

Antidepressants In General Practice And Psychiatry

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Abstract — Depression can be compared to a fire that occurs in our head. Gradually, it burns what used to be pleasurable, leaving only the feeling of emptiness and sadness. It influences thoughts, emotions, thinking and affects the everyday activities. Depression is a disorder characterized by a constant state of sadness and hopelessness. Depressed person loses interest in any activity that is usually brings pleasure, as well as the inability to perform daily living activities. These symptoms should be permanent (at least two weeks). Bad mood once a month, with or without a reason, cannot immediately be called depression. This insidious disorder destroys relationships, impedes normal functioning and can even lead to job loss. Accumulation of problems, the lack of support from family members and the lack of skilled help can lead to even more devastating behaviour and even suicide. This review article discusses the problems associated with the treatment of depression and the impact of this problem on the lives of Nations. The value of antidepressants in the treatment process discussed in details.

Index Terms — major depressive disorder, depression, antidepressants, bipolar disorder, daily living activities

I. INTRODUCTION

Depression is one of the most common mental illnesses found in all countries of the world. According to WHO, in 1998 major depression ranked fifth among all causes of the planet's morbidity and third among women's morbidity [1]–[6]. It is believed that by the end of 2020 depression will come in second place among the causes of morbidity, giving way to only coronary heart disease. The average age of onset of depression is 35–40 years, but in recent years the proportion of younger people (even adolescents) suffering from depression has increased [1], [5]–[9]. Depressive disorder limits work capacity, reduces social activity, leads to significant difficulties in maintaining interpersonal relationships, which negatively affects both the patient and his or her loved ones. and the well-being of society as a whole. In addition to the negative consequences associated with the costs of treatment, disability and premature death, there is also other damage that is not quantifiable. We are talking about inabilities and lost opportunities, which is especially important for young people [1], [5]–[9]. One of the main problems today, depressive disorders are not actively identified and properly diagnosed. A large-scale European epidemiological study of DEPRES, which examined more than 78,000 people, found that 69% of patients with depression did not receive adequate medication [10], [11]. Only 7.1% of patients with depressive episode were prescribed antidepressants. Attempts have been repeatedly

made to analyze the causes of the situation. Often patients believe that the problem can be solved without their active involvement, they say, everything “will go by itself”, so they do not take any action or try to cope with the disease on their own. It should be noted that a significant obstacle to seeking specialized psychiatric (mental) care is the preconceptions associated with mental illness and the fear of hospitalization. The study also noted that patients were often not satisfied with the quality of treatment: 37% of the patients surveyed were convinced that drug therapy would not help them; 10.7% are not satisfied with the treatment; 19.3% believe that the antidepressants they received earlier were not effective [11].

II. HOW CAN WE INCREASE THE EFFECTIVENESS OF TREATMENT FOR PATIENTS WITH DEPRESSION?

To improve the quality of medical and social care for patients with depression, it is necessary to ensure its earliest possible diagnosis and to prescribe treatment using effective antidepressants in adequate therapeutic dosages. Even with the correct diagnosis, treatment of depression is ineffective due to the fact that physicians use antidepressants in inadequate (“too small”) doses and for a relatively short time. In a large-scale study, which involved about a million patients who first sought medical help, it was shown that only 11% of patients received antidepressants in effective therapeutic dosages [5], [12]. Another pressing issue remains - high resistance to existing therapy. On average, 30–40% of cases of depressive disorders have shown resistance to prescribed therapy. Such a high proportion of patients who do not respond to the applicable drug therapy justify the synthesis of new, effective antidepressants, which will allow a more differentiated approach to the therapy of choice for different patients. When selecting antidepressant, we should take into account the clinical form of mood disorder, the patient's general health condition and principles of effective monotherapy, safety and tolerability [11]–[13]. Depressive, anxious, obsessive-compulsive, hypochondriacal, and somatoform symptoms in depressive psychopathological structure refers to various types of mental disorders [11]. However, as daily clinical practice shows, these psychopathological phenomena often coexist. Their clinical manifestations are based on changes at the biochemical level and impairment of neurotransmitter metabolism in the synapses of the brain [4], [10]–[12]. Symptoms associated mainly with a deficit of serotonin (suicidal thoughts, agitation, decreased libido, impaired appetite and irritability),

norepinephrine (apathy, lethargy, impaired concentration, loss of strength and fatigue), and mixed, caused by a deficiency of both serotonin and norepinephrine can be distinguished (loss of interest, depressed mood, decreased self-esteem, sleep disturbance and anxiety) [11]. 70- 80% of patients with depression are diagnosed with symptoms caused by a violation of both neurotransmitter systems. The drug of choice of which is based on a symptomatic principle, can increase the effectiveness of antidepressant therapy. So, for example, drugs from the group of selective serotonin reuptake inhibitors (SSRIs) inhibit the reuptake of serotonin only and mainly affect the symptoms caused by neuro-metabolic disorders of this particular neurotransmitter. This may explain why SSRIs are less effective than tricyclic antidepressants (TCAs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs), which affect both serotonin and norepinephrine metabolism. Antidepressants with double mechanism of action can significantly increase the effectiveness of treatment for patients with depression [5], [11].

