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REVIEW ARTICLE

Serum markers related to depression: A systematic review

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Depression has a multifactorial aetiology and is one of the most common neurological and psychiatric disorders that are associated with imbalance in certain inhibitory and excitatory neurotransmitters and impairment of the brain-derived neurotrophic factor (BDNF). This review study was conducted to investigate the effect of BDNF and neuromediators on the development and severity of depression. To conduct this systematic review, relevant publications that were published between 2000 and 2016 and were indexed in the *PubMed*, *Google Scholar*, *Scopus* and *Web of Science* databases were retrieved using the *depression*, *serum markers*, *neurotransmitters*, *serotonin*, *BDNF*, *dopamine*, *glutamate* and *gamma amino-butyric acid* search terms. A total of 89 articles were included in final analysis. Depression is associated with imbalance of certain neurotransmitters such as serotonin, dopamine, norepinephrine, melatonin and glutamate in the central nervous system and impairment of BDNF. Taken together, there is a significant relationship between depression and neuromediators, and the decrease and increase in these mediators plays a significant role in depression. Studies have also confirmed that the antidepressant effect of drugs and medicinal plants is essentially related to the serotonergic pathway, especially the 5-HT1A receptor, and drugs and medicinal herbs are likely to exert their antidepressant activity through altering dopaminergic and serotonergic systems.
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INTRODUCTION

Depression is a chronic disabling disease that affects one in six people in the United States (Kessler *et al.*, 2005). According to the World Health Organization (WHO)'s report, about 350 million people worldwide are suffering from depression, and by 2020, it will be the second leading disease, after cardiovascular diseases, in the world (Kessler *et al.*, 2003).

Depression is the main cause of the incidence of 50-70% of suicides (Lecomte and Fornes, 1998). Depression has certain symptoms such as loss of energy and motivation, feeling guilty, difficulty maintaining concentration, feeling depressed, sleep disorders, change in appetite, disappointment, thoughts of death and suicide (Eslami *et al.*, 2016; Etemadifar *et al.*, 2017). Different neuroanatomical regions have been introduced to express and control anxiety, depression and psychological behaviors, one of which is the limbic system, which regulates neuronal activity by genomic or non-genomic mechanisms through regulation of enzymes, neural mediators, etc (Khayeri *et al.*, 2016).

However, depression has a multifactorial aetiology (including biological, genetic, psychological and environmental factors), which is associated with the imbalance in different neurotransmitters (inhibitory and excitatory), as well as impairment of the brain neurotrophic factor (BDNF) in most cases (Maletic *et al.*, 2007; Maes *et al.*, 2011; Lopresti *et al.*, 2013; Mazaheri *et al.*, 2014; Rabiei *et al.*, 2014) so that it can be argued that depression is associated with a decrease in the transmission of functional amine-dependent neurotransmitters in the synapse and an increase in monoamines and glutamate in the synaptic cleft, which is the basis of the amine hypothesis of depression (Berk *et al.*, 2013).

Besides that, depression is associated with a de-

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crease in the plasma concentrations of important antioxidants such as vitamin E and coenzyme Q, as well as the reduction of the activity of oxidative enzymes, such as glutamine peroxidase. Other studies have shown that the cysteine at the 704 (Cys704) is associated with depressive disorders, decrease in the volume of hippocampal substantia nigra and reduction of anisotropy of the fragments in the prefrontal white matter (Smagin *et al.*, 2001; Callicott *et al.*, 2005; Watson and Mackin, 2009). This review was conducted with the aim of investigating neurotransmitters levels in different brain regions and the effect of neurotransmitters and BDNF on development and severity of depression.

To conduct this systematic review, relevant publications that were published between 2000 and 2016 and were indexed in the *PubMed*, *Google Scholar*, *Scopus* and *Web of Science* databases were retrieved using the *depression*, *serum markers*, *neurotransmitters*, *serotonin*, *BDNF*, *dopamine*, *glutamate* and *gamma amino-butyric acid* search terms. A total of 89 articles were included in final analysis.

Different neuromediators and their association with depression

Serotonin

Serotonin is one of these neuromediators. Serotonin acts on the functioning of the central nervous system (CNS) and cardiovascular, renal, immune and gastrointestinal systems; any disorder in the synthesis, metabolism and reuptake of serotonin leads to symptoms and diseases such as schizophrenia, depression, obsessive-compulsive disorder (OCD) and learning disability (Amiri *et al.*, 2016; Solati *et al.*, 2017a). Serotonin also affects many physiological activities, including mechanisms of anxious, appetite, sexual behavior, sleep-wake cycle and peristalsis (Oláh *et al.*, 2005). Decreased serotonin levels in the brain of Alzheimer's patients can lead to numbness, learning disabilities and aging(Kalbitzer, 2009).

