Recommendations of the World Health Organization on Depressive Disorders in Human Health and Modern Pharmacotherapeutic Approaches to Optimizing Antidepressant Programs in the Alcohol Addiction Clinic

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Abstract. The article highlights the current recommendations of the World Health Organization (WHO) on the optimization of antidepressant programs. Based on global WHO studies conducted in 36 countries with different income levels, it is proven that the low level of recognition and treatment of depression and anxiety disorders leads to significant socio-economic losses. Particular attention is paid to losses for households, employers, and states, as well as insufficient financing of mental health even in high-income countries. The economic feasibility of investments in mental health is substantiated, through treatment that includes psychotherapy, drug therapy or their combination with the support of WHO mhGAP recommendations. The relationship of depression with other non-communicable diseases and the risk of suicidal behavior is separately considered. In a practical context, cases of depressive disorders among workers are analyzed, in conditions of military operations, economic instability and substance abuse. The importance of compliance with labor legislation in the context of mental health protection is described. A clinical approach to the complex therapy of depression of alcoholic origin in the post-abstinence period with the use of trazodone and cocarnitine is proposed, which demonstrates effectiveness in overcoming pathological craving for alcohol and stabilizing the psycho-emotional state. The results of the study indicate the feasibility of long-term active and supportive therapy to prevent relapses.

Keywords: depression, comorbid disorders, pharmacotherapy, advanced training, labor discipline, trazodone and cocarnitine drugs, circulation, safety, State Pharmacopoeia of Ukraine.

Introduction. In modern conditions, citizens of Ukraine, especially internally displaced persons, minors, youth, and combatants, need medical and pharmaceutical assistance due to psychoneurological stress and depressive states [1-3].

Depression is not always perceived as a disease by the patient's relatives and the patient himself [4]. A bad mood lasts for weeks. Everything is seen in gloomy colors. Low performance, lack of concentration and attention, no desire to move and work. Such patients need medical and pharmaceutical assistance. Unfortunately, 5 out of 100 schoolchildren or young people are familiar with this condition. The risk of depression increases with age. Among young people, depression ranges from 15% to 40%. Among adults, depressive disorders occur in every 10th person. Women are 2 times more likely to experience depression. In older age, about 30% of citizens have already been in a state of depression.

WHO experts believe that depressive disorder (depression) is a common mental disorder. It includes depressed mood or loss of pleasure or interest in activities for a long time [5-7].

- About 3.8% of the population experiences depression, including 5% of adults (4% among men and 6% among women) and 5.7% of adults over 60 years of age;
- About 300 million citizens in the world suffer from depression;
- Depression is approximately 50% more common among women than among men;
- More than 10% of pregnant women and women who have just given birth worldwide experience depression;

- More than 700,000 people die from suicide each year, and suicide is the 4th leading cause of death among 15–29-year-olds;
- Depression is different from regular mood swings and worries about everyday life, which affect all aspects of life, including relationships with family, friends, and society;
- Depression can happen to anyone who has experienced abuse, serious losses, or other stressful events, and is more likely to develop depression;
- More than 75% of citizens in low- and middle-income countries do not receive modern, effective, and affordable treatment;
- Obstacles to effective care include lack of investment in psychiatric care, lack of trained health care providers and social stigma associated with mental disorders.

Being in a depressed state, a citizen (professional, student, entrepreneur, employee, schoolchild, unemployed, etc.) is looking for a way out of a difficult situation (absenteeism at work, unemployment, destroyed housing, family conflict, committing a crime, constant stress due to the "air raid" signal, etc.). Against the background of the above, when using psychoactive substances (for example, alcohol, adulterated alcoholic beverages, prohibited psychoactive substances), comorbid addictive disorders are formed, associated with Covid, post-Covid, long-Covid disorders [8-22].

The employer (head of the pharmacy, director of the enterprise, etc.) must ensure the right of a sick employee (pharmacist, doctor, laboratory assistant, scientist) to contact a health care institution. This is regulated by the relevant articles of the Labor Code of Ukraine (Articles 123, 124, 139-152, 153-173, 173^2-200). For example, Article 169 "Mandatory medical examinations of employees of certain categories" [23].

