



NEW THERAPEUTIC STRATEGIES IN THE TREATMENT OF DEPRESSIVE DISORDERS“ – REVIEW ARTICLE

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ABSTRACT

Depression, as a complex multifactorial disease, represents a major public health and functional mental health disorder, especially in the 21st century, affecting the individual as a whole in numerous ways. Depression can cloud our view of the world and make us see every problem bigger than it really is. The beginnings of depression show signs in middle to late adolescence, which can have fatal outcomes in such a still vulnerable age of an incompletely formed individual. Treatment of depression requires therapy with antidepressant drugs, the effect of which requires up to 6 weeks, sometimes combinations of drugs are needed, and side effects of therapy are common, such as loss of libido, headaches, sexual dysfunction, gastrointestinal complaints, anxiety and restlessness. Antidepressants achieve their effect in a third to half of treated cases, also there are cases of treatment-resistant depression (TRD) where patients do not respond to two cycles of different antidepressants. We intend to show and describe most recent pharmacological modalities such as antagonists of N-methyl-D-aspartate receptors (NMDAR), GABA modulators (GASPAMA) with also the use of psychedelics in improving clinical outcomes. We are also showcasing new technological measures dependent on devices as non-pharmacological options for treatment of depression, such as deep brain stimulation (DBS), transcranial magnetic stimulation (TMS) and many others. Treatment of depression has almost always been presented as a taboo subject. By reviewing established treatment methods and modern treatment methods, we strive to push the boundaries in the efficiency and effectiveness of therapy for depressive disorders.

KEYWORDS: N-methyl-D-aspartate receptors (NMDAR), GABA modulators (GASPAMA), deep brain stimulation (DBS), transcranial magnetic stimulation (TMS).

INTRODUCTION

It has been shown that the two most disabling mental health disorders are depressive and anxiety disorders, both of whom are among the top 25 leading causes of global health burden in 2019.^[1] Depression occurs twice as frequently in women as in men, with hormonal fluctuations believed to contribute to this difference, affecting metabolic processes.^[2] It is estimated that 10-20% of school-aged children experience symptoms of anxiety, depression, social isolation, and similar conditions, with parents and teachers often struggling to recognize these symptoms or patterns.^[3] Between 2010 and 2018, the number of adults with major depressive disorder (MDD) in the United States increased by 12.9%, from 15.5 million to 17.5 million. The proportion of adults aged 18 to 34 with MDD increased from 34.6% to 47.5%. Over this period, the economic burden of MDD in adults rose by 37.9%, from \$236.6 billion to \$326.2 billion (2020 figures). All components of this economic

burden increased, including direct costs, costs associated with suicide, and workplace costs, with the largest rise seen in workplace-related costs, primarily due to absenteeism (73.2%).^[4] Both pharmacological and non-pharmacological treatment models for depression have been established. Antidepressants are effective, but as many as third to half of treated patients do not respond to initial antidepressant treatments or have only a partial response.^[5] Non-pharmacological strategies are acceptable as a first-line of defense for mild forms of depression. If monotherapy fails, further treatment options include increasing the dose, switching to a different antidepressant within the same or another class, augmenting the antidepressant with psychotherapy or a non-antidepressant medication (such as lithium or antipsychotics), or combining two antidepressants.^[6] Patients who do not respond to a combination of two antidepressants after a prolonged period are considered to have treatment-resistant depression (TRD). Patients

typically experience the first effects of antidepressants after at least four weeks of treatment.^[7]

1. INNOVATIVE PHARMACOLOGICAL THERAPEUTIC MODALITIES IN THE TREATMENT OF DEPRESSION

1.1. N-methyl-D-aspartate receptor (NMDAR) antagonists

Proper function of glutamate, brains most common excitatory neurotransmitter, is disturbed in areas of the brain associated with emotion regulation. Levels of glutamate are elevated due to prolonged exposure to stress. This glutamatergic increase can cause synapse disruption and result in a deficit of gamma amino butyric acid (GABA), brains most common inhibitory neurotransmitter. Balance between Glutamate and/or GABA in different brain areas is considered to be one of the last common etiopathogenesis pathways to depressive disorders, therefore it can be used as a base for innovative antidepressant drugs.^[8]

