Novel Approaches to Depression Treatment: Integrating Pharmacological and Non-Pharmacological Strategies

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Abstract- ***Major depressive illness (MDD) is a persistent and incapacitating Psychological disorder affecting more than 280 million people worldwide. Depression is approximately 50% more frequent compared to men in women. Approximately 10% of women worldwide suffer from antenatal and postnatal depression. More than 700,000 people commit suicide annually. When it comes to causes of death, suicide ranks fourth among those between the ages of 15 and 29. Depression is characterized as an ongoing feeling of melancholy, despair, and a loss of interest in life, which affects one's thoughts, emotions, and general well-being. Antidepressants based on monoamines were initially developed for severe depression. However, due to delayed therapeutic effectiveness and one-third of patients showing partial response to single-drug therapy, alternative methods must be explored. Recent advancements include complementary medications and nonpharmacological treatments. This overview traces the historical development of antidepressants from their inception to modern advancements. Today's pharmacological techniques include targeting receptors like ketamine and GABA and addressing biological processes such as the HPA axis and gut microbiota. Novel non-pharmacological approaches like psilocybin therapy, CBT, ECT, TMS, and lifestyle interventions offer diverse treatment options for depression.***

Indexed Terms- ***Antidepressant , Major Depressive Disorder, Non-Pharmacological Therapy, Pharmaceutical technique***

I. INTRODUCTION

Depression is a neuropsychiatric illness defined by chronicity, recurring episodes, and severe impairment in everyday functioning. It may be a crippling mental disease that affects all parts of a person's life, including their emotions, thoughts, behavior, and physical health. The symptoms must be severe enough to interfere with daily functioning and persist for at least two weeks to qualify as depression. By 2030, depression disorders are expected to overtake all other causes of impairment worldwide, ranking as the second most common cause of disability internationally, according to the World Health Organization.(1) About 15% of people suffer from depression each year, and one in six people will experience depression at some point in their lives. According to research from Our World in Data, 3.4% of people worldwide suffer from depression, with a 2%–6% range of error. That translates to over 264 million people worldwide in 2024. (2) The likelihood of experiencing depression is approximately 50% higher in women compared to men. The depressive disorder affects around 10% of pregnant and postpartum women globally. This distinction has been due to variations in men's and women's psyche, hormone fluctuations, the consequences of parenting, and the behavioral paradigm of learned helplessness. Suicide claims the lives of almost seven million people every year, making it the fourth most common cause of death for persons between the ages of Fifteen and twenty-eight. Prolonged depressive illnesses severely impair an individual's functioning in a variety of domains, including the workplace and academia, and the possibility of suicide arises from extreme depression. Depression encompasses major depressive disorder, characterized by persistent low mood, diminished interest, and reduced energy, as well as dysthymia, a chronic form of moderate depression. Manic episodes, ranging from severe to mild, vary in frequency and intensity, impacting an individual's functionality.A number of trend exist for depressive episodes, such as: Single-episode depressive disorder denotes the initial and sole occurrence of depression. Recurrent depressive

disorder signifies multiple depressive episodes. Bipolar disorder entails alternating depressive and manic episodes, characterized by various symptoms including euphoria and increased activity. (3) Rather than having only one depressive episode throughout their lives, 10.3% of MDD patients experience recurring episodes.

Differentiating between major depressive episodes (MDE), which include bipolar disease, and major depressive disorder (MDD) is crucial. Bipolar disease is a common cause of MDE (16.6%) prevalence rates, which are greater than MDD (14.4%) represented in figure 1 (4). Individuals with MDD frequently have comorbid conditions such as obsessive-compulsive disorder, disorder of panic, addiction to substances, and social anxiety disorder. People with MDD who also have certain comorbid conditions are more likely to commit suicide. Elderly individuals contending with concurrent medical conditions are at an increased likelihood of experiencing depression. There are several theories as to the complex genesis of major depressive illness, including biological, genetic, environmental, and psychological variables. The central nervous system is linked to dysregulation of neurotransmitters such as glutamate, norepinephrine, dopamine, serotonin, and brain-derived neurotrophic factor (BDNF) (5). Antidepressants, targeting these neurotransmitter systems, are commonly used therapeutically. Suicidal ideation may stem from serotonin imbalances and more complex neuroregulatory mechanisms affecting neurotransmitter function. While many pharmacological and nonpharmacological treatments are available for Major Depressive Disorder (MDD), approximately 10–30% (6,7) of those suffering from MDD meet the prerequisites for treatment-resistant depression (TRD), also referred to as difficult-to-treat depression, because they do not respond to the first two pharmacological treatments tested. (8,9) In the 1960s, the initial antidepressant medications emerged in accordance with the monoamine deficit hypothesis, which suggests that major depressive disorder stems from a deficiency in monoamine neurotransmitters.