Prevention of deterioration of the health of subordinates by identifying the causes and conditions that caused the state of depression and comorbid addictive disorders contributes to the observance of labor discipline, the right of employees to career growth, promotion, and advanced training [24, 25].

That is, timely diagnosis of depression syndrome in the addiction clinic and the problem of optimizing antidepressant pharmacotherapeutic programs is an important aspect of stabilizing post-abstinence and remission periods in medical and pharmaceutical practice. Pathogenesis, pathokinetics, typology, classification, evolution, and issues of therapy of depression syndrome in the addiction clinic have always been the subject of active discussion in the professional environment of health care professionals [26-31].

In recent years, priority has been given to studies in which the authors use an integrated approach to the treatment of depressive disorders of post-intoxication genesis in accordance with the ICD-11 [32-57].

As researchers note, among the various drugs recommended as first-line drugs in the treatment of depressive disorders, one of the most popular are specific serotonergic antidepressants. This is a group of antidepressants that have relatively few side effects and are well tolerated (Trittico, active ingredient Trazodone). Along with blocking serotonin reuptake and increasing serotonergic neurotransmission, drugs in this group block 5-HT2 subtype receptors, which explains the low likelihood of exacerbation of anxiety, insomnia, and nervousness [30, 31, 58].

Good combination with metabolic and vitamin drugs, efficacy, tolerability, and safety confirmed by numerous clinical trials, allow the use of drug complexes in depression correction schemes in remission states in patients with associated addiction [59, 60]. This indicates the relevance and importance of developing a pathogenetically substantiated therapeutic direction using the antidepressant trazodone in combination with the metabolic cocarnitine.

Consideration of WHO recommendations for depressive disorders in human health and modern pharmacotherapeutic approaches to optimizing antidepressant programs is an extremely relevant problem in modern conditions to ensure labor discipline, provide appropriate medical and pharmaceutical services and the right to further career growth of specialists.

The purpose of the study was to review WHO recommendations for optimizing antidepressant programs in working conditions and career growth of healthcare professionals. Study

of the therapeutic possibilities of a comprehensive antidepressant program in clinical situations related to the correction of depressive disorders in the remission period.

Materials and methods. 37 patients were examined, men from 34 to 47 years old (mean age 38.9 ± 1.4) with comorbid alcohol addiction syndrome on the background of manifesting depressive disorders. The duration of the disease was up to 5 years in 7 patients, up to 10 years in 12, up to 15 years in 10, and over 15 years in 8. Binge-type alcohol addiction was observed in 29 patients.

For antidepressant correction, the pharmacotherapeutic complex trazodone + cocarnitine was used.

Use during pharmacotherapy of the drug complex:

- trazodone, which is a triazolopyridine derivative, has a predominantly antidepressant effect, with some sedative and anxiolytic effects. It quickly affects the mental (affective tension, irritability, fear, insomnia) and somatic symptoms of anxiety (palpitations, headache, sweating). Stabilizes the emotional state, improves mood, reduces pathological craving for alcohol. Effective for the treatment of anxiety-depressive states and sleep disorders, increases the depth and duration of sleep, restores its physiological structure and quality.
- cocarnitine is a rationally selected drug of a combination of metabolic substances and vitamins. Nicotinamide is one of the forms of vitamin PP, participates in redox processes in the cell, improves carbohydrate and nitrogen metabolism. Cocarboxylase is a coenzyme formed in the body from thiamine (vitamin B1) supplied from the outside. It plays an important role in carbohydrate metabolism, promotes the synthesis of nucleic acids, proteins, and lipids. Reduces the level of lactic and pyruvic acids in the body, promotes glucose absorption. Improves the trophism of nervous tissue. Cyanocobalamin (vitamin B12) increases protein synthesis in the body and promotes its accumulation. Activates the metabolism of carbohydrates and lipids. Reduces cholesterol levels in the blood, prevents fatty infiltration of the liver. Has a beneficial effect on the function of the liver and nervous system. Has a hypotensive and antiarrhythmic effect. Has a vasodilator effect, including on the coronary arteries. Disodium adenosine triphosphate trihydrate stimulates metabolic processes, has a hypotensive and antiarrhythmic, vasodilator effect, including on the coronary arteries.

