Depression and its treatment with trazodone

European Journal of Medical Technologies
2021; 1(30): 26-32

www. medical-technologies.eu
Published online 1.05.2021

Piotr Kuśnierz[1], Michał Meisner[1], Beata Sarecka-Hujar[2]

[1] Student of 6th year of Pharmacy, Medical University of Silesia in Katowice, Faculty of Pharmaceutical Sciences in Sosnowiec, Department of Basic Biomedical Science, Poland

[2] Medical University of Silesia in Katowice, Faculty of Pharmaceutical Sciences in Sosnowiec, Department of Basic Biomedical Science, Poland

Corresponding address:
Beata Sarecka-Hujar, PhD
Department of Basic Biomedical Science, Faculty of Pharmaceutical Sciences, Medical University of Silesia in Katowice, Poland
e-mail: bsarecka-hujar@sum.edu.pl
tel. +48 32 2699830

Abstract

The incidence of depression increases each year. It is estimated that this disorder will be as common as ischemic heart disease in the near future. Despite the increasing prevalence among the world population, the phenomena that cause the development of the disease remain not fully explained. Due to the link between the occurrence of depressive disorders and the upbringing of children in dysfunctional families, scientists conclude that the development of the disease may be influenced by sociological factors. One of the drugs showing significant therapeutic effect in the treatment of depression is trazodone. Due to the variety of doses and release profiles of the drug from various commercial preparations, trazodone appears to be one of the more effective substances used in the therapy of depressive disorders. The following article provides an overview of studies on the pathomechanism of depressive disorders and their treatment with trazodone.

Key words:

depression, treatment, trazodone, psychiatric disorder

Introduction

Depression is the most prevalent psychiatric disorder worldwide and a serious medical problem. According to the latest research, depressive disorders affect almost one in five people in the world, which makes them one of the most common causes of inability to function properly and enjoy life. In the US, this represents approximately 35 million adults who will experience an episode of the so-called „Major Depressive Disorder" (MDD). Moreover, depression is the leading cause of incapacity for work in the world - the financial burden to the economy caused by episodes of depression occurring in the population of the world was estimated at 83.1 billion of dollars in 2000 [1]. It reduces the quality of life and may be a cause of suicide [2].

Depression concerns women more commonly than men [3]. Australian study demonstrated that women in perimenopausal and postmenopausal stages had a higher risk of more severe symptoms of depression than women in the premenopausal stage without a history of depression [4]. Data predicted that depression will be the second most commonly diagnosed disease in the world, right after ischemic heart disease [1,5].

Among people who are characterized by a high tendency to depressive disorders there are students of medical faculties. The results of the meta-analysis of Rotenstein et al. [6], based on a large study group, showed that the incidence of depression or depressive symptoms among students it was 27.2%, while suicidal thoughts were reported by 11.1% [6].

Depressive disorders constitute a very wide group of disorders, which, based on the International Classification of Diseases and Health Problems, include the following entities: bipolar disorder, which are characterized by cyclically consecutive depressive and manic episodes or mixed episodes, depressive episodes (mild, moderate with or without psychotic symptoms), recurrent depressive disorders (repeated mild, moderate or severe depressive episodes with or without psychotic symptoms), cyclothymia (constant mood swings accompanied by multiple depressive periods and mild manic episodes) and dysthymia, which is a chronic depressed mood lasting more than 2 years [7].

According to generally accepted diagnostic criteria, the depressive syndrome is characterized by symptoms such as sadness, depression, discouragement, and lack of pleasure in activities that previously gave such pleasure. All these symptoms can be termed „anhedonia". It is the basic symptom of depressive disorders [1,7,8]. Additional symptoms include indifference leading to loss of interests, the inability to feel sad and joy, the appearance of suicidal tendencies, and psychomotor inhibition manifested by a slowdown in the pace of cognitive, memory and motor processes. Important symptoms in the diagnosis of the disease are also disturbances of circadian rhythms (excessive sleepiness or insomnia), diurnal mood swings in which the patient experiences a deterioration of mood in the morning and its improvement in the afternoon and evening. Some patients experience depressive delusions, and in many cases, they complain of a constant feeling of anxiety, tension and restlessness, which may result in chronic exhaustion. Depression is always accompanied by somatic complaints, which include chronic pain disorders (joint pain, headache, muscle pain), digestive tract disorders (diarrhea, constipation, nausea, increase or loss of appetite, abdominal discomfort, the irregularities in the urogenital (frequent urination, loss of libido) and cardiovascular (pain and tightness in the chest, shortness of breath and palpitations). Ailments in the cardiovascular system intensify in the case of coexistence of anxiety disorders, which are one of the symptoms of depression [7].