1.1.2. Ketamine

Ketamine, historically known primarily as an anesthetic, is a non-competitive antagonist of N-Methyl-D aspartate receptors (NMDAR). It is also a derivative of phencyclidine, it contains two enantiomers R-ketamine and S-ketamine. Ketamine increases the release of brain derived neurotrophic factor (BDNF), key agent involved in neural plasticity. It has been clinically proved that ketamine generates stronger, faster and more effective antidepressant effects in comparison to commonly used antidepressant drugs. Commonly used antidepressants can take effect after up to 6 weeks after administration, whereas in addition, a third of treated patients doesn't even show signs of improvement. Clinical experimentations of depressive disorders concluded that ketamine can be administered intravenously, intramuscularly and intranasally.^[9] Potential action mechanisms of ketamine are: antagonization of NMDAR (mechanisms mediated by NMDAR inhibition); inhibition of NMDAR of GABA-ergic interneurons and the role of ketamine metabolites (2R,6R)-HNK. Antagonization of NMDAR (mechanisms mediated by NMDAR inhibition) comprise of two sub theories of ketamine's mechanisms of action: extra synaptic inhibition of NMDAR and spontaneous activation blockage of NMDAR.^[10] Meta-analysis evaluated efficacy of ketamine in therapy resistant depression (TRD). Ketamine infusion showed effectiveness in mitigation of depressive symptoms in TRD. In seven placebo randomized control studies (RCTs), depression scores were significantly lower, 24 hours after ketamine administration in comparison to placebo. In addition there was also an antidepressant reduction effect 7 days after the initial treatment.^[11] Similar effect was found analyzing intranasal ketamine for TRD.

Treatment was implemented 2x a week. One randomized, double-blind, active control study (TRANSFORM-2) throughout 28 days, showed that

esketamine alleviate symptoms of depression when administered with common antidepressants in comparison with placebo.^[12,13] If the treatment continues until 6 months, relapse can be lowered for 51% of patients with remission only if they are still on their prescribed antidepressant medication.^[14,15]

1.1.3 Esketamine (ESK)

Action mechanism of ESK, active enantiomer of ketamine, differs from traditional antidepressants, which aim mono-amine-neurotransmitters such as serotonin, norepinephrine and dopamine. ESK modulates glutamatergic system as an NMDAR antagonist which is a glutamate subtype receptor. Antidepressant effects of ESK are comprehensively studied in various clinical trials estimating its efficacy and safety in the treatment of therapy resistant depression (TRD) and in patients with major depressive disorder (MDD). Key trials include ASPIRE I and II, which have shown significant and faster alleviation of depressive symptoms when ESK is added and applied as a nose spray with current antidepressant therapy regime in patients with TRD.^[16] TRANSFORM I and II, trials which have concluded that a prolonged antidepressant response is sustained as a result of continuous ESK therapy throughout an extensive period of time.^[17] Trials such as SUSTAIN-1 and SUSTAIN-2 upheld approval for nasal ESK administration in the treatment of MDD showing remarkable alleviation of depressive symptoms.^[18] HARMONY-1 trial accentuated ESK potential role in management of acute suicidal ideas or intentions specifically in patients suffering from TRD which have already tried committing suicide or had suicidal ideas.^[19]

1.1.4 Esmethadone

Esmethadone, commonly known as dextromethadone or d-methadone is an opioid non-active isomer of racemic methadone which binds to NMDAR with low affinity. Potential antidepressant effect of methadone could be explained through elevation of BDNF in plasma or changes in synaptic plasticity through NMDAR complex. These findings suggest that esmethadone leads to faster antidepressant effects facilitated by mTORC1 pathway in the medial prefrontal cortex (mPFC).^[20,21] Esmethadone shows affinity to the monoamine receptors. In a placebo controlled, double-blind study in patients with MDD that didn't respond to the primary antidepressant monotherapy or dual therapy, there was a significant alleviation of depressive symptoms after 4 days and 7 days since administering daily oral esmethadone.

