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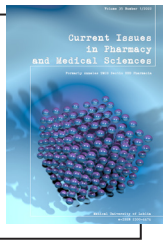

The monoamine theory of depression as a target to effective pharmacotherapy

Tomasz Karabin, Grazyna Biala, Marta Kruk-Slomka*

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

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ABSTRACT

Depression is one of the greatest current mental disorders. Depressive disorder may affect everyone and it causes difficulties in social functioning and may lead to death via suicide. Depression is a serious problem because number of its cases is increasing, especially after pandemic of COVID-19. The oldest and the most approved theory which explains mechanism of depression's development is a monoamine hypothesis. Effectiveness of most antidepressant drugs based on this theory. It assumes that the typical symptoms of depression are results of changed concentration of monoamines or incorrect monoaminergic transmission. The aim of this article is to present drugs which have influence on level of biogenic amines and are used in treatment of depressive disorders. Some of those drugs are the first choice in cure of this disease. In spite of adverse effects and often delayed onset of action of pharmacotherapy, it is still the first line in treatment of depression.

EPIDEMIOLOGY

Nowadays, globally, depressive disorders are the most common mental problem experienced – especially in the First World. About 280 million people are documented as suffering from depression. Indeed, World Health Organization (WHO) data from 2021 suggest that 3,8% of the entire population is affected, including 5,0% of all adults and notably, 5,7% of all people older than 60 years. Moreover, it is estimated that one-in-three women and one-in-five men have experienced at least one episode of depression by the age of 65 [1,2].

Although bad before, the situation worsened after the COVID-19 pandemic. Accordingly, global prevalence of depression increased by 25%. This came about due to the stress generated by social isolation, loneliness, fear of infection or death for self, family or friends [1,2].

Unfortunately, about 75% of all affected people do not have access to treatment. This is notably so in low-income and middle-income countries. That people with depression are not correctly diagnosed and do not receive treatment is a dangerous situation because depressive disorders cause difficulties in social functioning and may lead to death via suicide or murder-suicide [1,2].

* **Corresponding author**
e-mail: marta.kruk@umlub.pl

THE FACTORS OF RISK

Depression may affect everyone regardless age, gender or race. However, there are some correlation between age and depression. Environmental stressors are another set of factors associated with development of depressive disorder in specific ages. Examples of such include job loss, death of spouse, divorce, unwanted pregnancy, social isolation, rape, war, etc.

Depression often starts at adolescence or at the young adult age. In this age group, the prevalence of depression may be connected with family history, adverse life events, negative attitudes about their abilities, poor sleep, hormonal changes, or/and concomitant disorders both physical and mental. Risk factors in older adults may be connected with loss of a spouse or partner, having chronic poor health conditions, poor physical health, loneliness, being female or of low economic status or low education level and living alone. The strongest symptoms of depression are observable in young adults, those of older age show weaker manifestations [3].

In terms of gender and psychiatric epidemiology, the group hardest hit by depression are women. The most affected are women of child bearing age. Here, 10-20% of all women after childbirth experience postpartum depression [3,4]. Other factors of development of depression are genetic. Literature data report that, compared with the general population, someone with a first-degree relative diagnosed with depression (a parent, sibling, or child) could

be three times more likely to be diagnosed with depression in their lifetime. Research also suggests that women could be more susceptible to the genetic influences associated with depression than men. There is also a heritable component to depression. The large number of genes related with the development of this disorder include apolipoprotein E (APOE ε2 and APOE ε4), the guanine nucleotide-binding protein (GND3), the methylenetetrahydrofolate reductase (MTHFR 677T), dopamine transporter (SLC6A3), serotonin transporter (SLC6A4) and the dopamine receptor gene (DRD 4) [3,5].