According to the monoamine hypothesis, those who are depressed have low serotonin, norepinephrine, and dopamine levels. Based on this idea, many antidepressant drugs have been created that boost monoamine levels in the synaptic cleft by inhibiting their breakdown or blocking their reuptake. This prompted the creation of the first class of antidepressants, which included tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Following the discovery of serotonin's involvement in major depressive disorder (MDD), two new first-line therapies for the disorder were developed: selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Traditional antidepressants are effective, but they have some noteworthy adverse effects and a delayed beginning of action. Remarkably, almost one-third of patients show resistance to conventional antidepressant treatment (10).

Utilizing complementary therapies and investigating novel biological targets aim to enhance depression treatment, offering tailored pharmacological strategies and innovative approaches for managing Major Depressive Disorder effectively.

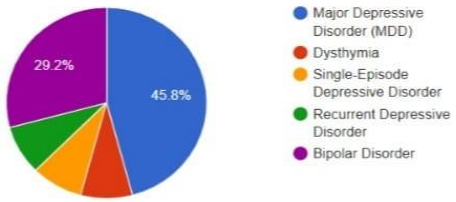

Figure 1: Types and trends of depressive episodes

II. PHARMACOLOGICAL ANTIDEPRESSANT

This section reviews the current antidepressants accessible to patients. They are presented chronologically, beginning with their development However, these antidepressants are Despite being crucial tools for treating MDD patients, their use has significant limitations: side effects, risks associated with administration, a delayed start to antidepressant therapy, or insufficient effectiveness. As a result, we concentrate primarily on the effectiveness and potential of these drugs in this section. Off-label uses and restrictions in MDD treatment.

2.1 Monoamine Oxidase Inhibitors

MAO inhibition was discovered to have antidepressant effects when treating tuberculosis patients with iproniazide (11). Scientists hypothesized that a lack of catecholamines, including norepinephrine, dopamine, and possibly serotonin, could lead to depression. The relationships among MAOI inhibition and improved mood in patients with depression provided evidence in favor of this theory. The class of enzymes known as MAOs is responsible for the metabolism and subsequent inactivation of monoamine and indolamine neurotransmitters, including tyramine, dopamine, epinephrine, norepinephrine, and serotonin (12). The intestines, liver, brain system, platelets, and mitochondrial membranes are all home to MAO. Two subtypes exist for it: MAOA and MAOB. It is believed that the most direct correlation between the antidepressant effects of MAOIs and inhibition of MAOA, which catabolizes serotonin, norepinephrine, and tyramine, exists.(13). Antidepressants, such as MAOIs, were originally considered to work directly on nerve terminals by increasing neurotransmitter amine levels. However, such increases occur within days after starting medication, whereas the therapeutic benefits do not appear for weeks. More recent ideas have centered on receptor-mediated pre- and post-synaptic processes(14,15). Phenelzine, isocarboxazid, and tranylcypromine are MAOIs that irreversibly decrease MAO activity.

2.2 Tricyclic Antidepressant

TCAs, like MAOIs, target the breakdown of monoamine neurotransmitters. By inhibiting reuptake transporters, The norepinephrine transporter (NET) and 5-HT presynaptic receptors become less sensitive to TCAs, leading to an accumulation of NET and 5-HT in the presynaptic cleft. The contents of 5-hydroxytryptamine (5-HT) and norepinephrine transporter (NET) in the synaptic cleft rise in the absence of protein transport and postsynaptic breakdown, which is thought to improve mood and lessen symptoms of MDD.

However, tricyclic antidepressants (TCAs) exhibit numerous adverse effects due to their as competitive antagonists at adrenergic receptors on the postsynaptic membrane, muscarinic, and histamine receptors (16). The three TCAs that were initially developed were doxepin (DXP), imipramine, and clomipramine (17,18). Despite having a similar mode of action, each of these drugs has advantages depending on the signs that the patient is experiencing.

Regrettably, TCAs may have severe adverse effects. antagonistic interactions between muscarinic, adrenergic, and postsynaptic histamine receptors resulted in varying degrees of deleterious consequences, including sleepiness, pregnancy difficulties, and cardiac anomalies such as irregular arrhythmias and myocardial infarctions, and cardiac conduction (19). Convulsions, an accelerated heart rate, and cyanosis were among the withdrawal symptoms that appeared 24 hours after the foetus was exposed to CLO. TCAs are no longer the first line of antidepressant therapy due to the availability of more potent treatments like SSRIs or SNRIs (20).TCAs have been examined for recurring migraines, insomnia, alcohol dependence, and neuropathic ocular pain, with encouraging outcomes, although side effects remain a problem.