The aim of the present review was to sum up available data on pathogenesis of depression and usage of trazodone in the treatment of depressive disorder.

Pathomechanism of depressive disorders

Despite such a high incidence of these disorders, the mechanisms of formation are still not understood, and current therapy of MDD tends to be ineffective in a large group of patients. Many studies suggest that the childhood of the studied individuals, in particular exposure to stress, is of great importance in the development of depressive disorders. Traumatic events in early life contribute to the development of

individual differences in the ability to react and cope with subsequent stressful situations. Victims of parental abuse or neglect are significantly more likely to develop mood disorders, and studies of children in care indicate that global deprivation causes persistent behavioural and cognitive deficits. Animal models that separate mother and rodent offspring suggest that the offspring of separated puppies are more docile and generally develop more passive lifelong stress coping strategy. Events causing severe psychological discomfort in early life permanently change endocrine responses to stress and increase susceptibility to addiction to psychoactive substances in adulthood. Moreover, individual differences in maternal behaviour, such as licking, grooming, and adolescent care may influence offspring's responses to stressful situations. Puppies growing up in natural conditions, provided with proper care, show a significantly increased mental resistance in adulthood. The results of the above-mentioned studies seem to be very important in the face of the growing problem of the breakdown of marriages, children brought up in incomplete families and constantly growing percentage of people with depressive disorders [1].

The pathomechanism of depressive disorders, although thoroughly analyzed in many scientific studies, still remains largely unclear. Since 1965, attempts to treat depressive disorders have been based solely on the hypothesis that all symptoms of the disease are caused only by deficiencies in the neurotransmitters serotonin and noradrenaline in specific areas of the brain and by fluctuations in dopamine levels. Based on scientific reports, it was possible to confirm the role and importance of these three neurotransmission pathways in the etiology of depression. The data show significant changes in the functioning and sensitivity of 5-HT, α, β and DA receptors in patients with depression. Moreover, ample evidence clearly suggests a possible antidepressant-like effect of 5-HT, α, β and DA receptor modulators in animal tests and models of depression. These findings confirm the heterogeneous nature of depressive disorders, but its specific pathomechanism remains unclear and requires further research. Undoubtedly, innovative strategies for treating depression should include various approaches, but most of all modulation of serotonergic, adrenergic and dopaminergic receptors [5].

Over the years, the theory has evolved, and scientists have begun to notice the relationship between the occurrence of depressive disorders and changes not only in the serotonergic, dopaminergic and noradrenergic systems, but also in the cholinergic and GABAergic systems. In brain studies of people suffering from depressive disorders, many abnormalities in the functioning of the brain circuits, the functioning of which are based on these neurotransmitters, have been found. The modulators of the above-mentioned receptors show a significant antidepressant effect in many preclinical studies [5,7,9]. In addition, the causes of depression began to be found in increased inflammatory processes and changes in neuroplasticity, i.e. the ability of the nervous tissue to reorganize and repair itself [5].

One of the processes underlying the development of the disease, which are not directly related to fluctuations in monoamine concentration, are hormonal imbalances in the hypothalamic-pituitary-adrenal axis (damage to the negative feedback mechanism responsible for regulating blood cortisol levels), the function of which is the body's response to stress. It has been proved that there is a clear relationship between disturbances in this system's functions caused by stress, in particular long-term stress, and the occurrence of depressive disorders. It is associated with damage to the structure of the hippocampus and additional intensification of the disturbance of the hormonal balance and disturbance of the processes of neurogenesis [5,7].

Another theory that deviates from the previously accepted doctrine of fluctuations in the concentration of monoamines in the brain as a cause of depressive disorders is the theory that considers the role of inflammatory processes in the pathogenesis of the disease. Literature data show that in groups of patients suffering from depression, there is a significantly increased level of pro-inflammatory proteins and an increase in the expression of genes encoding these proteins, not only in peripheral tissues, but also in the cerebrospinal fluid, compared to healthy

subjects [8]. Brain dysfunction caused by too high levels of pro-inflammatory proteins is largely visible in the striatum, which concentrates dopaminergic neurons. Inflammatory cytokines are known to interfere with dopaminergic neurotransmission, including the synthesis and release of dopamine in rodents and non-human primates, leading to mental disorders and motivational deficits. Therefore, the described theory can be linked with fluctuations in dopamine concentration. Moreover, people who do not suffer from depression, but have elevated levels of proinflammatory proteins such as TNF, interleukin-6 and CRP, were characterized by a higher frequency of anhedonia-like symptoms. It is also worth mentioning that the effects of inflammation on dopaminergic signalling may worsen over time. Dopamine plays an important anti-inflammatory role in the brain, and the reduced availability of dopamine may further intensify the inflammatory effect through a positive feedback loop, causing chronic inflammation associated with decreased dopamine levels [8].