It should be mentioned that depression may be the only one disease that a patient is afflicted with, or the depressive state can be brought about by an underlying medical condition. People who suffer from other illnesses have depression more often than the healthy population. Statistically, the greatest prevalence of major depressive disorder (MDD) is in the patients with disease like Parkinson's Disease (51% of all patients have MDD), pain syndromes (about 50%), malignant tumors (20-40%), thyroid disorders (20-30%), diabetes mellitus (10-27%), heart attack (16-28%), stroke (23-35%), coronary heart disease (17-20%), AIDS (12%), and Alzheimer's Disease (11%). Other diseases connected with depressive disorders are: COVID-19, Cushing's Disease, traumatic brain injury, Huntington's Disease, multiple sclerosis. In the aforementioned situations, depression can be induced by the worsening medical condition of the patient or may also be induced via the drugs used in the treatment of the primary disease (Figure 1) [1,6,7].

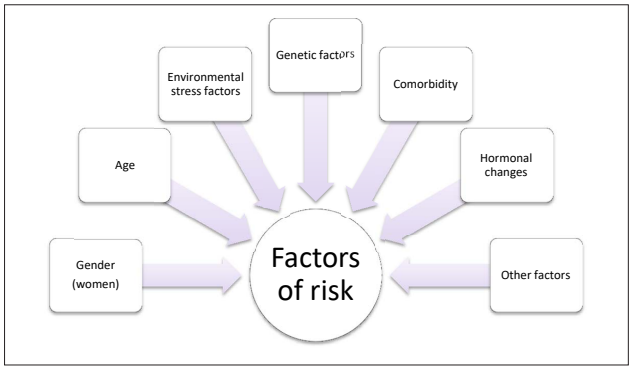

Figure 1. Factors of risk of depressive disorders

THE CLASSIFICATION AND CAUSES OF DEPRESSION

There are many types of depressive disorder. According to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V), depressive disorders are divided into:

- Disruptive mood dysregulation disorder – seen in children up to 12 years of age. Indicative are displays of persistent irritability and frequent episodes of extreme behavioral decontrol. Children with this disorder often will develop unipolar depressive disorder or anxiety disorders.
- MDD – is the classic condition. MDD includes a singular major depressive episode, but this disorder is mostly recurrent. The duration of MDD is at least 2 weeks and some remissions may occur between the episodes. Changes in affect (emotion), cognitional and neurovegetative functions are noticeable.
- Persistent depressive disorder (dysthymia) – is a chronic form of depression. Dysthymia is diagnosed when duration of event is at least 2 years in adults or 1 year in children.
- Premenstrual dysphoric disorder (PMDD) – is a specific form of depression that sometimes begins following ovulation and remits within a few days of menstruation. Although this disorder lasts only a few days in a month, it impacts on functioning.
- Substance/medication-induced depressive disorders – occur after taking of certain drugs or substances of abuse. These include cocaine, alcohol, opioids, amphetamine or some prescribed drugs like reserpine, steroids, L-DOPA and antibiotics.
- Depressive disorder due to another medical condition – is mainly caused by the worsening medical condition of a patient. A limited list of examples is provided above [6].

THE SYMPTOMS OF DEPRESSION

People with depression have certain specific common symptoms which include, among others, feelings of worthlessness or guilt, as well as fixation on past failures or self-blame. Moreover, sadness, loss of interest in activities or lack of pleasure (anhedonia), irritable mood, low self-worth, tiredness, hopelessness about the future, poor concentration, loss of appetite or weight changes, psychomotor activity changes, sleep disturbance (insomnia etc.) may also appear. Additionally, depressed people may experience thoughts about dying. At its worst, depression can lead to suicide. All of these symptoms have a negative impact on physical and social functioning. About 80% of all people facing depression have some form of impairment in their daily functioning. Over 700 thousand people die by suicide every year [1,3,6,8].

THE CAUSES OF DEPRESSION

The pathophysiology of depression is still poorly understood. Several hypotheses have been advanced, however, to try to explain its mechanism [8]. The biogenic amine (monoamine) hypothesis was the first. According to this hypothesis, the typical symptoms of depression are the results of changed concentration of monoamines or incorrect monoaminergic transmission. This is described by the Basic Emotion Theory (BET), put forward for the first time in the 1950s. BET suggests that there are actually only a limited number of basic emotions, and all other emotions are composed of these. Ekman's BET, for instance, proposes that there are seven basic emotions: fear, anger, joy, sadness, disgust, contempt and surprise [9]. According to the hypothesis, as the brain contains huge amounts of noradrenergic, dopaminergic and serotonergic neurons, as well as monoamine neuromodulators (among others, serotonin (5-HT), noradrenaline (NA), and dopamine (DA)), these might be the primary neural basis for all emotions.