Many antidepressants work to increase serotonin levels in synapses, including selective serotonin reuptake inhibitors (SSRIs) that increase serotonin concentrations in the CNS. It can therefore be argued that the reduction of serotonin in the brain causes depression and, in more severe cases, Alzheimer's and cardiovascular disease (Sauer *et al.*, 2003; Salmon, 2007).

Under stressful conditions, with a low serotonin level, there is a significant increase in the immune system proteins that play an important role in Alzheimer's and cardiovascular disease. That's why most depressed and hostile people whose levels of serotonin are low are affected by heart disease, Alzheimer's disease, and other illnesses that increase the response to the immune system. In this way, the use of serotonin-enhancing drugs for depression can also reduce the risk of heart disease and Alzheimer's (Sauer *et al.*, 2001; Eliecer *et al.*, 2003). Serotonin also has an inhibitory effect on the function of the N-methyl-D-aspartate (NMDA) receptor through centrally releasing ascorbic acid, and can thus reduce anxiety and depression (BJ; Diplama JR).

BDNF

BDNF is another factor involved in depression. BDNF in humans is coded by the BDNF gene located on chromosome 11(Maisonpierre *et al.*, 1991; Binder and Scharfman, 2004). BDNF, a member of the neurotrophin family, is one of the neuronal growth-associated factors that are commonly expressed in the brain and surrounding tissues. BDNF acts in certain neurons of the central and peripheral nervous system for survival, growth, and differentiation of neurons and formation of new synapses(Acheson *et al.*, 1995; Huang and Reichardt, 2001).

BDNF is active in areas of the brain that are involved in learning, memory and thinking, such as the hippocampus, cortex and anterior cranial fossa (Yamada and Nabeshima, 2003). BDNF is also expressed in the retina, motor neurons, kidneys, saliva and prostate (Mandel *et al.*, 2009) . This factor triggers intracellular cascades, and ultimately produces and differentiates new neurons by binding to certain tyrosine kinase receptors. The neurotrophic depression hypothesis states that depression is related to the reduction of BDNF and its treatment reduces depressive behaviors and increases BDNF

levels(Duman, 2002). Clinical trials have shown that serum BDNF levels are significantly higher in depressed people than in healthy people (Karege *et al.*, 2002; Karege *et al.*, 2005).

Dopamine

Dopamine is another neuromediator involved in depression, which is expressed in the areas of the brain that regulate movements, feelings and emotions. Dopamine, as a stabilizing agent of the brain, plays a very important role in regulating the flow of information from the brain to other parts of the body (Solati *et al.*, 2017b). Dopamine also has a great influence on the control of movements and thoughts(Millan and Brocco, 2003).

Dopamine is one of the mediators of the CNS that acts as a dopaminergic mesolimbic pathway. Impairment of the dopaminergic mesolimbic pathway plays a key role in the development of depression and mediation of drug rewards(White and Wang, 1984). Dopamine acts on the brain through two groups of dopamine receptors, D1 and D2. The D1 receptors include D1 and D5 receptors, and the D2 receptors include the D2, D3 and D4 receptors (Nasehi *et al.*, 2010). The activation of the D1 receptors activates adenylate cyclase and increases the cyclic adenosine monophosphate (cAMP) in the cell, while the activation of D2 receptors reduces the adenosine monophosphate (Sealfon and Olanow, 2000). These dopamine D2 receptors play an important role in the treatment of diseases including depression.

In general, dopamine plays an important role in the incidence of addiction and has a dual ability in the pathogenesis or pharmacotherapy for the CNS diseases, such as Parkinson's and schizophrenia (Angrist *et al.*, 1973). Dopamine also plays an important role in the incidence of psychotic behaviors and motor and behavioral disorders such as depression and other mental illnesses(Strange, 1996). Considering the relationship between dopamine and other neurotransmitters such as serotonin, GABA, acetylcholine and glutamate, as well as their involvement in the regulation of anxiety and depression, it is also necessary to note that perhaps the anxiolytic effect of D2 agonists is related to these relationships (Shirayama and Chaki, 2006).

