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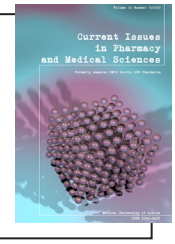

Different molecular targets, one purpose – treatment of depression

Magdalena Burat*, Ewa Gibula-Tarlowska, Ewa Kedzierska

Chair and Department of Pharmacology and Pharmacodynamics, Medical University of Lublin, Poland

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ABSTRACT

Although vast scientific progress has been made, the current pharmacotherapy of depression is still not fully effective. In adults, depressive disorders are among the most common diseases in industrialized countries, impact upon all aspects of family and working life and significantly disturb social functioning. Moreover, increasingly, they affect children and teenagers.

Depressive disorders have a complex etiology. This includes a number of mechanisms that are not yet fully understood. Therefore, the current review concentrates on bringing to the foreground the many molecular areas involved in occurrence of this disease. The work highlights the notion that depression has a complex pharmacology and inevitably requires the adoption of individual pharmacotherapy. This manuscript concentrates on currently used drugs drawn from diverse therapeutic groups and presents new promising targets for the treatment of depression. This is a particularly important issue due to the continuous lack of effective therapy and the constant search for new drugs and molecular targets for its treatment.

INTRODUCTION

Depression and its accompanying symptoms are a common cause of disability in the world. It is estimated that, globally, they strike down almost 350 million people – a figure that is growing. Indeed, according to WHO, in 2030, depression will affect a higher percentage of patients than heart diseases. Despite the wide access to a large group of drugs, not all patients respond to current treatment [1].

A mental illness, depression manifests itself in low mood, anhedonia and a decrease in psychomotor drive. Additionally, it is characterized by gastrointestinal problems (heartburn, bloating, loss of appetite), fatigue, insomnia and palpitations. It should be also emphasized that in extreme cases, the patient's life may be endangered since most suicide incidents are thought to be caused by depression. Moreover, the initial symptoms of depression – abdominal pain or headache – are a source of mistakes in diagnosis, not only among patients, but also in the medical community [2,3].

There are various theories explaining the causes of depression. Apart from personal risk factors (including traumatic experiences), many pathological changes in the human body are observed [4]. The basic concept of depression etiology is based on the dysfunction in neurotransmission – especially of monoamines, such as serotonin (5-HT), norepinephrine (noradrenaline, NA) and dopamine (DA). It is emphasized that inappropriate transmission through glutamatergic receptors also leads to depressive symptoms. Additionally, genetic factors may determine the inheritance of this disease from generation to generation. Furthermore, previous studies have uncovered a correlation between the decrease of brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and neurotrophin-3 (NT-3) concentration and depression. These factors belong to the class of neurotrophins, which may modulate monoamines levels. Several other theories on the origins of depression include hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis or an increase in pro-inflammatory cytokines level, especially tumor necrosis factor α (TNF-α) and interleukins (ILs). Each theory explains certain pharmacological targetable aspects of the mechanisms of depression, and advances the need for new therapeutic substances [5,6].

Research into depression highlights the limitations of currently available antidepressants, including the significant latency for treatment response and modest rates of efficacy. Additionally, studies underline the concern that the most commonly used agents require several weeks to months of administration before a therapeutic response is observed. Beyond the aforementioned, it is stressed that only one-third

* **Corresponding author**
e-mail: magdaburat@gmail.com

of patients respond to the first prescribed antidepressant and another one-third will only respond following multiple trials that can take many months to years. Importantly, it should be emphasized that approximately one-third of all individuals diagnosed with depression fail to respond to two or more first line antidepressant treatments and need individual multi drug therapy [1,3].

Frequently, depression also co-occurs with other diseases, i.e. cardiovascular, diabetes, Alzheimer's and Parkinson's, having a disadvantageous effect on their therapeutic process. Additionally, along with the deterioration of the patient's mental state, he or she will fail to follow therapeutic recommendations, which may reduce recovery rate [7].

Understanding the pathophysiology of depressive disorder has progressed considerably, but it is well known that no single mechanism is involved in this process. Moreover, there is a particular need for novel treatment options. Therefore, we briefly review currently available pharmacological treatment strategies and emerging targets for antidepressant drug discovery.

MATERIALS AND METHODS

A literature search was performed using PubMed, Google Scholar, Scopus and Web of Science databases (the time frame of the literature: 1995-2020). Structural formulas were independently developed on the basis of drugbank sites with IUPAC names.