DA modulates reward and motivating functions, working memory, behaviour and attention. DA is connected with feeling of joy. NA modulates the processing of working memory, and regulates behavior and attention. NA is also

related to emotional arousal, "fight or flight" behavior or "fear and anger" emotion. 5-HT is the largest cohesive neurotransmitter system in the brain and plays different roles – depending on which receptor is activated or blocked, it modulates sleep, sedation, memory and thermal regulation, and inhibits compulsory thoughts.

Subtypes of 5-HT receptors are presented and described in Table 1. The monoaminergic hypothesis of depression indicates that the underlying pathophysiologic basis of depression is a depletion in the levels of 5-HT, NA and DA in the central nervous system (CNS) [3,8,9,10].

Table 1. Expected therapeutic effects resulting from the modulation of the function of variety subtypes of 5-HT receptors [9,14]

Subtypes	Modulation of function	Effects
5-HT_{1A}	Agonism of postsynaptic receptor or antagonism of presynaptic receptors	5-HT_{1A} autoreceptors play an important role in the self-regulation of the serotonergic system. Their activation inhibits neuronal discharges and reduces release of 5-HT. 5-HT_{1A} heteroreceptors are involved in regulating the release of various neurotransmitters: Acetylcholine (ACh), DA, glutamate.
5-HT_{1B}	Agonism of postsynaptic receptor or antagonism of presynaptic receptors	5-HT_{1B} autoreceptors regulate the synthesis and release of 5-HT locally. The 5-HT_{1B} postsynaptic receptors are located mainly in the centers of motor control (such as the basal ganglia), where they control the synaptic transmission of other neurotransmitters. Studies have shown that 5-HT_{1B} receptors play a role in depression, anxiety, migraines, locomotor activity, aggressive behavior and the potentiating of the action of other drugs.
5-HT_{1D}	Clinical significance of these receptors are less clear. Concentration of 5-HT_{1D} receptors is higher in suicidal victims with confirmed history of untreated depression. Changes in 5-HT_{1E} may affect cognitive functions and memory.	
5-HT_{1E}		
5-HT_{1F}		
5-HT_{2A}	Antagonism	The blockade of 5-HT_{2A} receptors enhances 5-HT_{1A} receptor-mediated neurotransmission in the cortical and limbic regions, an activity associated with antidepressant efficacy. 5-HT_{2A} receptors are involved in the regulation of mood, motor behavior and appetite.
5-HT_{2B}	Agonism	The 5-HT_{2B} receptor is expressed mainly in peripheral tissues, especially in the liver, kidneys, and heart, and its distribution in the brain is low. 5-HT_{2B} receptors directly and positively regulate the activity of serotonin neurons.
5-HT_{2C}	Both 5-HT_{2C} agonists and antagonists have been shown to be active in animal models of depression	Like 5-HT_{2A} receptors, they are involved in the regulation of mood, motor behavior and appetite.
5-HT_{3}	Antagonism	Blockade of 5-HT_{3} receptor leads to increased level of 5-HT, DA, NA, ACh and histamine.
5-HT_{4}	Agonism	The 5-HT_{4} receptor subtype is involved in the modulation of synaptic plasticity.
5-HT_{6}	Antagonism	5-HT_{6} receptor has been found to play a role in learning and memory, as well as in the central regulation of hunger and satiety behavior.
5-HT_{7}	Antagonism	The physiological role of 5-HT_{7} receptors is to regulate circadian rhythm, sleep and mood.

According to theory, the amount of monoamines decreases due to increased activity of monoamine oxidase (MAO – the enzyme which degrades monoamines in the synaptic cleft), or to decreased function of the transport proteins which play a crucial role in nerve-nerve communication and monoaminergic transmissions. Herein, transport proteins enhance presynaptic reuptake, and as a result, they decrease availability of neurotransmitters in the synaptic cleft, hence, they reduce the degradation of monoamines by MAO.