Effect lasted a week after its last dosage. It has been reported that esmethadone doesn't have: clinically significant opioid effects, there isn't a significant possibility of human misuse and also it has been shown that there is a small chance of esmethadone's depressive effect on the respiratory center.^[22]

1.1.5 Dextrometorphan

Dextrometorphan exhibits effects through NMDAR inhibition and monoamine stimulation of serotonin and noradrenaline. Dextrometorphan administration has been approved by the FDA in a combination with bupropion. They blend their various antidepressant action mechanisms in one serving as a novel remedy. In their respective combination they increase the availability of noradrenaline inhibiting its reuptake and acting as a nicotinic acetylcholine receptor (nACh) antagonist. Bupropion increases availability of dopamine blocking its reuptake, while as dextrometorphan increases glutamate and serotonin concentration acting as a NMDAR antagonist.^[23] Phase 2 trials showed superior remission rates in TRD patients treated with dextrometorphan and bupropion combination after 6 weeks of tracking in comparison with bupropion as a monotherapy option.^[24] In a grand phase 3 trial, GEMINI study, dextrometorphan and bupropion combination, administered twice a day resulted in a significant lowering of MADRS scores after 1 week and maintaining these scores even 6 weeks longer in comparison with placebo.^[25,26]

1.2. GABA modulators (GASPAMA)

GABA modulators act as antidepressants modeling selective allosteric positive gamma-amino-butyric acid receptor A (GASPAMA). There are suggested evidence that, neurotransmission of GABA system on extra synaptic localizations, such as cortical and subcortical neuroaxis play a central role in pathogenesis of depressive disorders. This is especially observed in postpartum depressive disorder (PPD) and premenstrual dysphoric disorder (PMDD). In for mentioned disorders there is a drastic reduction of hormone progesterone and neuroactive steroid allopregnanolone. The result is a sudden drastic interruption disinhibition effect of extra synaptic GABA A receptors localized on projections of main glutamatergic neuron in the PFC and the hippocampal region. Dysfunction of these projections result in mood changes leading to depressive or anxious mental states. GASPAMA binds to allopregnanolone neuroactive sites of extra synaptic GABA-A receptors so they could positively modulate and open chloride ion channels.

The outcome is membrane hyper conductivity of GABA A receptors which results in inhibition of glutamatergic neurons. Ultimately inhibition of glutamatergic neurons will lower the possibility of generating successful action potentials (AP). GASPAMA antidepressant therapy will increase GABAergic activity in neurotransmission, neurogenesis and synaptic conductivity cortical and subcortical areas.^[27-31]

1.2.1 Brexenalone

GABA is the main inhibitory neurotransmitter in the central nervous system (CNS). Positive modulation of GASPAMA results in an inhibitory effect on neurotransmission. It is believed that this modulation is

the therapeutic essence of brexenalone. Brexenalone is a neurosteroid, that simulates alloprenanolone. Recently approved by the FDA in 2019 for therapeutic use in PPD through intravenous infusion during a period of 60 hours under medical supervision.^[30-33] One conducted randomized, double-blind, placebo controlled phase 2 trial and one phase 3 trial showed promising results in treating PPD with brexenalone. Clinical examinations showed severe decrease of HAM-D depression scores, faster onset and sustainable results, after 60 hours of treatment with brexenalone in comparison to placebo.^[34,35]