1. MODULATION OF MONOAMINERGIC NEUROTRANSMISSION

The most common theory focuses on the monoamine hypothesis of depression. It assumes that monoamine neurotransmitter deficiency is the cause of this disease [5]. In fact, there is a huge amount of data supporting the view that 5-HT (in particular) and catecholamines-containing neuronal systems are altered in depressed patients. Presently, it is known that at least seven distinct serotonergic receptor classes are distributed throughout the body with stimulatory (5-HT_2, 5-HT_3, 5-HT_4, 5-HT_6, 5-HT_7) and inhibitory (5-HT_1, 5-HT_5) effects. Each receptor class has a proper subclass, and their large number indicates a great commitment to the body's regulatory processes [8,9]. 5-HT is responsible for daily rhythm, mood, memory and psychomotor drive. The synthesis process consists of two steps. Initially, a hydroxylation process occurs, catalysed by tryptophan hydroxylase (TPH). A short-lived intermediate product of this reaction is 5-Hydroxytryptophan (5-HTP). Subsequently, a decarboxylation reaction with relatively nonspecific aromatic L-amino acid decarboxylase (AADC) results in a final product deemed 5-Hydroxytryptamine (5-HT) (Fig. 1). 5-HT from the synaptic cleft is returned into the cell by the 5-HP transporter, where it is either metabolized by MAO or sequestered into secretory vesicles by the vesicular transporter [10].

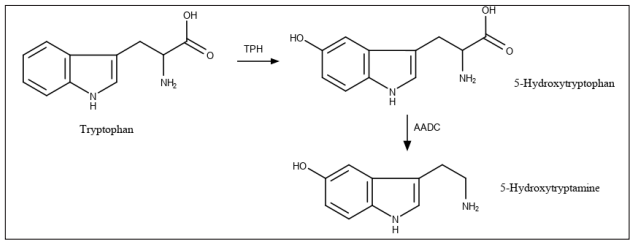


Figure 1. Synthesis of serotonin [10]

However, 5-HT is not the only neurotransmitter involved in the mechanisms of depression. Studies have indicated that NA and DA catecholamines also have a significant role in its pathogenesis. Researches demonstrate that noradrenergic and dopaminergic pathways are closely related to the serotonergic, and drugs activating these systems are effective in the treatment of depression. Therefore, the objective of antidepressant therapy, through monoamine system modulation, is to increase the neurotransmitter concentration in the synaptic cleft through various mechanisms [11,12].

1.1 Monoamine reuptake inhibitors

The low concentration of amine in the synaptic cleft may be modulated in different ways. Drugs may inhibit specific proteins transporting the neurotransmitters (reuptake carriers), i.e. the serotonin transporter (SERT), NA transporter (NET) and DA transporter (DAT). As a result, the monoamines persist longer in the synaptic cleft and have a therapeutic effect on the human body by enhancing activation of postsynaptic receptors [13]. At first, tricyclic antidepressants (TCAs) were the foundation of antidepressant therapy. Unfortunately, they possess a non-selective mechanism of action, because they inhibit reuptake of both catecholamines and 5-HT, and additionally modulate the effects of many receptors, including adrenergic, cholinergic and histamine (not involved in depression therapy). Such wide receptor activity possesses the risk of inducing many adverse effects such as increased body weight, dizziness, dry mouth, sleepiness or constipation. Newer drugs are characterized by higher selectivity against one neurotransmitter. They may inhibit double NA and serotonin (SNRI), only norepinephrine (NARI), only serotonin (SSRI) or only DA reuptake (Table 1) [14-16].

Table 1. Groups of drugs belonging to specific antidepressants [14-17]

Mechanism	Nonselective (TCAs)	Selective			
		NA/5-HT (SNRI)	**NA** (NARI)	**5-HT** (SSRI)	**DA/NA** (NDRI)
Drugs	Imipramine Desipramine Nortriptyline Amitriptyline Clomipramine Opipramol Dibenzepin	Venlafaxine Duloxetine Milnacipran	Maprotiline Reboxetine	Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	Bupropion

When using reuptake inhibitors, antidepressant effects appear in time delay. Herein, increased concentration of neurotransmitter in the synaptic cleft interacts with the receptors on the postsynaptic membrane. Subsequently, reduction in the number of receptors and their sensitivity to amines ("down regulation") as compensatory mechanisms are observed. The following neuradaptive changes then result in the desired therapeutic effect [11].