Problems in the functionality of monoaminergic receptors may also occur. Abnormalities of receptor functions can result from decreased receptor affinity or decreased receptor numbers. This, in turn, leads to impaired neurotransmitter-receptor coupling (Figure 2) [3].

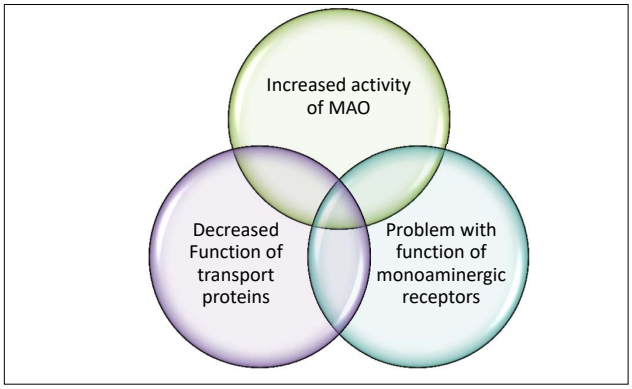

Figure 2. Monoamine hypothesis – the reasons of depressive disorders

Other hypotheses have been advanced. The most popular are based on certain factors such as genetic factors, environmental stress factors, endocrine factors, immunologic factors, and on the effects of growth hormone, thyroid hormones, neuroinflammation, and neurogenesis [3]. All of those factors are important in pathophysiology of depression, but in this article the monoamine hypothesis will be discussed in the context of effective pharmacotherapy of depression.

TREATMENT

Treatment of depressive disorder is related to its severity and pattern, and encompasses physical, psychological and social aspects. What is important is that if the depressive disorder is due to an underlying medical condition, the first disease must be addressed to ensure effective treatment of the depressive disorder [7,11].

Non-pharmacological therapies

We currently have two options for treating/controlling depressive disorders: non-pharmacological and pharmacological. A shared decision-making approach is needed to choose between non-pharmacological therapies based on values, preferences, clinical and social context. In many cases, the first line of depression treatment should include psychological treatments, such as behavioral activation, cognitive behavioral therapy and interpersonal psychotherapy. Interpersonal psychotherapy is applied to identify and change problems in social and personal relationships that contribute to depression [1,11].

Other non-pharmacological therapies like electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), vagal nerve stimulation (VNS), sleep deprivation, consciousness based healing and neurosurgery are used in

treatment of severe treatment-resistant depression when pharmacology or psychotherapy (or both) are not effective [11].

ECT is a therapy which stimulates the brain. ECT should only be given to achieve a rapid, short-term improvement when the other treatment strategies failed, or when the patient's condition is potentially life-threatening. The main side effect of ECT is amnesia [11]. The mechanism of action of TMS and VNS is similar to ECT, and rely on the employment of electromagnetic energy to alter brain activity. Those methods require more study [11].

While non-pharmacological therapies of depression reduce some symptoms of depression, the most effective therapy is a combination of non-pharmacological and pharmacological therapies, especially for the treatment of mild-to-severe depression.

Pharmacotherapy

Pharmacological therapy is the most popular therapy of depressive disorders. In this part of the article, the drugs most commonly used in the treatment of depression will be discussed, with particular emphasis on their therapeutic effectiveness and side effects.

Generally, antidepressants are effective, but their effectiveness is connected with many factors. Standard monoaminergic antidepressants have response at the rate of 60%. Unfortunately, about 40% of all patients have treatment resistant depression, and monotherapy is not effective. Additionally, antidepressant drugs have delayed action. It takes several weeks – two to six, to notice any significant symptom relief. Delayed onset of action is related to adaptive changes of 5-HT receptors (such as desensitization of autoreceptors). The ideal antidepressant has fast onset of action and great therapeutic efficacies with minimal side effects, but such drug does not exist [8,11-13].