1.2.2 Zuranalone

Zuranalone has been developed as an improvement of brexenalone with high oral bioavailability and biological half-life adequate for daily administration.^[30,31] In august 2023. FDA approved Zurzuvae in treatment of PPD.^[36] Its usage has been recorded in the treatment of parkinsonism, insomnia and bipolar disorder.^[37-40] Zuranalone acts synergistically with benzodiazepines in a non-competitive way and at the same time lowers necessary benzodiazepine dosage simultaneously reducing side-effect risks.^[41] Results from various studies indicate that zuranalone improved HAM-D depression scores and alleviated symptoms of depression in women with PPD in comparison with placebo. These effects were noticeable at the 3rd day mark of treatment and were sustained up until the 45th day.^[42] In a double-blinded study involving 543 patients with MDD, zuranalone (50 mg daily dosage) generated drastical alleviation of depressive symptoms with effects noticeable up until the 33rd day of treatment.^[43] Results of an open study, phase 2 in treating patients with bipolar disorder with daily 30mg of zuranalone during 2 weeks showed promising results manifesting through mood and anxiousness improvement and overall functioning.^[44]

1.2.3 Ganaxalone

Ganaxalone is an alloprenanolone analogue with similar bioeffects that can be administered orally even in outpatients conditions. Alloprenanolone is a neuroactive steroid metabolite of progesterone and a positive modulator of extra synaptic GABA-A inhibitory receptors acting 10x times stronger than benzodiazepines. Ganaxalone has not yet been examined in detail as a potent antidepressant on a larger population sample, which only leaves a future task for researchers. During a medical trial which examined ganaxalone as an effective antidepressant therapy option for women with MDD in postmenopausal showed that during the 8 weeks of administration, MADRS, IDS-SR, CGI-S and other depression scores were improved. 2 weeks after lowering the dosage depression scores were maintained.^[45]

1.3 Psychedelics

Action mechanism of classical psychedelics is in their agonistic effect on subtype serotonin 2A receptor.^[46] As an antidepressant, their influence is exposed through increase of neuroplasticity and brain entropy which leads

to a certain form of relaxation.^[47] Current research suggest that psychedelics as antidepressants show promising preliminary results, further research is needed, especially phase 2 and 3 grand trials.^[48]

1.3.1 Ayahuasca

Ayahuasca, contains psychedelic tryptamine, N,N-dimethyltryptamine (DMT) and monoaminoxidase inhibitors (MAOI). On a molecular level, pre-clinical and clinical evidence suggest a complex pharmacological profile that ayahuasca as a drink represent. It includes modulation of serotonergic, glutamatergic, dopaminergic and endocannabinoid systems. Ayahuasca as a complex compound interacts with vesicular monoamine transporter (VMAT), trace amino acid receptor 1 (TAAR1) and sigma-1 receptor. Furthermore ayahuasca components positively modulate neurotrophic and inflammatory factors which results in neuroprotective and neuroplastic effects. Evidence from open, randomized, placebo-controlled clinical studies display promising results that indicate fast and significant antidepressant effects that manifest even after the 1st day of intervention with ayahuasca.^[49,50] One small, randomized trial compared one dosage of lyophilized ayahuasca drink (1,1mg/kg) with placebo.

There were proven statistical differences in alleviating depressive symptoms which were evident after 7 days in favor of ayahuasca in comparison to placebo.^[51] Open, uncontrolled study involved patients with recurrent depression received an oral dosage of ayahuasca (2,2ml/kg) and were assessed with MADRS; HAM-D and other depression scales on the 1st, 7th, 14th and 21st day after the treatment. Results indicated there was a significant improvement on depression scores.^[52]