Treatment of depressive disorders

Treatment with antidepressants is estimated to be effective in 50% of patients. This may be due to the fact that the diagnosis of depressive disorders is based solely on behavioral symptoms, which means that drugs are not selected in terms of their impact on the pathomechanism of the disease.

Pharmacotherapy of depressive disorders is based on the use of drugs that are designed to reduce the deficit of neurotransmitters and improve serotonergic and noradrenergic neurotransmission leading from the brain stem to the limbic system and cortical and subcortical structures [7].

One of the drugs commonly used in the treatment of depressive disorders is trazodone. It is a drug from the group of serotonin reuptake inhibitors that block serotonergic receptors [7,10].

Trazodone – characteristics and application of preparations

Trazodone was introduced into medicine in Europe and Asia in the early 1970s. In the United States got approved for marketing in 1978. In later years, it has been introduced in other countries for use in the treatment of depression in adults. In addition to its antidepressant properties, trazodone is effective in the treatment of other diseases, which include, among others: insomnia, anxiety disorders, post-traumatic stress disorder, eating disorders, obsessive-compulsive disorders, disorders caused by taking other psychoactive substances, sexual disorders. Moreover, it is used in the treatment of pain, as well as in the treatment and rehabilitation after ischemic stroke [7],[10]. Among the potential applications, the main indications for the use of trazodone are: severe depression with agitation or motor inhibition and anxiety, eating disorders, sleep and concentration disorders, sexual disorders and depressive syndromes with suicidal thoughts [7]. The data indicate that trazodone can be used in the treatment of addiction to benzodiazepines, as an adjunct in fibromyalgia (in combination with pregabalin), and in the treatment of acute akathisia caused by the use of neuroleptics [11,12].

The mechanism of action of the drug is based on the inhibition of serotonin reuptake from the synaptic cleft, and also by blocking 5-HT2 serotonergic, α-adrenergic and histamine H1 receptors. Additionally, the use of the drug reduces the number of postsynaptic 5-HT1A receptors [7]. It has been suggested that the simultaneous blockade of the serotonin reuptake protein and blockade of 5-HT2A and 5-HT2C receptors have a synergistic effect, improve treatment tolerance, and enhance the antidepressant effect. The blockade of these types of receptors also reduces the intensity of side effects in relation to other antidepressants [13]. As a derivative of phenylpiperazine and triazolopyridine, the drug is structurally very different from compounds belonging to the group of selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) and monoamine

oxidase inhibitors (MAOIs). It has a smaller effect on the cholinergic system compared to drugs from the TCAs group and therefore has a much smaller effect on the heart function [10].

Due to its different structure and complex mechanism of action, trazodone, which has a triazolopyridinone ring in its structure, is the subject of research in the synthesis of new generation neuroleptics [14]. The blockade of 5-HT2 serotonergic receptors is an important component of the mechanism of action of atypical neuroleptics [7].

Trazodone is well absorbed from the gastrointestinal tract after oral administration, it does not tend to accumulate in specific tissues of the body. If ingested shortly after food ingestion, there may be an increase in the amount absorbed from the gastrointestinal tract, peak plasma concentrations may be lower than in the fasted state, and the time to peak concentration will be delayed. Peak plasma concentrations of trazodone are achieved within one hour of ingestion or 2 hours of ingestion with food. To a large extent (approx. 89-95%) it is bound to proteins. It is extensively metabolised by the liver, mainly by CYP3A4. Less than 1% of an orally administered dose is excreted unchanged from the body, and 70-75% of the 14C-labeled trazodone molecules are removed from the body within 72 hours along with the urine [10].

Several pathways, not fully explored, are involved in the metabolism of trazodone, and the most active metabolite is meta-chlorophenylpiperazine [10]. This compound shows agonistic properties towards the 5-HT2C receptor, therefore the use of high doses of the drug may cause anxiety disorders [7].