At present, in the group of the currently used antidepressant drugs, we can mention:

- **Monoamine Oxidase Inhibitors (MAOIs)**

  MAOIs was the first class of antidepressant drugs available for pharmacological therapy and they were used very often in the past to treat different forms of depression, as well as other nervous system disorders, e.g., phobia or panic disorder, social anxiety disorder and Parkinson's Disease (selegiline). The different types of MAOIs approved by the FDA include isocarboxazid, phenelzine, tranylcypromine, moclobemide, and selegiline. Those agents inhibit the activity of the MAO enzyme. As a result, 5-HT and NA are not broken down and their concentrations rise and mood improves [12].

  Currently, these medicines are rarely used because they have many side effects, among others, anticholinergic effects, orthostatic hypotension, and sexual dysfunction. Additionally, they have serious interactions with other drugs and foods containing tyramine (e.g., cheese, wine, chocolate, certain fish), because tyramine is also broken down by MAO. At present, MAOIs are only a treatment option when all other medications are unsuccessful [12].

- **Tricyclic Antidepressants (TCAs)**

  Currently available TCAs include amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, amoxapine, doxepin, protriptyline and trimipramine. They act by blocking the reuptake of 5-HT and NA, but they are not selective and interact with other receptors, such as the histaminergic H1, H2, muscarinic cholinergic, alpha adrenergic and opioid receptors [12,14].

  TCAs are used in treatment of depression, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), schizophrenia (clomipramine), Tourette's disorder (clomipramine), attention deficit hyperactivity disorder (ADHD) (desipramine, imipramine), insomnia (doxepin) and pain associated with fibromyalgia and diabetic neuropathy [11].

  Similarly as MAOIs, TCAs are currently not among the first-line treatment options. They have many adverse effects like anticholinergic effects, cardiac arrhythmias and QT interval prolongation, sedation, weight gain, and extrapyramidal effects, e.g., pseudoparkinsonism motor symptoms [12].

- **Selective serotonin re-uptake inhibitors (SSRIs)**

  SSRIs are the most commonly prescribed group of antidepressant drugs. Available SSRIs include Fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram. The mechanism of their action is an inhibition of re-uptake of 5-HT. Today, these drugs are regarded as the first line treatment as they are safer than the previously mentioned antidepressant medicines [8,12].

  SSRIs have many indications to use. Besides depression, they are prescribed to treat panic disorder, anxiety disorders, e.g. PTSD or OCD, bulimia, PMDD, bipolar I disorder (fluoxetine) and vasomotor symptoms of menopause (paroxetine) [12,14].

  Adverse effects of SSRIs include agitation and nervousness or sedation and fatigue, headache, insomnia, sexual dysfunction, gastrointestinal upset, loss or gain of weight, serotonin syndrome and discontinuation syndrome [12].

- **Noradrenaline – dopamine re-uptake inhibitors (NDRIs)**

  NDRIs inhibit re-uptake of NA and DA. They are newer than the first-generation antidepressants and include amineptine or bupropion. Although, bupropion has no appreciable activity on 5-HT concentrations in the CNS, bupropion produces similar depression remission rates when compared to SSRIs. Bupropion is used to treat MDD, seasonal effective disorder (SED), and is also approved for smoking cessation. Additionally, in combination with naltrexone, it is used to treat obesity. In August 2022, the FDA approved the combination of bupropion and dextromethorphan to treat MDD. Dextromethorphan is a antitussive medication and it is also an uncompetitive antagonist of the NMDA-glutamate receptor. Moreover, it inhibits re-uptake of 5-HT.

  Unfortunately, dextromethorphan is rapidly metabolized by CYP2D6 and is not used in monotherapy in the treatment of depression. Bupropion has its own antidepressive properties and, in addition, is a potent antagonist of CYP2D6. As a result, combining buproprion with

dextromethorphan results in the half-life of dextromethorphan being prolonged. In a study, a combination of these drugs was found to be superior to bupropion monotherapy. The chosen combination is based on monoamine and neuroplasticity theories of depression [14,15,16]. The most serious side effect of bupropion is the development of seizures. Other side effects include insomnia, agitation, dry mouth and constipation [15].