1.3.2 Psilocybin

Psilocybin is a prototype of classic psychedelics. It produces perceptive distortions and mind altering states, agonistically aiming the serotonin subtype receptor 2A. Considerations are that fast induced neuroplasticity changes and immediate „psychedelic trips“ contribute to fast antidepressant effects noticeable after just one or two dosages of psilocybin.^[53] Psilocybin increases: positive self-reflection attitude, better social behavior, empathy and decreases perception of negative emotions.^[54,55] In a randomized controlled trial, patients with MDD which were not on any antidepressant medications, received two oral dosages of psilocybin throughout 4 weeks. Effect on alleviating depressive symptoms was significant and were noticeable even after the 1st of administration.^[56] During an open clinical trial, patients with TRD were scored with several depression scales throughout 6 months. Analysis showed improvement of depression scores and the general idea was that psilocybin was more effective in patients with primary MDD rather than secondary MDD.^[57,58]

2. INNOVATIVE NON- PHARMACOLOGICAL THERAPEUTIC MODALITIES IN THE TREATMENT OF DEPRESSION

2.1 Deep brain stimulation (DBS)

DBS represents a neurosurgically implanted electrode which delivers continuous electrical stimulation to specific neuroanatomical brain structures resulting in short-term and long-term therapy effects for different neuropsychiatric disorders.^[59] Common neuroanatomical areas aimed for DBS are: subcallosal cingulate gyrus (SCG), ventral capsule/ventral striatum (VC/VS), anterior limb of internal capsule (ALIC), nucleus accumbens (NAc) and many more.

DBS possesses several advantages in relation to other forms of interventional procedures because of its reversible and adjustable nature ensuing an optimal therapeutic effect.^[60] Key aspect in treating depression disorders with DBS is modulation and individualization of impulse conduction.^[61] In a study that followed long – term outcomes of DBS of SCG throughout 8 years showed that ¾ of patients met the response criteria for more than half of the study duration. Response and remission rates were maintained at >50% and > 30%, respectively, through years 2. to 8. during follow ups. The majority of participants experienced a robust and durable antidepressant response to DBS of SCG (94.). DBS of lateral habenule (LHb) was conducted in 6 patients with bipolar depression and in 1 with unipolar depression. 3 patients responded to the treatment, while 1 did not.^[62] In a study conducted by Millet et al., patients were implanted with electrodes in NAc and caudate nucleus. There were no patient responses after the first 4 months of NAc stimulation or after the second 4 month stimulation of caudate nucleus. However, during the last 6 months of NAc stimulation, stimulation parameters were adjusted and there was signs of response and remission rates of 75% and 25% respectively.^[63,64] Dual target DBS case study of VC/VS and SCG by combining stimulations, reported remission up to 75 weeks after the initial postoperative control.^[63] Results from studies involving DBS of various neuroanatomical areas demonstrate at least 50% response rate which opens the gate for further detailed examinations.

2.2 Transcranial magnetic stimulation (TMS)

TMS is a novel antidepressant treatment based on application of short magnetic pulses to the brain which results in cortical stimulation. It is a non-invasive technique that does not require craniotomy or seizure induction to stimulate neurons. Repetitive transcranial magnetic stimulation (rTMS) consists of delivering pulses in a repetitive sequence. Action mechanism of TMS is based on synergy of electrical and magnetic energy in order to induce electromagnetic phenomena. An electromagnetic coil is placed on the scalp and an effective pulsating magnetic field is created that depolarizes cortical neurons for a short time and causes changes in neural neurophysiology.^[65,66] The newest modality of rTMS is theta burst stimulation (TBS), in

which relatively larger amounts of stimulation can be delivered to the brain in a shorter time interval.^[67] Neural excitability stimulation can be regulated either by high (10-20 Hz) or low (1Hz) frequency, on which basis TMS modalities are separated.^[68]