1.2 MAO inhibitors

Monoaminoxidase (MAO) is an enzyme that occurs as two isoforms: monoaminoxidase – A (MAO-A) and monoaminoxidase – B (MAO-B), and modulates the concentration of amines, ensuring their physiological balance. The relevant substrates are decomposed through oxidation reactions, wherein 5-HT is mainly degraded by the MAO-A isoform (Fig. 2), while NA and DA can be oxidized by both types of the enzyme. MAO also has the ability to regulate the concentration of other amines such as adrenaline, tryptamine or tyramine [18,19].

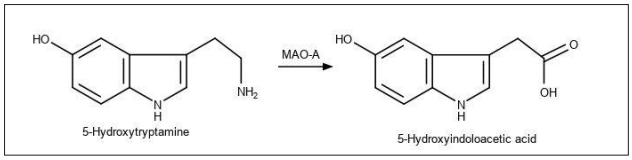


Figure 2. Mechanism of serotonin oxidation by MAO-A

MAO inhibitors can be classified into three basic types (generations), taking into account their selectivity and type of inhibition. The first generation includes iproniazid, phenelsin, isocarboxazide and tranylcypromine. These are non-selective and irreversibly inhibit MAO. However, the lack of targeted action of these drugs led scientists to search for newer, more selective substances. Drugs of the second generation act selectively, but still irreversibly block the activity of MAO-A or MAO-B. The third generation, i.e. moclobemide, toloxatone, befloxatone and brophoromine, are MAO-A selective and are reversible inhibitors. In contrast, the selective MAO-B inhibitors (selegiline, rasagiline) are irrelevant with regard to depression therapy. Nevertheless, currently, they are widely used in the treatment of Parkinson's disease [20].

1.3. Atypical mechanisms and approaches

In addition to the classical approach to treating depression by using inhibitors of monoamines reuptake or metabolism, a group of drugs exist that are characterized by different mechanisms to the aforementioned. These are generally known as 'atypical', and advances in understanding the brain neurophysiology of depression have led to the development of 5-HT modulators and stimulators, called, in short, 'SMS'. They act as agonist or antagonists on more than one type of postsynaptic 5-HT receptor and additionally inhibit 5-HT reuptake to varying degrees, while having minimal effects upon NA reuptake. The SMS group include:

- trazodone, which inhibits SERT activity, but also acts as an antagonist of 5-HT_{2A}, 5-HT_{2C}, H_1, α_1 and α_2 receptors [21].
- nefazodone, the structure and mechanism of action of which resembles that of trazodone. It weakly inhibits SERT, and antagonizes and down regulates 5-HT_{2A} receptors, with increased activity at the 5-HT_{1A} receptor sites [22,23].
- vortioxetine, which increases the 5-HT concentration in the synaptic cleft and interacts with many subtypes of 5-HT receptors. It is a partial agonist of 5-HT_{1A} and 5-HT_{2B} receptors, and is an antagonist of 5-HT_{3A} and 5-HT_7 receptors, but can also modulate the activity of other neuronal systems [24].
- vilazodone inhibits SERT and is a serotonin 5-HT_{1A} partial agonist/reuptake inhibitor, whence it is also called 'SPARI' [25]. This special mechanism allows an increase of 5-HT concentration in the synaptic cleft to a greater extent than through SSRI and it accelerates the achievement of the antidepressant effect [26].

In addition, two drugs exert antidepressant effect, mainly by way of modulating NA neurotransmission through influence on α_2-adrenergic receptors. These drugs are:

- mirtazapine, which possesses a dual mode of action and is a noradrenergic and specific serotonergic antidepressant (abbreviated as NaSSA). It acts by blocking α_2-adrenergic presynaptic autoreceptors and heteroreceptors located on serotonergic nerve terminals, thereby increasing NA and 5-HT release. Additionally, it antagonizes 5-HT_2 and 5-HT_3 receptors, inducing neurotransmission via 5-HT_{1A} receptors. Moreover, it has a high affinity for the histamine H_1 receptor, providing hypnotic effects [27-29].
- mianserin, similarly to mirtazapine, it increases the release of NA to the synaptic cleft by blocking inhibitory presynaptic α_2-adrenergic autoreceptors. Furthermore, it is an antagonist of histamine H_1 receptors as well, but it has only a small impact on central serotonergic mechanisms [30].