Trazodone metabolism is accelerated in smokers, but it is not influenced by age, sex, or concomitant use of benzodiazepines. As the most important examples of drugs that do have pharmacokinetic interactions with trazodone, ritonavir, indinavir and ketoconazole should be mentioned, as they slow down its metabolism [10].

As with many other drugs, the use of trazodone may have side effects. These include nausea, vomiting, diarrhea or constipation. However, these symptoms are not severely exacerbated due to the fact that the anticholinergic effect of trazodone is relatively weak compared to other antidepressants. On the part of the circulatory system, ailments such as orthostatic hypotension, prolonged QT interval on the electrocardiogram and various types of arrhythmias may occur. Other general side effects of the drug include drowsiness, lightheadedness, fatigue, weight changes, muscle aches and blurred vision. In addition, dry mouth, muscle aches and headaches may occur. Side effects disappear with the passage of time in which the drug is used, or after lowering the dose [10]. An interesting, but relatively rare side effect of using the drug is priapism, i.e. spontaneous long-term erections [7]. It also occurs when many neuroleptics are used, both typical and atypical. The mechanism of the phenomenon is not fully understood, but it is assumed that drugs' ability to block α - adrenergic receptors is involved in its formation[15].

Some studies have shown that the use of trazodone in children, adolescents and young adults (up to 24 years of age) may lead to the emergence of suicidal thoughts in those people when treating major depressive disorder. Nevertheless, scientists agree that this fact should not be a reason for discontinuing the use of the drug in severe depression, as the risk of suicide during an untreated disease is many times higher [10].

The effect of trazodone on the developing fetus in pregnant women is not fully understood and does not appear to increase the incidence of major malformations above the baseline rate of 1-3%. To minimize the risk of symptoms of depression returning, trazodone treatment may be resumed or an alternative antidepressant medication known to be safe in pregnancy may be used. Trazodone passes into breast milk. Lactating women should discontinue the drug due to its unknown effects on the child's body. If discontinuation of trazodone therapy is not an alternative, breastfeeding should not be started or it should be discontinued [10].

Due to the specificity of the action of antidepressants, the need to get the body accustomed in the initial stages of treatment and to avoid severe side effects, it is necessary to adjust the dosage. It is carried out depending on the treatment phase (gradual increase in the dose in the initial phase of treatment and decrease in the final phase before complete withdrawal of the

drug), but also according to the age and metabolism of the patient. The rules for starting treatment with an antidepressant are rather unchanged, regardless of the drug group being used. Treatment begins with a dose which is 1/4–1/3 of the target daily dose [7]. Depending on the type of depressive disorder, different drug forms may also be selected, e.g. in the treatment of major depression with trazodone, immediate release formulations are selected, while for the treatment of various types of depression with or without anxiety, modified release forms are preferred. In addition, the modified-release forms are characterized by a reduction in the number and intensity of side effects, because their use does not cause such significant fluctuations in drug concentration in the blood plasma [12]. Results of meta-analysis performed by Lisa Holper of Psychiatric Hospital in Zurich, the dose of antidepressant should be gradually increased (according to the degree of tolerance of the organism) to the therapeutic dose, which considers the occurrence of side effects during treatment [16].

For immediate-release trazodone, the recommended daily starting dose is between 75–150 mg. Tablets can be divided into 2 or 3 parts, the target daily dose is 300 mg. You should take it in several divided doses, the biggest one is given in the evening. In patients who may be in hospital, the daily dose has been increased to 600 mg. In the case of geriatric patients, it is very common practice to reduce the initial daily dose even below 75 mg [12].

Modified release trazodone differs slightly in its dosage regimen to the form described above. The delayed-release preparation in the initial period of use is administered in a dose of 75–150 mg once in the evening before bedtime, which improves the quality of rest. The amount of the drug is increased up to 300 mg in two divided doses, and in the case of patients in hospitals, it is possible to increase the dose to 600 mg in divided doses, none of which may exceed 150 mg. In the elderly, the initial dose is very low, e.g. 25 mg, to test the tolerance of the drug by the patient's body. It is also recommended that a single dose of delayed-release preparation administered to seniors should not exceed 100 mg [12].