High-frequency rTMS is considered to stimulate the activity of the cerebral cortex, while low-frequency rTMS has a predominantly inhibitory effect. High-frequency stimulation of the left dorsolateral prefrontal cortex (DLPFC) alleviates symptoms of depression. Low-frequency cortical stimulation of the right DLPFC helps to relieve symptoms of both depression and anxiety.^[69,70] In a study researching efficacy of bilateral rTMS in the PFC, patients who were subjected to stimulation of left DLPFC showed lower levels of cortisol in their saliva. Results from this study were limited due to small sample size and restricted number of TMS session.^[66] In a trial conducted by Chen et al. it was disclosed that high-frequency and low-frequency rTMS applied to the left and right DLPFC were equally effective.^[71] Additional potential mechanisms of action of rTMS demonstrated through several studies are based on the correlation between cerebral metabolic activity and increased blood flow through the PFC. It is considered that rTMS increases antidepressant bioavailability, increases monoamine release and circulation which leads to neuroplastic changes. Pilot study involving 15 drug-resistant patients demonstrated an increase in cerebral blood flow volume during TMS. Blood flow was measured at the beginning and end of each TMS session. Frontal hemoglobin (fHbC) concentration was found to be associated with treatment outcomes, with increased fHbC during magnetic induction being inversely related to MASDR scores. This study was limited by its small sample size and because cerebral blood flow was not measured during TMS treatment.^[72] Dunner et al examined the long-term effects of rTMS after one year of first treatments. 62.5% patients who achieved remission at the end of the acute treatment remained in remission one year after the start of rTMS. However, 36.2% of these patients received repeated sessions of rTMS within a month of completing the acute treatment. Therefore, although the rTMS response appears to have been sustained in most patients, it must be noted that these patients continued to receive antidepressants and to maintain rTMS sessions as needed.^[73]

2.3 Vagus nerve stimulation (VNS)

VNS is an invasive form of neuromodulation which bases on pulse generator implantation within the chest cavity and leading wires to the electrode wrapped up around the left cervical bundle of vagus nerve. This technique was approved by the FDA in treatment of depression, epilepsy and obesity.^[74] Vagus nerve projects on the solitary nucleus and locus coeruleus, key areas of serotonergic and noradrenergic activity, and it's believed that these areas have major roles in the pathophysiology of depressive disorders.^[75] Several

studies showed that there is an increase of 5-Hydroxyindoleacetic acid (5-HIAA), foremost serotonin metabolite, in the cerebrospinal fluid after VNS treatment. Later studies revealed serotonin and noradrenaline enhancement after prolonged VNS treatment.^[76] Effects of the VNS was proved to be in correlation with global neurotransmitter regulation (i.e. Noradrenaline) and increased gene expression for synthesis of BDNF and basic fibroblast growth factor (bFGF).^[77] 5 year study compared and measured patients who experienced MDD (unipolar or bipolar) lasting at least two or three years with those who had failed four or more depression treatments (including electroconvulsive therapy). The VNS group in this study had better clinical outcomes than the usual therapy group, as evidenced by a significantly higher five-year cumulative response rate and a significantly higher remission rate.^[78] Aaronson et al. studied parameters of VNS stimulation as well as comparing which frequency and amplitude gives the best results. The study showed that all three groups had a significant improvement in depressive symptoms at the end of the acute phase. Improvements were more sustained in the medium- and high-dose groups at the end of the longer-term phase (50 weeks). The study findings provided an interesting conclusion that even the low-dose group had significant antidepressant effects.^[79] In a recent study, effects of VNS were explored on hippocampal volumes in patients with TRD. There was registered increase in the volume of the left and right hippocampus, which was also followed by clinical responses. These findings indicate a role for hippocampal volume as a marker of VNS response in TRD and further support the proposed mechanisms of VNS.^[80] Transcutaneous vagus nerve stimulator (tVNS), a new, non-invasive, portable form of VNS is self-administered. It stimulates the auricular branch of the vagus nerve that takes part in innervation of the human ear.^[81] Cutaneous vagus nerve stimulation of the branches in the ear leads to afferent stimulation of the brain stem (tractus nucleus solitarius) and further to higher regions of the brain through neurons of the second (thalamus) and third order (to the primary sensory cortex) within the brain.^[82] tVNS is only applied on the left ear so that bradycardia is avoided.^[83] It is believed that tVNS affects multiple physiological functions, such as: reduction fire of AP in the central nucleus of the amygdala, suppression of epileptiform activity, changes in resting EEG, increased intracortical inhibition, enhancement of maladaptive neuronal plasticity, changes in neuropeptides, and modeling of serotonergic and noradrenergic pathways associated with potential anxiolytic and antidepressant effects.^[82]