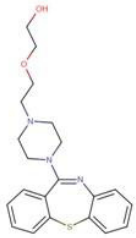
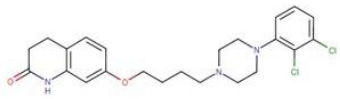
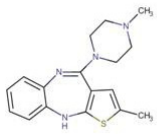
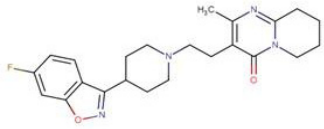
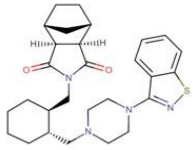
Among patients suffering from depression with coexisting circadian rhythms and sleep-wake cycle disturbances, effective improvement may be achieved by being prescribed agomelatine. This is a new antidepressant with a unique and complex pharmacological profile. It acts as an agonist at melatonin (MT_1 and MT_2) receptor sites, hence, it has hypnotic properties, and is an antagonist at serotonin 5-HT_{2A} and 5-HT_{2C} receptor sites, which guarantees its antidepressant activity. Additionally, agomelatine affects various stages of neurogenesis in the hippocampus and increases cell proliferation and neurogenesis in the dentate gyrus [31,32].

New antipsychotics with additional antidepressant action

Antipsychotics (neuroleptic drugs) are mainly used to treat schizophrenia. However, recent clinical studies have demonstrated their effectiveness as antidepressant drugs. Thus, they are used as add-on treatment [33].

The main mechanism of action of these drugs is based on modulation of dopaminergic transmission, i.e. D_2 receptors blockade. Depending on the structure, they may be selective D_2 antagonists or also interact with other receptors, i.e. muscarinic, serotonin, histamine, adrenergic. Scientists have noted that the effectiveness of these new antipsychotics in the treatment of depression depends on the specific mechanism of action connected with their effect on serotonergic receptors (Tab. 2). The group of neuroleptic drugs with antidepressant activity includes quetiapine, aripiprazole, olanzapine, risperidone and lurasidone [33-36].

Table 2. Antidepressant mechanism of antipsychotic drugs

Mechanism of action	Structure
QUETIAPINE High affinity and antagonistic effects on 5-HT_{2A} and 5-HT_{1A} receptors makes this drug effective as monotherapy in acute bipolar depression [36]	 2-[2-(4-Dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol
ARIPIPRAZOLE This is a partial 5-HT_{1A} and 5-HT_{7} receptor agonist and a 5-HT_{2A} receptor antagonist. These properties contribute to its antidepressant effects. In addition, its pharmacological effect is enhanced by agonistic properties at 5-HT_{2C} receptors [25]	 7-{4-[4-(2,3-dichlorophenyl)piperazin-1-yl] butoxy}-1,2,3,4-tetrahydroquinolin-2-one
OLANZAPINE The antidepressant effect of this drug comes about by blockade of 5-HT_{2A} and 5-HT_{2C} receptors. Olanzapine and fluoxetine polytherapy are considered most effective in treating severe depression [33]	 5-methyl-8-(4-methylpiperazin-1-yl)-4-thia-2,9-diazatricyclo[8.4.0.0^{3,7}]tetradeca-1(14),3(7),5,8,10,12-hexaene
RISPERIDONE Having a strong affinity for 5-HT_{2A} and 5-HT_{7} receptors, it acts as an antagonist. In low doses and used in conjunction with the SSRI, the antidepressant effect is enhanced [33,34]	 3-{2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl}-2-methyl-4H,6H,7H,8H,9H-pyrido[1,2-a]pyrimidin-4-one
LURASIDONE By modulating serotoninergic receptors (5-HT_{1A}, 5-HT_{2A}, 5-HT_{7}) it improves cognitive function and exhibits antidepressant activity [37]	 (1R,2S,6R,7S)-4-{[(1R,2R)-2-{[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]methyl}cyclohexyl]methyl}-4-azatricyclo[5.2.1.0^{2,6}]decane-3,5-dione

Modulation of glutaminergic neurotransmission

The glutaminergic system plays an important role in the mechanism of depression formation. In the physiological state, the main neurotransmitter, glutamic acid (Glu), binds to the N-methyl-D-aspartic acid (NMDA) receptor and triggers it by activating subsequent signal pathways [38]. However, excessive glutaminergic transmission in the structures responsible for brain neuroplasticity and the processing of emotions, such as the prefrontal cortex and hippocampus, causes neuronal degradation in these areas. This process may lead to the generation of depressive symptoms in patients. These observations led to expanded research of compounds with antidepressant potential which reduce glutaminergic neurotransmission by inhibiting NMDA receptor activity [39].