The main method of studying patients is clinical-psychopathological. Along with the clinical diagnostic method, the Hamilton Depression and Anxiety Scale (HDRS) was used to assess the dynamics of the patient's condition and the effectiveness of trazodone pharmacotherapy. However, over the past 50 years, the Hamilton Depression and Anxiety Scale (HAM-D) has been modified into 11 versions and applied to different groups of patients in psychiatric, narcological, medical, scientific and health care institutions [61].

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Results and discussion. According to WHO experts, during emergencies, 1 in 5 citizens suffers from depression and anxiety [62, 63]. Thus, between 1990 and 2013, the number of people suffering from depression or anxiety increased by almost 50% from 416 million to 615 million. About

10% of the world's population is affected. Mental disorders account for 30% of the global burden of non-fatal diseases. Humanitarian emergencies, ongoing conflicts, or hostilities in areas where vulnerable civil society lives (for example, Kharkiv region), further increase the need for expanding treatment options and pharmacotherapy.

In Ukraine, the share of the population suffering from depression is 6.3%. According to the rating published on the Country Cassette portal, Ukraine has become the country with the highest number of people suffering from depressive health disorders in the world [64, 65].

Depression is reported to be a common global problem, affecting approximately 3.4% of the world's population, or approximately 264 million people, as follows (Figure 1):

- in Ukraine, ranked 1st, the proportion of the population suffering from depression is 6.3%;
- the USA and Australia, with a rate of 5.9%, ranked 2nd and 3rd;
- Estonia – 4th place (5.9%);
- Brazil – 5th place (5.8%);
- Greece – 6th place (5.7%);
- Portugal – 7th place (5.7%);
- Belarus – 8th place (5.6%);
- Finland – 9th place (5.6%);
- Lithuania – 10th place (5.7%);
- Solomon Islands, East Timor, Papua New Guinea, and the Federated States of Micronesia rank last in the ranking, with depression occurring in 2.9% to 3.1% of citizens.