III. WHAT NEW ANTIDEPRESSANT REGIMENS CAN BE GIVEN?

The increase in the incidence of depression posed a number of issues for specialists in various clinical subspecialists (biologists, physiologists, genetics, general practitioners and family physicians, psychiatrists, psychologists, psychopharmacologists). The further advancement of scientific research, the development of psychotherapy for depression and the possibility of its prevention depend on their solution: 1. To which category of disorders, emotional or cognitive, does depression belong? 2. Is depression strengths of emotional manifestations or weaknesses it? 2. What is the reason for the changes of emotional and cognitive manifestations? 3. How to explain the effectiveness of the same drugs for depression of different origin? 4. How does the subjective experience of depressed patients correlate with the existing classification of the severity of clinical manifestations of depression? 5. What do psychiatrists and patients expect from modern antidepressants? 6. What determines therapeutic strategy? The main objectives of therapy remain overcoming depressive symptoms and returning patients to a full functioning. Tasks are not easy, because the presentation of depression is subject to biological rhythms. The prevailing opinion among psychiatrists that TCAs relieve patients from depression faster than other drugs. TCA drive depression into the depths, protecting patients for some time from experiencing this unpleasant condition, and physicians from their own powerlessness in the treatment of depressive symptoms. The introduction of SSRIs into practice has confirmed the monoamine concept of the pathogenesis of depressive disorders. A theoretical frame for the creation of SSRIs was the serotonin concept of depression. Although this group of drugs is heterogeneous in their chemical structure, their characteristic feature is the reuptake of serotonin from the synaptic cleft deep into the neuron without affecting other neurotransmitters. The drugs of this group have been found the widest application in psychiatric and medical practice in the treatment of depression and other related disorders. Discussing the practice of using antidepressants, it is worth mentioning the

description of use the drugs that contribute to the recovery of depressed patients. An alternative therapeutic approach is the creation of antidepressants with double efficacy. The therapeutic effect of these drugs is aimed at releasing and supporting those mental processes that contribute to the long-term effect and returning patients to a full performance of daily living activities. This approach to therapy requires, first of all, the joint work of the patient and the physician, their trust in each other and the methods of therapy used. In this sense, psychopharmacotherapy has reached a fairly high level. Hundreds of drugs with antidepressant activity have been introduced into clinical practice, each of which has contributed to the extension of our knowledge about depression and the mechanisms of its development.

IV. WHAT HAS CHANGED IN THE TREATMENT OF DEPRESSION SINCE THE ADVENT OF THE FIRST ANTIDEPRESSANTS?

Until the end of the 50s of the last century, a generally accepted pharmacological method of treating depression did not exist. In clinical practice, psychostimulants (amphetamines) were used to treat depression, while opiates and barbiturates were used in “agitated” and “anxious” mental conditions [14], [15]. The effectiveness of such therapy was low; therefore, the introduction of electroconvulsive therapy into psychiatric practice was a real revolution in the treatment of depression. In the mid-1950s, two antidepressants, imipramine and iproniazide, were first introduced into clinical practice [14]–[16]. Imipramine, the progenitor of the TCA class, has been used to date. Iproniazide was originally intended to treat tuberculosis, but its antidepressant properties were subsequently identified. Monoamine oxidase inhibitors (MAOs) and TCAs have retained their importance in clinical practice to date. A distinctive feature of the first-generation antidepressants characterized by wide range of activity mechanisms: they enhanced the neurotransmission of serotonin, norepinephrine, dopamine, and acted on the postsynaptic membrane receptors and auto-receptors. However, a large number of side effects of these drugs were associated with a wide spectrum of receptor action. According to the monoamine concept, a key role in the origin of the disorders was assigned to lowering the level of monoamines (primarily serotonin) mainly in the frontal cortex. Scientists sought to create a drug that selectively had an effect on the metabolism of serotonin in the brain, resulting in a new class of antidepressants — selective serotonin reuptake inhibitors (SSRIs). But can these drugs be considered fully selective? Apparently not, because, in addition to the serotonergic system, they act on a number of other receptors of the presynaptic and postsynaptic membranes. Medications such as fluoxetine, sertraline, and paroxetine are more likely polyvalent, rather than selective antidepressants. Essentially, escitalopram remains the only “true selective” SSRI. The transmission of serotonin is a common to this class of drugs. The results of numerous clinical studies and daily medical practice indicate that far from all types of depression are treated effectively with serotonergic antidepressants, about 50% of depression are resistant to treatment with antidepressants of the SSRI group [2], [8], [9], [11], [12].