Recent studies have shown that Ketamine, a well-known anaesthetic drug with an antagonistic property against NMDA receptors, exerts antidepressant activity. The drug's blockade of NMDA receptors in the prefrontal cortex and the hippocampus limits the neuronal atrophy in these areas that is typically observed in patients with depression. In addition, ketamine can modulate other systems involved in the pathomechanism of the disease. For example, it reduces the concentration of IL-6, TNF-α, protein-1 activator and other cytokines involved in inflammatory processes. Moreover, due to holding a similar mechanism to reuptake inhibitors, ketamine increases the concentration of monoamines in the synaptic cleft. Its antidepressant effect is also attributed to interaction with the μ opioid receptor and increasing of endocannabinoid signaling [40]. Of interest, extended studies have indicated that the S-enantiomer of ketamine – esketamine – has 4 times stronger effect than ketamine and thus allows for smaller dosages. The exact mechanism of esketamine's antidepressant effect is not entirely clear. Still, in 2019, this drug was approved for the treatment of depression in an atypical form of administration – nasal spray. However, it is emphasized that its strong affinity for NMDA receptors may induce psychosis. Hence, research continues in order to asses the benefit/risk ratio of this drug in the treatment of depression [41,42].

Regarding tianeptine, another atypical antidepressant, major depressive disorders and chronic stress are associated with hyperactivity of the HPA axis (elevated level of corticosterone/cortisol in the plasma and cerebrospinal fluid and hypersecretion of corticosteroids, in rodents and humans, respectively) [43]. As a result, brain regions engaged in emotions, perceptions, memory and cognitive function, such as hippocampus, amygdala and prefrontal cortex are reported to undergo structural modifications. These are characterized by neuron dendrite shrinkage, glial cell loss, and/or impairments in neuroplasticity and cellular resilience. In fact, actual preclinical literature demonstrates the key role played by changes of glutamate. The atypical nature of tianeptine results from the fact that unlike most antidepressants, it does not inhibit the reuptake or metabolism of monoamines. The antidepressant action of this drug is based on improving neuroplasticity of the brain and cognitive functions, including neuroprotective effects on the HPA [44-46]. Tianeptine normalizes the following changes by modulation of glutamatergic neurotransmission, as well as by increasing the gene expression for neurotrophic factors such as BDNF and NGF, that are decreased in depression [47]. Thus, the antidepressant effect of tianeptine is part of the neuroplasticity hypothesis of depression and manifests itself in the regulatory effect on neural plasticity processes that are disturbed by chronic stress [46].

Modulation of opiod receptor

Severe depressive disorder very often requires special forms of treatment and molecular targets. One of these is the endogenous opioid system. This consists of opioid μ (mu), κ (kappa) and δ (delta) receptors and their endogenous ligands: endorphins, enkephalins, dynorphins and endomorphins [48]. For many years, opioid receptors modulation has largely focussed on their analgesic effects. However, more

recent attention has turned to their role in the regulation of stress responses, anhedonia and mood. A known effect of opioid receptor stimulation is their ability to induce euphoria [49], yet, stimulation of opioid receptors in the limbic areas responsible for the regulation of emotional processes, causes intensification of neurogenesis in these brain regions. They also mediate the production of monoamines, i.e. 5-HT and DA, and inhibit the release of NA.

Despite concerns about the risks of abuse and dependency, μ opioid receptors agonists, like oxycodone, oxymorphone and the partial agonist of these receptors - buprenorphine, have been shown to be beneficial in patients in treating drug resistant depression [50-53]. Moreover, buprenorphine in combination with opioid receptor antagonists, i.e. naloxone and naltrexone, has been found to reduce suicide attempts [48,54]. The antidepressant effect of buprenorphine may be also attributed to the modulation of nociceptin/orphanin FQ (N/OFQ) receptors [55]. However, explaining the exact mechanism of antidepressant effects of this drug requires further studies.

It has been stated that activation of the κ opioid receptors in both human and rodents induces dysphoric and prodepressive like effects. This effect has led to the idea that selective κ opioid receptor antagonists might possess therapeutic potential as antidepressant drugs [56]. In addition to μ and κ, δ opioid receptors may also play a role in the regulation of hedonic tone and the response to stress. However, while activation of these receptors has been shown to be antidepressant in a number of preclinical behavioural studies [49], activation also may lead to convulsions [57,58]. Still, recently, δ opioid receptor agonists without seizure-like properties have been developed [59].