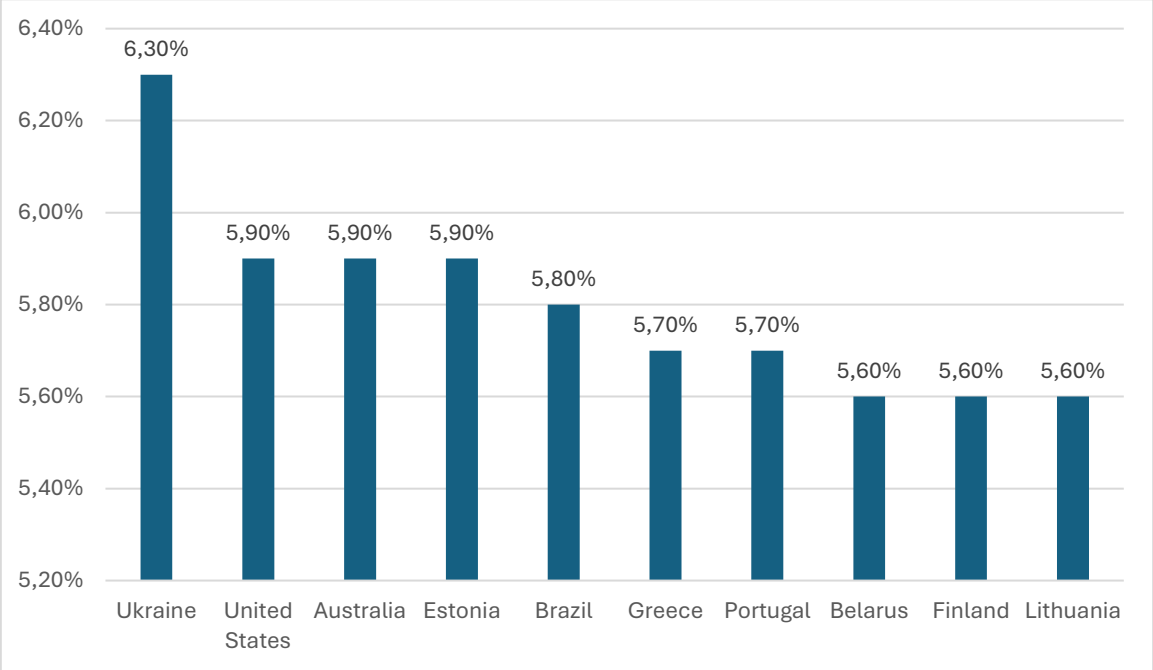

Fig. 1. Ranking of the 10 countries with the highest rates of depression [64, 65].

Need to note that the neurological differences that distinguish patients with depression are at least partly hereditary [66]. Genetic studies indicate that individuals who have close relatives (e.g., parents or siblings) who suffer from depression are 20–30% more likely to suffer from depression. Unlike diseases that are associated with a specific defective gene (e.g., cystic fibrosis), depression is likely to be associated with multiple genes.

However, depression causes difficulties in all aspects of a person's life and functioning, including in society and at home, at work and school, in transportation and on the street. Depression is a major risk factor for suicide, accounting for over 700,000 deaths each year. Suicide is the 4th leading cause of death among adolescents and young adults aged 15–29 years [50, 67, 68].

During a depressive episode, the sufferer experiences a depressed mood, feelings of sadness, irritability, emptiness, fatigue, lack of motivation, and a sense of loss of pleasure or interest in

activities. A depressive episode is different from regular mood swings. They last most of the day, nearly every day, for at least two weeks. A depressive episode is classified as mild, moderate, or severe depending on the number and severity of symptoms [69–72]:

- ❖ feelings of sadness, tearfulness, emptiness, or hopelessness;
- ❖ outbursts of anger, irritability, or frustration even over trivial matters;
- ❖ loss of interest or pleasure in most or all usual activities, such as sex, hobbies, or sports;
- ❖ sleep disturbances, including insomnia or excessive sleeping;
- ❖ fatigue and lack of energy, so even small tasks take extra effort;
- ❖ loss of appetite and weight loss or increased food cravings and weight gain;
- ❖ anxiety, agitation, or restlessness;
- ❖ slowed thinking, speech, or body movements;
- ❖ feelings of worthlessness or guilt, focusing on past failures or blaming yourself;
- ❖ problems with thinking, concentrating, making decisions, and remembering things;
- ❖ frequent or recurring thoughts of death, suicidal thoughts, suicide attempts or suicide;
- ❖ unexplained physical problems such as back pain or headaches;
- ❖ feeling unhappy without knowing why.

Thanks to the continuation of multidisciplinary studies [30, 42, 56, 57, 73-81] and studies conducted by the authors based on the Avicenna drug treatment clinic, depressive disorders were detected in all 37 patients (men, aged 34 to 47 years). They were distinguished by a variety of psychopathological manifestations and were characterized by the presence of somatic and vegetative disorders against the background of a pronounced craving for alcohol: depressed mood, ideational and motor inhibition, a feeling of internal tension and anxiety, restlessness, feelings of longing, fear, irritability, explosiveness, hypochondria, decreased interest in usual activities, loss of initiative in communication, sleep disturbances, dreams about alcohol, attacks of anger or apathy.

During pharmacotherapy, patients were prescribed:

- ➢ trazodone in an initial dose of 75 mg 2 times a day. From the 4th day, the dose was increased to an individually therapeutically effective dose depending on the severity of symptoms and the speed of onset of the effect. The average was 300 mg/day in 2 doses. After achieving stabilization of the condition on the 12^{th} 14^{th} day of pharmacotherapy, the dose was reduced to 150 mg/day. Further administration of the drug was recommended for relapse prevention for up to 30 days;
- ➢ trazodone was combined with the administration of the drug cocarnitine intramuscularly, 1 ampoule of the drug once a day. The course was up to 6-7 days. Cocarnitine was used immediately after preparation. It should be red in color. The use must be carried out under the control of laboratory tests.