Glutamate

Glutamate is another neuromediator. Glutamate is a excitatory neurotransmitter in the chemical synapse of the vertebrate nervous system. Glutamate is a neuromediator that generates various cellular cascades in chemical synapses. Glutamate is also one of the main neurotransmitters in the CNS, which stimulates the neurons, creating potential for action. This neurotransmitter is involved in the development of behavioral diseases, such as depression, through its receptors, which include two groups, ionotropic and metabotropic(Aggleton, 1992; Davis and Shi, 2000; Neugebauer *et al.*, 2004; Taylor, 2014), such that it imports positive ions (sodium and calcium) into the cell and has the potential for positive action. The ionotropic glutamates have three groups of receptors, AMPA, kainate and NMDA receptors(Masu *et al.*, 1991).

Increased glutamate secretion and increased receptor density in the subcortical structures are among the most important changes in anxiety and depressive behaviors. NMDA receptors of glutamate in the nucleus of the central amygdala cause a series of activities and behavioral changes such as control of water and food intake as well as control of anxiety and depression(Adamec *et al.*, 1998). Alcohol also intensifies aggression, depression and anxiety through the glutaminergic system. Other mechanisms involved in the pathophysiology of depression are the imbalance of the dopaminergic, glutaminergic and gABAergic systems(Newman *et al.*, 2012; Tran *et al.*, 2013).

In addition, mGluR receptors, mainly located in the post-synaptic membrane, increase the release of intracellular calcium via phospholipase C. It seems that glutamate via this receptor and this circuit also plays an important role in the pathology of anxiety and depressive disorders(Conn and Pin, 1997; Brady and Conn, 2008). The glutamate stored in the vesicles is released from the pre-synaptic cell due to neuropulses and acts on the post-synaptic cells via inotropic and methototropic receptors (G protein) (Bhargave, 1981; McEntee and Crook, 1993).

gamma-Aminobutyric acid (GABA)

GABA is another neurotransmitter that plays a major role in depressive and anxiety behaviors; the function of this neurotransmitter is dependent on the effects of ascorbic acid. GABA is the most important inhibitory neurotransmitter, which is released by afferent and inhibitory intermediate neurons on the cell body and dendrites of pyramidal neurons, and its effect depends on the type of postsynaptic receptors. Other inhibitory neurotransmitters including somatostatin, serotonin and histamine are also present in the hippocampus, which can improve GABA function (Harrison and May, 2009).

The GABA neurotransmitter reduces firing of the brain cells, thereby reducing the anxiety-related messages transmitted from the cortex. But if a person is under intense stress or anxiety, the brain consumes all existing GABAs and thus anxiety and depression develop in the individual; therefore, the GABAergic pathways also exert inhibitory effect on the release of many other neurotransmitters that mediate anxiety-inducing actions(Camps *et al.*, 1990). The creation of a dystrophin-associated protein complex using GABA receptors in the hippocampus, cortex and cerebellum can be involved in the physiology of emotional and psychological disorders. Due to the impairment in message transmission, synaptic communication and receptor systems, the genetic variants of the GABA gene are very suitable candidates for genetic susceptibility to psychological disorders (Gornick *et al.*, 2005).

The role of changes in cholesterol levels in the development of mental disorders is through the GABA neurotransmitter. Serum cholesterol levels increase due to stress. Increased cholesterol contributes directly to anxiety and depression by altering the sensitivity of GABA receptors; the effects of anxiety on cholesterol levels are mediated by intensified lipoprotein lipase activity and increased free fatty acids. On the other hand, an increase in cholesterol may directly affect the sensitivity of GABA receptors to anxiety. Cholesterol levels may also indirectly manipulate the receptor function and membrane binding proteins by decreasing neuron membrane fluidity, thereby altering or disrupting the function of the lipid lobes. The effects of anxiety and depression on cholesterol levels are exerted by increasing lipoprotein lipase (LPL) activity. LPL is an enzyme that hydrolyzes chylomicron triglycerides when chylomicron is exposed to vascular endothelium, releasing fatty acids and glycerol, which are converted to triglycerides through certain processes. It can be stated that stress, anxiety and depression increase the levels of cholesterol in a way that the activity of the sympathetic system increases. Based on the hypothesis *Increasing the sympathetic activity causes neuroderrhea activity to increase*, it activates the stimulation mechanism of LPL, which leads to an increase in free fatty acids(Monteleone *et al.*, 2005; Gabriel, 2007).