It should be emphasized that rebalancing opioid receptor dysregulation in stress induced mood disorders is not as simple as targeting a single opioid receptor. Therefore, unique pharmacological agents are needed that target many opioid receptors. A better understanding of the role of opioid receptor heterodimers and ligands can lead to finding promising new drugs for depression.

Novel pharmacological strategies

Antidepressants alleviate the symptoms of most cases, but a number of patients do not find relief and the remission process is too low. One of the recent theories indicates that the endocannabinoid system plays a role in the formation and treatment of depression.

An exogenous compound that modulates the activity of this system was found in *Cannabis sativa* (cannabis). The plant contains over 100 chemical compounds with similar chemical structure, known as cannabinoids. The main psychoactive compound in cannabis is Δ-9-tetrahydrocannabinol (Δ9-THC). This drives the recreational use of marijuana on such a large scale. However, cannabidiol (CBD), a compound devoid of psychoactive effects, exhibits pharmacological potential in the treatment of depression. In fact, research shows that it harmonizes neurotransmission in the limbic areas mainly involved in emotional control, as it affects $5HT_{1A}$ receptors that modulate responses to stressful stimuli [60]. Moreover, preclinical studies have revealed that CBD has a protective effect in the progressive neurodegenerations of the prefrontal cortex and hippocampus without influence on cognition. In addition, it improves sleep architecture. Although CBD has a wide range of pharmacological activities, the exact mechanisms are still unknown. Therefore, it is necessary to expand research into the molecular targets for CBD and its impact on the human body [61].

Recent research also emphasizes the involvement of the cholinergic system in the process of depression. Here, enhanced levels of acetylcholine (Ach) not only affect the respiratory and cardiovascular systems, but also lead to severe central nervous system (CNS) changes causing psychosis and depression. This thesis is confirmed by the observations that the anticholinergic agent, scopolamine, by blocking the M receptors, demonstrates antidepressant effects, especially in severe bipolar depression [62].

The drug vasopressin also demonstrates the ability to modulate the HPA axis described in the previous section. Yet, while scientists have demonstrated that compounds with antagonistic properties against vasopressin receptors (V) have antidepressant potential, it is necessary, to extend research into the efficacy and safety of this type of drug [63].

The cytokine hypothesis considers that external, e.g. psychosocial stressors, and internal stressors, e.g. organic inflammatory disorders or conditions may trigger depression via inflammatory processes, and, thus, increasing levels of inflammatory mediators are observed in depressed patients. Among these are tumor necrosis factor α (TNF-α) and interleukins (IL-6, IL-1β). Research has shown that abnormal levels of inflammatory cytokines interfere with HPA axis. Moreover, they disturb the functioning of neurotransmitters (5-HT, NA, DA, Glu) at the level of synthesis, release and finally metabolism. According to this theory, clinical efficacy of antidepressant treatments may be enhanced by concurrent administration of agents with anti-inflammatory effects, such as cyclooxygenase-2 inhibitors [63-65].

Substance P (SP) also presents pro-inflammatory properties. As a neurotransmitter and neuromodulator, it takes part in the organism's response to pain, and stress. In addition, it modulates certain mental disorders, i.e. depression. SP acts on the neurokinin-1 (NK-1) receptors that occur in many brain areas responsible for the processing of emotions (hippocampus, prefrontal cortex). Therefore, the NK-1 receptor antagonists, casopitant and orvepitant, have been tested for their effectiveness in major depressive disorders (MDD) and have revealed pharmacological potential. The specific contribution of SP to the pathophysiology of depression is still not precisely defined, so it is important to find the exact mechanism and test available drugs, as well as search for new compounds [65,66].

CONCLUSIONS

Depression is a complex mental disorder with complicated and not fully understood etiology. Moreover, currently available antidepressant drugs are notoriously problematic, with limited effectiveness, suboptimal remission rates and troubling side-effect profiles. Nevertheless, in recent years views on the pathophysiology of depression have evolved, and this has sparked interest in a myriad of novel

neuropsychopharmacological approaches. In fact, modification of already formed therapeutic substances and extension of molecular mechanisms of depression may contribute to finding even more successful therapies.

ORCID iDs

Magdalena Burat https://orcid.org/0000-0002-5114-2848
Ewa Gibuła-Tarłowska https://orcid.org/0000-0001-7791-0633
Ewa Kędzierska https://orcid.org/0000-0002-2648-6075

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