2.4 Transcranial direct current stimulation (tDCS)

tDCS is a non-invasive method which bases on applying direct current in strength from 1 mA to 2mA via electrodes directly to the scalp in order to stimulate and induce changes in cortical excitability. Anode stimulation creates depolarization of neuronal membranes and induces faster triggering of AP in

neurons whereas cathode stimulation leads to neuronal hyperpolarization and inhibition.^[84] There has been reported several favorable effects of tCDS in treating neuropsychiatric disorders (i.e. depression & schizophrenia) and in rehabilitation of cognitive, motoric and sensory functions after a stroke.^[85] Grand study consisting of 120 patients with unipolar depression, divided in three groups compared only tCDS treatment with antidepressants (sertraline group only) and with combined tCDS + sertraline group. Results showed improvement of MADRS results for the group of patients who received combined tCDS + sertraline treatment in comparison to other groups.^[86]

2.5 Transcranial photobiomodulation (tPBM)

tPBM is a promising, novel therapeutic modality which relies on outer light source, especially in near range infra-red lighting (NIR) and red lighting for biological and therapeutical effects.^[87] Proposed action mechanism of tPBM is supposed to be based on improving mitochondrial metabolism after NIR energy absorption by cytochrome C oxidase.^[88] Laser of low levels (LLL) or light emitting diodes (LED) could be used as a light source.^[89] Study from 2022. tested the efficacy of LLL and low dosage tPBM with limited number of sessions (2x a week during 6 weeks) in patients with MDD in comparison with placebo (false group). Study outcomes were quantified by HAM-D and QIDS scores. Based on the results there was no statistical differences between the two examined groups.^[90] Results from other studies suggest that tPBM is a safe and potentially effective treatment however different stimulation parameters complicate final conclusions.^[91] Future studies should clarify ideal stimulation parameters, effectiveness and safety profile of this treatment.

CONCLUSION

Selection of antidepressants should be based on four reasons: finding a balance between efficacy and tolerability, matching the drug to the type of depression and its characteristics, safety (risk of overdose, interactions with other drugs or medical disorders) and the fourth reason, patient preference. Some groups need special consideration, such as elderly patients and women during pregnancy and breastfeeding. There is a need for the development, testing and better understanding of new drugs or treatment methods, ideally with a rapid onset of action, better tolerability and with the potential for greater efficacy compared to existing antidepressants in patients for whom current antidepressant therapy is unsuccessful. Recent pharmacological treatments focus on the induction of new pharmacokinetic and pharmacodynamic pathways. New strategies in the treatment of depressive disorders also include knowledge and recognition the form of depression as well as the selection of an adequate drug or modality of treatment according to the patient's preferences and the given moment in the evolution of the disease. Non-pharmacological novelties are developed as a result of resistant forms of depression, they depend on

the latest technologies and represent a significant difference compared to current non-pharmacological forms of depression treatment. The effectiveness of new non-pharmacological modalities in depression treatment are reflected in: higher rates of response, higher rates of remission as well as less serious side effects, thus expanding the therapeutic range for the treatment of various depressive disorders. Affordability, availability and cost of the procedures, as well as the general stigma in seeking help for treatment of depressive disorders, make it difficult to include these measures in the next stages of research. We expect that the integration of these modalities into treatment of depression will continue to develop, which could ultimately lead to more personalized and effective treatment for patients.

Conflict of Interest: The authors declare no conflicts of interest.

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