The sustained release tablets have a dosing regimen slightly different from that used for the delayed release tablets. Initially, 75–150 mg is given at bedtime, every three days increasing the dose by another 75 mg, which is half a tablet. For geriatric patients, a daily dose of 75 mg and dose titration are planned based on the individual patient tolerance of the drug. Studies have shown that both forms of modified release are characterized by similar efficacy in the treatment of depressive disorders, moreover, they exhibit several properties that make them superior to traditional forms of immediate release. These properties include the possibility of starting treatment with a higher dose of the drug, which results in the relief of depression symptoms in the initial phase of treatment, and the reduction of daily fluctuations of concentration in the plasma of the active substance, which contributes to the reduction of the intensity of side effects. The obvious advantage is also taking the preparation once a day, which is a more convenient alternative for the patient [12].

The dosage of trazodone may differ significantly from the above mentioned schedules when the drug is to be used for a different indication in children. Research shows that the treatment of insomnia in children gives the most measurable benefits when the dose is precisely defined for the patient's age [17]. In patients with increased body weight, the choice of trazodone dose during long-term treatment should be based on body weight considered normal for a particular patient, and not on total body weight, even if it differs significantly from normal weight [10].

Conclusions

Depression affecting an increasing part of society, combined with the unclear mechanism of its formation and the need for an individual approach to each patient, is a serious problem that must be faced by doctors, pharmacists and all persons involved in the broadly understood health protection.

Trazodone seems to be an interesting alternative to other drugs used classically in the treatment of depression, thanks to its different structure it has become the subject of research on a new generation of neuroleptics.

References

1. Ménard C, Hodes GE, Russo SJ. Pathogenesis of depression: Insights from human and rodent studies. Neuroscience 2016; 321: 138–162.
2. World Health Organization Depression Fact Sheet, Available online at: http://www.who.int/mediacentre/factsheets/fs369/en/ (accessed on 9 June 2021).
3. Ferrari AJ, Somerville AJ, Baxter AJ, et al. Global variation in the prevalence and incidence of major depressive disorder: A systematic review of the epidemiological literature. Psychol Med 2013; 43: 471–481.
4. Mulhall S, Andel R, Anstey KJ. Variation in symptoms of depression and anxiety in midlife women by menopausal status. Maturitas 2018; 108: 7–12.
5. Pytka K, Podkowa K, Rapacz A, et al. The role of serotonergic, adrenergic and dopaminergic receptors in antidepressant-like effect. Pharmacol Reports 2016; 68: 263–274.
6. Rotenstein LS, Ramos MA, Torre M, et al. Prevalence of depression, depressive symptoms, and suicidal ideation among medical students a systematic review and meta-analysis. JAMA - J Am Med Assoc 2016; 316: 2214–2236.
7. Janiec W. Kompedium farmakologii. 2015; 6–17.
8. Carmichael O, Lockhart S. Neurotrophins and. Brain Imaging Behav Neurosci 2012; 289–320.
9. Pytka K, Dziubina A, Młyniec K, et al. The role of glutamatergic, GABA-ergic, and cholinergic receptors in depression and antidepressant-like effect. Pharmacol Reports 2016; 68: 443–450.
10. Khouzam HR. A review of trazodone use in psychiatric and medical conditions. Postgrad Med 2017; 129: 140–148.
11. Bossini L, Casolaro I, Koukouna D, et al. Off-label uses of trazodone: A review. Expert Opin Pharmacother 2012; 13: 1707–1717.
12. Cuomo A, Ballerini A, Bruni AC, et al. Clinical guidance for the use of trazodone in major depressive disorder and concomitant conditions: Pharmacology and clinical practice. Riv Psichiatr 2019; 54: 137–149.
13. Fagiolini A, Comandini A, Dell'Osso MC, et al. Rediscovering trazodone for the treatment of major depressive disorder. CNS Drugs 2012; 26: 1033–1049.
14. Shi W, Wang Y, Wu C, et al. Synthesis and biological investigation of triazolopyridinone derivatives as potential multireceptor atypical antipsychotics. Bioorganic Med Chem Lett 2020; 30: 127027.
15. Greiner T, Schneider M, Regente J, et al. Priapism induced by various psychotropics: A case series. World J Biol Psychiatry 2019; 20: 505–512.
16. Holper L. Optimal doses of antidepressants in dependence on age: Combined covariate actions in Bayesian network meta-analysis. EClinicalMedicine 2020; 18: 100219.
17. Oggianu L, Ke AB, Chetty M, et al. Estimation of an Appropriate Dose of Trazodone for Pediatric Insomnia and the Potential for a Trazodone–Atomoxetine Interaction. CPT Pharmacometrics Syst Pharmacol 2020; 9: 77–86.