Analyzing the results of complex pharmacotherapy with the use of the drug trazodone, first, we determined:

- ✓ its ability to facilitate the possibilities of therapeutic compliance with the patient, to influence against mood deterioration with irritability, anxiety, fears, sleep disorders;
- ✓ as a result – stopping of the obsessive craving for alcohol. In most observations, from the 4^{th} 6^{th} day, a pronounced effect of trazodone on the pathological craving for alcohol was noted, its severity decreased; from the 9^{th} 10^{th} day, a therapeutic effect of trazodone was noted in stopping depressive and anxiety disorders, which positively correlated with the levels of the Hamilton scale indicators;
- ✓ the appearance of activity, improved contact, sociability. Patients became more "softer", more responsive, and more willingly went to psychotherapeutic contact with a doctor. Patients felt a "rush of strength", the appearance of "vigor", subjective improvement, and "ease" of the mental process;
- ✓ a decrease in anxiety, dysphoria, activation was observed in patients on average on the 12^{th} 14^{th} day of therapy.

Subsequently, approximately 2 weeks after the start of antidepressant pharmacotherapy, there was:

- more gradual stabilization of mood, normalization of sleep and appetite;
- the behavior of patients was noticeably improved within 20-30 days;
- patients expressed fewer complaints and claims, doubts about the need to undergo a full course of treatment disappeared;
- the effectiveness of the drug proves the close connection between affective and addictive symptoms and indicates the possibility of antidepressant intervention with the use of the drug trazodone to optimize the therapy of patients with AD in outpatient settings.

It is important to note that the authors' research conflicts with the conclusions of WHO experts. The costs of treating patients and health outcomes in 36 low-, middle-, and high-income countries were calculated. It was found that [83, 84]:

- low recognition and access to treatment for depression, a common mental disorder, and anxiety leads to global economic losses of trillions of US dollars each year;
- losses are borne by households, employers, firms, and governments:
- households lose money when people cannot work;
- employers suffer when workers become less productive and unable to work;
- governments are forced to pay higher costs for health care and socio-economic security.
- in many countries, support for people with mental health disorders is absent or very limited;
- even in high-income countries, almost 50% of people with depression do not receive treatment;
- on average, only 3% of government health budgets are invested in mental health, ranging from less than 1% in low-income countries to 5% in high-income countries;
- investing in mental health makes economic sense. Every US$1 invested in scaling up treatment for depression and anxiety leads to a return of US$4 in improved health and functioning;
- pharmacotherapy includes antidepressants, or a combination of psychotherapy and pharmacotherapy. Both approaches can be provided by non-specialist health workers after brief training and using the WHO mhGAP intervention guide;
- over 90 countries across all income levels have introduced or expanded programs that provide treatment for depression and other mental disorders using the recommendations in this intervention guide:
- a strong link has been found between depression and other non-communicable disorders and diseases;
- depression increases the risk of developing associated comorbid cardiac, hormonal, and addictive disorders;
- depression is also an important risk factor for suicide, which claims hundreds of thousands of lives each year;
- patients with depression usually have several of the following: loss of energy; change in appetite; sleeping more or less; anxiety; decreased concentration; indecisiveness; restlessness; feelings of worthlessness, guilt, or hopelessness; and thoughts of self-harm or suicide;
- expanding mental health services will contribute to achieving one of the goals of the Sustainable Development Goals, adopted by the UN General Assembly in 2015: to reduce by one third, by 2030, premature mortality from noncommunicable diseases through prevention and treatment of the population and to promote mental health and well-being in relation to public health [84, 85].

