intense itching upon contact with water) in BCR-ABL1-negative myeloproliferative neoplasms can significantly reduce the quality of life of cancer patients. The anxiolytic hydroschizin, which has antihistamine and anticholinergic effects, may be effective in patients with this pathology [84]. Limitations of use, side effects, and drug interactions. The most common side effects of benzodiazepines include sedation, dizziness, drowsiness, respiratory depression, coordination, and confusion [76].The anxiolytic hydrochlorothiazide, which has antihistamine and anticholinergic effects, may be effective in patients with this condition [84]. Limitations of use, side effects, and drug interactions. The most common side effects of benzodiazepines include sedation, dizziness, drowsiness, respiratory depression, incoordination, and confusion [76].The anxiolytic hydrochlorothiazide, which has antihistamine and anticholinergic effects, may be effective in patients with this condition [84]. Limitations of use, side effects, and drug interactions. The most common side effects of benzodiazepines include sedation, dizziness, drowsiness, respiratory depression, incoordination, and confusion [76].

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