The role of ionic channels, particularly potassium and calcium channels in psychiatric disorders such as depression is through the GABA neurotransmitter. The blockage of these channels leads to depolarization of cell membrane, which can lead to contraction of the vascular smooth muscle or the secretory actions of certain cells, including neurotransmitter secreting cells. These channels play a large part in many physiological actions, including adjustment of heart rate, muscle contraction, release of neurotransmitters, nervous irritability, insulin secretion, etc (Coetzee *et al.*, 1999; Martens *et al.*, 1999). Voltage-dependent calcium channels act as one of the key mechanisms for importing calcium into the cell. These channels mediate calcium entry in response to the membrane depolarization and regulate intracellular processes, such as the secretion of neuromediators and gene expression. The activity of these channels is essential for combining cell surface electrical signals and intracellular physiological events.

The role of GABA receptors, especially GABAB receptor, is associated with depression and the mediation of the effects of antidepressants (Matsumoto, 1989; Catterall, 1995). The GABAB receptor plays an important role in the secretion of neurotransmitters in the nerve terminals via acting on calcium and potassium ion channels that are widely distributed in the nervous system(McKernan and Whiting, 1996). The blockage of potassium channels activates voltage-dependent calcium chan-

nels and the entrance and the increase in the intracellular concentration of this ion by creating cell depolarization (Göthert, 1980). Increasing intracellular calcium, in turn, increases the amount of depletion of neurotransmitters from noradrenergic and serotonergic nerve terminals. Calcium channels, especially voltage-dependent ones, play an important role in the development of certain behaviors such as depressive behaviors (Shefner and Osmanović, 1991; Biała, 1998).

Table 1: Different biomarkers in the development of mental diseases and behavioral disorders

Biomarkers	Sample	Results
Norepinephrine and cortisol	Human	In this study, a significant association was observed between 24-hour secretion of norepinephrine and cortisol secretion, and anxiety severity (Hughes et al., 2004). This study showed that the secretion of cortisol and norepinephrine among women indicates that depression and anxiety are associated with intensified sympathetic nervous system activity and that this system may play an important role in this disorder and be effective on the autonomic nervous system disorder in depression and anxiety.
Dystrophin proteins alongside gamma-aminobutyric acid	Human	The dystrophin proteins alongside gamma-aminobutyric acid (GABA) receptors are located in the hippocampus, cortex, and cerebellum, and GABA can be involved in the physiology of emotional and psychological disorders (Gornick et al., 2005).
NMDA receptors	Mice	Pharmacological studies and studies conducted using transgenic animals indicate that the NMDA receptors can affect various aspects such as anxiety, fear and depression (Barkus et al., 2010; Amiri et al., 2016; Kordjazy et al., 2016).
Norepinephrine and cholesterol	Human	The association between increased noradrenergic activity and high levels of cholesterol in patients with psychiatric disorders, such as depression and panic patients, represents that these patients are predisposed to cardiovascular disease (SHIOIRI et al., 1998).
Glutamate receptors	Human	This study showed that the change in the synaptic transmission of glutamate via mGlu2/3 receptors is considered a cause of schizophrenia (Patil et al., 2007).
Melatonin	Human	In clinical studies, it has been shown that the decrease in the production and secretion of melatonin play a role in the development of behavioral disorders such as depression (Pacchierotti et al., 2001; Tuunainen et al., 2002).
Serotonin	Human	Reducing the amount of serotonin in the brain, in patients with Alzheimer's disease, leads to insomnia, dysfunction and aging. It is likely that the reduction of serotonin in the brain causes depression and, in more severe cases, Alzheimer's disease (Meneses et al., 2011).
5-HTTLPR	Human	They showed that the 5-HTTLPR polymorphism acted on serotonin-mediated activation of platelet, smooth muscle cell proliferation or risk factors such as depression or stress response. They also showed that depression was a risk factor for heart attack (Tjurmina et al., 2002; Eliecer et al., 2003).
Norepinephrine and dopamine	Mice	It has been shown that the levels of norepinephrine and dopamine in certain regions of the brain increase in mice with genetic depression and other genetic psychiatric diseases to the levels several times higher than that in normal mice (Zangen et al., 1999).
Melatonin	Mice	The effect of melatonin on animal models of depression has been investigated in a concentration-dependent manner. Usually, this neurohormonone at low concentrations has antidepressant effects, and at high concentrations, it can induce or exacerbate depression (Mantovani et al., 2003; Bourin et al., 2004) .