- **Selective noradrenaline re-uptake inhibitors (NARIs)**

  Reboxetine, maprotiline and viloxazine are selective inhibitors of re-uptake NA. Viloxazine also binds to 5-$HT_{2B,}$ 5-HT_{2C} and other receptors. These drugs are used to treat depression and ADHD, cataplexy, narcolepsy (viloxazine) and pain disorders, but may cause serotonin syndrome, seizures and increased heart rate [14,15].
- **Serotonin – noradrenaline re-uptake inhibitors (SNRIs)**

  SNRIs inhibit re-uptake of both 5-HT and NA. Available agents include duloxetine, venlafaxine, desvenlafaxine and milnacipran. SNRIs are used to treat MDD, anxiety disorders, panic disorder, fibromyalgia, osteoarthritis (duloxetine), stress incontinence in women (duloxetine) and neuropathic pain. Side effects of SNRIs include CNS depression, decreased appetite, hypertension, insomnia and serotonin syndrome [12,14].

The novel groups of antidepressant drugs:

Although the afore-mentioned drugs are efficient in the treatment of depressive disorders, they have many side effects and delayed onset of action. Therefore, in the next part of this manuscript, we would like to describe novel agents that have been found to have better efficacy or faster onset of action or require less effective dosage or show less severity of adverse effects. Unfortunately, one drug with all of these properties does not exist at present.

- **Serotonin 5-HT2 receptor antagonist re-uptake inhibitors (SARIs)**

  Trazodone

Trazodone is a serotonin 5-HT_{2A} and 5-HT_{2C} receptor antagonist and selective serotonin re-uptake inhibitor. The antidepressant effects of trazodone result from the inhibition of receptor uptake, which normally decreases circulating neurotransmitters, contributing to depressive symptoms. It also blocks H_1 receptors and alpha-1 and alpha-2 adrenergic receptors. More than half of all patients prescribed have significant therapeutic response to trazodone in the first week of usage. Moreover, trazodone is used in the off-label treatment of many diseases such as insomnia, anxiety, dementia, Alzheimer's disease, substance abuse, eating disorders, schizophrenia, fibromyalgia and pain. Common side effects of trazodone include: somnolence and dizziness. Other side effects seen are prolongation of cardiac QT-interval, dry mouth, nervousness, decreased of memory, alertness and cognition - especially in elderly patients. After trazodone administration in males, priapism may also occur – a painful and persistent incidence of penile tissue erection [14,15].

Nefazodone

Nefazodone is an antagonist of 5-HT_{2A} receptors and inhibitor of 5-HT re-uptake and blocks alpha-1 adrenergic receptors. Currently, this drug is seldom prescribed because nefazodone may cause hepatic injury – including cases of life-threatening hepatic failure [14].

- **Noradrenergic and specific serotonergic antidepressants** (NaSSAs)

  Mirtazapine

Mirtazapine enhances neurotransmissions of NA and 5-HT by blocking alpha-2 presynaptic adrenoceptors. This results in increased release of serotonin at the nerve terminals. Moreover, mirtazapine is a strong antagonist of the 5-HT_2, 5-HT_3 receptors and increases 5-HT_{1_A} activity. However, mirtazapine also binds to H_1 receptors and causes sedation. This is the main adverse effect of this agent. Still, mirtazapine is an agonist of the opioid receptors and as a result it has pain-relieving effects. In addition, it has a hormonal effect that reduces cortisol levels within the body. Mirtazapine is effective in treating moderate to severe depression. The drug also treats symptoms which are associated with depression such as disturbed sleep, lack of appetite and anhedonia. Patients on mirtazapine showed significant improvement in symptoms of MDD within the first 1–2 weeks [14,15].

Mirtazapine is also used off-label as a drug for insomnia and to increase appetite and prevents nausea and vomiting after surgery. Side effects of mirtazapine include sedation, somnolence, increased appetite, weight gain, dizziness, transient elevations in cholesterol levels and impaired liver function [14,15].

Mianserin

The mechanism of action of mianserin is similar to that of mirtazapine. Mianserin is an antagonist of alpha-2 presynaptic adrenoceptors, H_1 receptors and some 5-HT receptors. Mianserin is used in depression and anxiety treatment, but, currently, in most markets, it has been phased out in favor of mirtazapine. Mianserin has adverse effects such as sedation and hematological problems [14].