Why are SSRIs not effective enough? The fact is that depressive symptoms are quite heterogeneous; they are based on both metabolic disorders of serotonin and norepinephrine. That is why the next step in the development of psychopharmacotherapy for depression was the search for drugs with a double mechanism of action, affecting both the serotonin system and norepinephrine, enhancing their transmission. It was assumed that drugs of the SNRI class will retain the tolerance and safety characteristic of the SSRI class, but they will be much more effective due to the double mechanism of action. The synthesis of dual antidepressants is a new round in the history of depression therapy, which represents a spiral development. Evolution took place from tricyclic antidepressants to selective drugs, followed by a return to the idea of the multivalence of antidepressants. We are talking about the synthesis of drugs that enhance the transmission of serotonin, norepinephrine and, possibly, dopamine (which determines their clinical effectiveness), but intact to the receptors of the presynaptic and postsynaptic membranes.

V. WHEN ARE SELECTIVE SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS INDICATED?

Three drugs from the SNRI group were synthesized: milnacipran, venlafaxine and duloxetine. These drugs affect the neurotransmission of serotonin and norepinephrine, but fundamentally differ in the features of their pharmacokinetics and pharmacodynamics. What are the differences between these drugs? If you take venlafaxine, then this is a drug that is more of a serotonergic antidepressant. In the low and medium dose range, it mainly affects the transmission of serotonin and only in high doses shows its noradrenergic properties. Duloxetine is a rather powerful noradrenergic stimulant, which can lead to the development of side effects associated with metabolic disorders of the noradrenaline system. Duloxetine often leads to increased anxiety and the development of symptomatic hypertension. If we talk about milnacipran, then the principal feature of the drug is the balance of serotonergic and noradrenergic mechanisms of action that is the equivalence of enhanced transmission of both serotonin and norepinephrine in any dose range [2], [8], [9], [11], [12], [16]–[18]. The question arises: what is the practical importance of the balance of serotonergic and noradrenergic mechanisms of action? A balanced increment in the transmission of serotonin and norepinephrine plays an important role in the harmonious reduction of symptoms of depression such as depressed mood, loss of interest, sleep disturbance and anxiety. The balanced increment in the transmission of serotonin and norepinephrine provides a low level of both serotonergic and noradrenergic side effects when using an antidepressant in any dose range, as well as in the case of rapid increase in doses. This reduces the risk of a significant reciprocal increase in the transmission of dopamine and with prolonged use – reduces the density of muscarinic receptors, which is associated with cognitive impairment. A number of symptoms of depression (apathy, lethargy, impaired attention and concentration as well as associated cognitive impairment) are more associated with a lack of neurotransmission of norepinephrine than with serotonergic impairment. With such depressions, SSRIs are

not effective enough and SNRIs become the drugs of choice. Depressed patients with a deficiency of transmission of norepinephrine tend to report their condition as severe chronic fatigue. In such patients, social activity decreases and low level of cognitive functioning is observed. Another clinical variant of depression is elderly depression. In such patients, depressive symptoms merge and are practically inseparable from symptoms associated with impaired cognitive functions. The question arises, what should be considered for the therapy in such patients? TCAs are not suitable, as they can enhance cognitive impairment and cardiac toxicity. In such situations, SSRIs are often used. This is justified from the point of view of safety and the desire to minimize side effects especially, in the elderly. SNRIs are very helpful for this group of patients, as it contributes to an increase in the content of norepinephrine in the frontal cortex and, accordingly, to an improvement in some cognitive functions. These drugs are more effective than SSRI class [2], [11], [19]. Another problem is the therapy of classic presentation of depression. Most practicing psychiatrists are inclined to believe that SSRIs in the treatment of moderate to severe depression are inferior to TCAs in their effectiveness. The greater effectiveness of the TCA is associated with the important role of impaired neurotransmission of norepinephrine in the genesis of phases of depression. A possible alternative to TCAs in the treatment of such depressions are antidepressants with a dual mechanism of action. SNRIs are effective in the treatment of depression of varying severity, in its tolerability and safety of use and it corresponds to the level of serotonergic antidepressants [11], [19].

VI. CONCLUSIONS

Depressive disorders are group of disorders that are dominated by a depressed mood. They occur in mood disorders, somatic disorders, adjustment disorders, poisoning and side effects of drugs, other psychiatric disorders such as schizoaffective disorders, post-psychotic depression, anxiety, bipolar disorders, and substance withdrawal syndromes. It should be remembered that depression is not a common disorder, nor a manifestation of weakness. It cannot be eliminated by "taking hold of yourself". The main role in the treatment of depression plays pharmacotherapy, the effects of which develop, most likely, after 2 weeks. The decision on the ineffectiveness of the drug and the change in treatment should only be made when a satisfactory effect cannot be obtained within 6 weeks. The main antidepressants include drugs whose action is due to the inhibition of the capture of monoamines, which play the role of mediators of the central nervous system, in particular, norepinephrine and (or) serotonin. Antidepressants have different effects on different brain receptors. Physicians should carefully select the required antidepressant.

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