DISCUSSION

Depression is a multifactorial disease associated with changes in the levels of neuromediators, BDNF, genetic disorders, environmental factors such as lifestyle, which comprise the main etiology of depression. Recent studies have shown that change in the levels of neurotransmitters is important because it is one of the main causes of depression, such that it has been argued that serotonin is associated with many human diseases, especially behavioral diseases, such as depression, through the V serotonin transporter.

Different genetic studies in this field have focused on 5-HTTLPR polymorphism and in lower degrees on the inner VNTR located near the exon 2 (Lesch *et al.*, 1999), so that at the TM8 transporter serotonin site, a miss sense mutation type occurs (I425V), which leads to a change in the second transport structure and its activity. The people who carry this change (valine instead of isoleucine 425) are often susceptible to obsessive compulsive disorder, and other illnesses such as aspergill syndrome (a type of autism), sociophobia, anorexia, nervous tic disorder, depression and excessive alcohol use. They also have the LL 5-HTTLPR genotype. The stimulation of serotonin transporter, with nitric oxide and cGMP, increases serotonin uptake rate by as much as doubling, thereby resolving this problem to some extent(Murphy and Lesch, 2008).

Another factor in causing depression is BDNF. This factor is linked to two receptors located on the cell surface; TrkB (TrkB) and NGF (a receptor for low molecular weight growth factors, which is also known as P75) (Patapoutian and Reichardt, 2001). BDNF, both in the form of a monomer and in the form of a dimer, binds to these receptors at the cell surface, causes them to be duplicated; then each of them phosphorylates the other, and in the next step, by launching intracellular cascades, they activate the proteins involved in the differentiation and growth of neurons.

BDNF may also affect the activity of various neurotransmitter receptors including the alpha-7 nicotinic receptor and can thus play a role in causing depression.The function of neurotrophic factors is related to the activity of a neural network and the expression of BDNF is regulated by neural activity (Mellstrom *et al.*, 2004; Fernandes *et al.*, 2008). Recent clinical studies that have been performed on serum or plasma levels of BDNF in patients with depression, have shown that the plasma levels of BDNF in depressed people are lower than in normal people. Although the source of BDNF in the circulation is unknown, BDNF is found both in plasma and in the plasma, a large amount of circulating BDNF is stored in human platelets (Fujimura *et al.*, 2002). BDNF can cross the blood-brain barrier in both directions, and BDNF that is present in the circulation can originate from the brain neurons (Pan *et al.*, 1998).

Other studies have shown that plasma levels of BDNF are lower in depressed people who do not take antidepressants compared to patients who receive these drugs. It has been observed that in depressed individuals, following the reduction of BDNF, intracellular cascades that activate the proteins associated with the differentiation and growth of neurons decrease and the lack of differentiation and growth of these cells causes behavioural disorders, including depression (Lee *et al.*, 2007).

The term *dopamine* is made up of two parts: *dope*, which in medicine means happiness and *amine*, meaning amino acid. Dopamine therefore means happiness-inducing amine. In general, dopamine-dependent messages play a major role in neuronal growth, anterior brain differentiation and impulse production. In addition, the activators of D1 and D2 dopamine receptors influence proliferation, migration and differentiation of neurons; the role of dopamine as the most important excitatory neurotransmitter in developing depression is that the activation of the D2 receptor inhibits the intracellular adenylate cyclase, resulting in a rapid decrease in the intracellular cAMP level.

It has been determined that calcium release from intracellular reservoirs is controlled by the effect of inositol triphosphate (IP3) by cAMP. Therefore, the rapid reduction of cAMP due to declined ade-

nylate cyclase activity reduces intracellular calcium levels, thereby causing an inhibitory process in many intracellular processes. As known, calcium is one of the factors influencing the activation of the intracellular signal cascade. Inhibition of the intracellular signal cascade reduces the activity of the proteins associated with differentiation of the neurons and thus leads to depression (Tricklebank *et al.*, 1984; White and Kalivas, 1998).

It can also be concluded that there is a direct correlation between the severity of depression and the degree of the D2/D3 binding affinity in the striatum (Martinez *et al.*, 2010). Some studies have shown a reduction in the level of affinity between dopamine receptor D2 in the striatum of people with social anxiety and depression(Schneier *et al.*, 2000), and some studies have pointed to the abnormality of the dopamine transporter levels in the striatum in affected individuals(van der Wee *et al.*, 2008).