Thus, the WHO recommendations on depressive disorders of human health and modern pharmacotherapeutic approaches to optimizing antidepressant programs in the clinic of alcohol addiction are considered. The authors' research raises an extremely relevant problem in modern conditions to ensure labor discipline at the enterprise, ensure access to timely medical care and guarantee the right of specialists who comply with the Labor Code of Ukraine to further career growth. It is important that the research clashes with the conclusions of WHO experts, which calculated the costs of treating patients and health outcomes in 36 countries with low-, middle- and high-income levels. It was established that the low level of recognition and access to treatment of

depression leads to global economic losses of a trillion US dollars each year; losses are borne by households, employers, firms and governments; governments are forced to pay higher costs for healthcare and socio-economic security; Even in high-income countries, nearly 50% of people with depression do not receive treatment; on average, only 3% of the national health budget is invested in mental health, ranging from less than 1% in low-income countries to 5% in high-income countries. There is a strong link between depression and other non-communicable disorders and diseases. Depression increases the risk of substance use disorders and diseases such as diabetes and heart disease. Depression is also a significant risk factor for suicide, which takes hundreds of thousands of lives each year. In a depressed state, patients seek a way out of a difficult situation (absenteeism from work, unemployment, broken housing, family conflict, committing a crime, constant stress due to the "Airborne Alarm" signal). They begin to abuse psychoactive substances (in particular, alcohol). In turn, the employer must ensure the employee's right to go to the hospital, which is regulated by the relevant articles of the Labor Code of Ukraine (Articles 123, 124, 139-152, 153-173, 1732-200). For example, Article 169 – mandatory medical examinations of employees of certain categories, which will contribute to the observance of labor discipline and the improvement of the employee's condition by identifying the causes and conditions that caused the deterioration of health (depression). The therapeutic possibilities of complex therapy with the use of the antidepressant trazodone and the metabolic cocarnitine in clinical situations related to the correction of depressive disorders in the post-abstinence period of alcohol addiction are considered. A group of patients (37 patients) was examined, in whom after stopping the withdrawal syndrome there were complaints about the actualization of pathological craving for alcohol against the background of manifesting depressive disorders. Clinically, synchronization of post-abstinence symptoms and depressive pathology was revealed. Clinical data obtained during the study show that the proposed complex algorithm has a wide spectrum of activity against depressive disorders of alcoholic origin. To achieve stable therapeutic effects, the course of active therapy should be at least 20-30 days, for the prevention of relapses, maintenance therapy is recommended in courses of 12-14 days.

Conclusions.

1. Ukraine has the highest prevalence of depression in the world — 6.3%, which is almost twice the world average (3.8%). This indicates a serious need for the implementation of comprehensive measures to protect mental health.
2. Vulnerable categories of the population, in particular internally displaced persons (IDPs), youth, minors, and combatants, who are under psychoneurological stress and often suffer from depressive states, require special attention.
3. Depressive disorders significantly affect the general condition of a person and his behavior, which can lead to the abuse of psychoactive substances, in particular alcohol, especially in difficult social circumstances (loss of housing, conflicts, unemployment, air anxiety, etc.). This increases social risks and increases the burden on the healthcare system.
4. It is necessary to strengthen the role of employers in supporting employees who face mental disorders, ensuring that they can seek medical help in accordance with the current labor legislation of Ukraine (in particular, Article 169 of the Labor Code).
5. Pharmacotherapeutic approaches to the treatment of depression in patients with alcohol dependence have proven their effectiveness. Clinical research data show that the use of trazodone and cocarnitine helps achieve stable remission, reduce pathological craving for alcohol, and improve overall mental health.
6. Providing the population with high-quality, effective, and affordable medicines, as emphasized by WHO experts, is a key task of the Ministry of Health of Ukraine, government agencies and health care institutions. Particular attention should be paid to the compliance of drugs with quality indicators, standardization, certification requirements of the State Pharmacopoeia of Ukraine.
7. Improving the mental health system is directly related to achieving the Sustainable Development Goals reducing premature mortality from non-communicable diseases by 2030 through prevention, treatment, and social support.

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Data availability statement. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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