- **Serotonin modulators and stimulators (SMSs)**

  Vortioxetine

Vortioxetine is classified as a serotonin modulator and stimulator (SMS). It is an antagonist of 5-HT_3, 5-HT_{1D} and 5-HT_7 receptors, an agonist of 5-HT_{1A} receptors and a partial agonist of 5-HT_{1B} receptors, but it also acts as a 5-HT re-uptake inhibitor. Vortioxetine is approved for the treatment of MDD. The most common side effect is nausea. Adverse effects also include hypertensive crisis, increased risk of suicide, pancreatitis, sexual dysfunction, headaches, and dry mouth [14,15].

- **Selective partial agonist and re-uptake inhibitors (SPARIs)**

  Vilazodone

Vilazodone is a selective serotonin re-uptake inhibitor and a partial agonist of 5-HT_{1A} receptors. Vilazodone enhances 5-HT transmission and has no effect on NA and DA transmission. The partial agonist activity of this medication has led to its suggested co-administration to help reduce the time to effectiveness of SSRIs. Through its partial agonism of 5-HT_{1A} receptors vilazodone has faster onset of action, greater efficiency and better tolerability than SSRIs. Moreover, vilazodone has reduced sexual adverse effects and weight gain. Like vortioxetine, vilazodone is approved for the treatment of MDD. Side effects include

diarrhea, nausea, vomiting and insomnia, dry mouth, dizziness, fatigue, abnormal dreams, decreased libido, arthralgias and palpitations [14,15]. The drugs described above are presented in Table 2.

Table 2. Antidepressants of monoamine hypothesis

Antidepressants of monoamine hypothesis		Indication
MAOIs	isocarboxazid, phenelzine, tranylcypromine, moclobemide, selegiline,	depression, phobia, panic disorders, social anxiety disorder, Parkinson's Disease (selegiline)
TCAs	amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, amoxapine, doxepin, protriptyline, trimipramine,	depression, OCD, PTSD, schizophrenia, Tourette's disorder, ADHD, insomnia, pain associated with fibromyalgia, diabetic neuropathy,
SSRIs	fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram	depression, panic disorder, anxiety disorders, bulimia, PMDD, bipolar I disorder, vasomotor symptoms of menopause,
NDRIs	amineptine, bupropion	MDD, SED, smoking cessation, obesity,
NARIs	reboxetine, maprotiline, viloxazine	depression, ADHD, cataplexy, narcolepsy, pain disorders,
SNRIs	duloxetine, venlafaxine, desvenlafaxine, milnacipran	MDD, anxiety, panic disorders, fibromyalgia, osteoarthritis, stress incontinence, neuropathic pain,
SARIs	trazodone, nefazodone	depression, insomnia, anxiety, dementia, Alzheimer's disease, substance abuse, eating disorders, schizophrenia, fibromyalgia and pain
NaSSAs	mirtazapine, mianserin	depression, disturbed sleep, lack of appetite, anhedonia, anxiety,
SMSs	vortioxetine	MDD
SPARIs	vilazodone	MDD

CONCLUSION

Treatment of depressive disorders is difficult, and about 40% of all cases of depression are drug-resistant and the standard approach to treatment is not enough. Besides treatment, diagnosis is also difficult. Even though list of possible antidepressant agents is extensive, not one is perfect. Many have adverse side effects or delayed onset of action. The frequency of depression is increasing, hence many studies are needed and more therapies need to be developed.

The monoamine hypothesis has been the main theory underlying pharmacological treatment for many years. Most drugs prescribed for depression are based on the notions put forward in this theory. Novel groups of medicines which affect the concentration of monoamines are still being researched, among others, SARIs, NaSSAs, SMSs, and SPARIs. In spite of disadvantages, such as delayed onset of action and adverse effects (e.g. sexual dysfunction, serotonin syndrome), these drugs are often the first choice in the treatment depression and in related diseases such as anxiety, panic disorders, phobia, pain disorders etc.

ORCID iDs

Marta Kruk-Słomka: https://orcid.org/0000-0001-9201-7181
Grażyna Biała https://orcid.org/0000-0001-8270-9635

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