Although some researchers have reported inconsistent results(Schneier *et al.*, 2009), much evidence emphasizes some abnormality in the dopaminergic system of the patients. For example, impaired concentration, fatigue, lack of interest in everyday routines and social relationships, decreased self-esteem and depression are seen in depressed people. Patients also consider dopaminergic drugs as the most effective medication for short-term treatment of this disorder(Mikkelsen *et al.*, 1981).

Another amine mediator involved in the onset of depression is the excitatory glutamate neurotransmitter, which is one of the most important chemical stimulants in the CNS. This neurotransmitter acts as a chemical messenger in most excitatory synapses. Glutamate is released due to synaptic plasticity and memory formation through pre-synaptic membrane depolarization via a calcium -dependent process, and plays its role by activating specific receptors on neurons and glial cells (Khalphi, 2013).

Glutamate system is the most important system of the hippocampus. The hippocampal glutamate system acts on the function of a wide range of neurotransmitter systems, so that the hippocampal glutamate neurons exert their effects both through different receptors and through the pathway that inhibits tonus contraction in the target regions of the mesolimbic pathway, so that activation of glutamate receptors causes induction of a ion inflow in mesencephalic dopaminergic neurons through sodium channels; and subsequent activation of post-synaptic D1 receptors by acting on post-synaptic receptors and activating protein kinase A, in a calcium-dependent manner, increases the excitatory effect of NMDA receptor in the frontal lobe. This evidence suggests the interaction between dopamine receptors and NMDA receptor at the cell surface, and thus the activation of glutamate receptors leads to anxiety and depression.

Recent studies have shown that NMDA receptors contribute fundamentally to emotional behaviors such as fear, anxiety and depression. It is believed that these amino acids can act as a neurochemical mediator (Bast *et al.*, 2001; David *et al.*, 2005). Another issue is that there are receptors, known as sigma receptors, with antidepressant activity in the limbic system that regulate the NMDA receptor, which is a very important pathway of antidepressant action. In this way, glutamate is also an important factor for incidence of depression (Akhondzadeh *et al.*, 2003).

Another important neuromediator in the development of depression is GABA that is the most important inhibitory neurotransmitter in the brain. These receptors are divided into three groups: GABAA, GABAB and GABAC; the GABAA receptor binds to the chlorine channels, and the GABAB receptor, by binding to the G protein, reduces the entry of calcium and increases potassium flow into the cell (59 and 60). Research indicates that the GABAergic system, along with dopaminergic and glutaminergic systems, plays a role in depression, but there are inconsistent results regarding the role of GABAA and GABAB receptors in developing depression. Being exposed to shock and depression in rats reduces GABAB receptors.

The study of Borman et al. showed that GABAB receptors are present in the serotonin and catechol-

amine neurons of the brainstem. The available evidence regarding the interaction of GABAergic and serotonergic systems indicates that that they interact with each other so that serotonin increases GABA secretion through the pre-synaptic serotonin receptor and consequently causes GABAB-mediated neurotransmission. On the other hand, stimulation of GABAB receptors increases serotonin secretion. But other studies have reported that the effect of GABA on serotonin is inhibitory, so that GABA receptor antagonists increase serotonin levels.

Many studies have shown that stimulation of the GABAergic system reduces the activity of the sympathetic system and decreases release of norepinephrine. But the results of some studies indicate that GABAB receptor stimulation may increase the effect of norepinephrine or increase its release in the hippocampus and cortex. Therefore, it can be concluded that GABAB receptor has a dual role in antidepressant activity, and also GABAB involvement in calcium and potassium ion channels, which are widely distributed in the nervous system, plays an important role in the secretion of neurotransmitters in nerve terminals (Göthert, 1980; Shefner and Osmanović, 1991; Biała, 1998). In addition to neurotransmitters and mediators, hormonal and protein changes also play a role in the development of behavioral disorders and depression. Table 1 shows different biomarkers involved in the development of mental diseases and behavioral disorders.

CONCLUSION

According to numerous studies, it can be concluded that the incidence of depression is highly associated with changes in the pattern of various neurotransmitters (serotonin, dopamine, noradrenaline, melatonin and glutamate in the CNS and impairment of theBDNF, so that the increase or decrease of some of these neuromediators causes various behavioral conditions, including depression. The evaluation of these parameters is conducted by a single scale and a specific implementation algorithm.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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