2.3 Selective serotonin reuptake inhibitors

In the 1960s, scientists discovered that serotonin may play a part in major depressive disorder (MDD). Selective serotonin reuptake inhibitors (SSRIs) were developed as a result of a suggested therapy approach that included blocking serotonin reuptake to increase postsynaptic serotonin receptor activation. The first SSRI to receive FDA approval was fluoxetine, and numerous others with less adverse effects came after. SSRIs raise serotonin levels in the synaptic cleft, but their effects take time to become effective—typically two to three weeks (21). Research on the mechanism of action of antidepressants extends beyond the synapse's increased serotonin levels to include the facilitation of hippocampal neurogenesis. (22). Because of their well-tolerated side effects and all-around effectiveness, SSRIs are the first choice for treating depression in patients of all ages. However, a number of adverse effects were documented by patients, such as gastrointestinal discomfort, obesity, gynecomastia, headaches, anxiety, nausea, diarrhea, and sleeplessness (23). The study investigates SSRIs' mechanisms like mTOR phosphorylation, inflammatory pathway modulation, and enhanced

receptor expression to improve antidepressant therapy effectiveness.

2.4 Serotonin and norepinephrine reuptake inhibitors

The subsequent "atypical" antidepressant, venlafaxine was launched in the U.S. market in 1993, with a pharmacological focus on inhibiting the serotonin and norepinephrine transporters.(24) Serotonin and norepinephrine are two important neurotransmitters linked to depression whose reuptake is inhibited by SNRIs. The primary mechanism of action involves inhibiting presynaptic neuronal reuptake of 5-HT (serotonin) and norepinephrine after their release into the synaptic cleft. The duration of these monoamines in the central nervous system's synaptic cleft is prolonged when reuptake is inhibited. Therefore, postsynaptic receptor activation increases, as does postsynaptic neuronal transmission. Venlafaxine (1994), Milnacipran (1996), Duloxetine (2004), Desvenlafaxine (2008), and Levomilnacipran (2013) are the five major SNRIs currently authorized by the Food and Drug Administration (FDA) for use in the United States.(25) Venlafaxine inhibits dopamine reuptake while also decreasing serotonin and norepinephrine reuptake. (26) Levomilnacipran differs from other SNRIs in that it inhibits norepinephrine reuptake twice as effectively as serotonin .Neuropathic pain may be alleviated by the SNRI duloxetine. Duloxetine reduces chemotherapy-induced nerve pain by suppressing p53, p38 phosphorylation, and NF-κB activation. SNRIs' efficacy in treating neuropathic pain and depression needs exploration.

III. NEW PHARMACOLOGICAL TECHNIQUES

Recent pharmacological advancements introduce novel antidepressant techniques targeting receptors like ketamine, GABA, opioid, NMDA, and peroxisome proliferator-activated receptors, offering alternative pathways beyond traditional treatments. New antidepressants explore effects on the HPA axis and gut microbiota, aiming for targeted, effective depression treatments with minimized side effects.

a. Antidepressants that target receptors

3.1.1 Ketamine and Esketamine for the Treatment of Depression

For more than 50 years, noncompetitive NMDAR antagonists such as ketamine (R, S) and its S-enantiomer, intranasal esketamine, have been utilized as clinical anesthetics. (69) Given ketamine's rapid onset of action compared to traditional antidepressants Its identification for the treatment of MDD and TRD has been celebrated as a paradigm-shifting advancement. has been acclaimed as a groundbreaking advancement. Two primary theoretical frameworks have been proposed to account for the ketamine/esketamine antidepressant effects. In the initial model, ketamine inhibits presynaptic NMDARs on inhibitory neurons, thereby enhancing presynaptic glutamate release in the medial prefrontal cortex (mPFC). In the second model, postsynaptic NMDAR on excitatory neurons in the Schaffer-collateral route is inhibited by ketamine, which enhances synaptic efficacy in the hippocampus. It is crucial to acknowledge ketamine's function as a use-dependent NMDAR antagonist, also referred to as an open-channel blocker.in order to understand these two models. An inactivated NMDAR's ion channel pore usually contains Mg^{2+} ions, which keep ketamine from entering (70). There are two processes required in order to break down the Mg^{2+} barrier and activate NMDAR. The ligand-binding process is the initial step that opens the channel pathway. The alternative mechanism entails an augmentation in cation influx, which causes ionic repulsion to force the Mg^{2+} ions outside of the pore. An influx of cations may be induced by the activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) or other cation-permeable ion channels. (70, 71). Preclinical research has demonstrated that the swift antidepressant effect of ketamine is attenuated when an antagonist is used prior to therapy.

3.1.2 γ-Aminobutyric Acid.

The GABAergic system, encompassing both ionotropic (GABAARs) and metabotropic receptors (GABABRs), modulates neuronal inhibition in the CNS . Benzodiazepines and barbiturates act on ionotropic receptors, offering anxiolytic effects.

Disruptions in GABA regulation are evident in MDD, with reduced GABA neuron production in the orbitofrontal cortex and decreased cortical GABA levels in postnatal depression. SSRIs elevate cortical GABA post-therapy, alongside increased GABA-active steroids. GABAergic treatments like valproate and muscimol show antidepressant potential . GABA's interaction with the 5-HT system and its role in ketamine response underscore its relevance in depression (30,31).

3.1.3 Opioid Receptor

The endogenous opioid system, which includes the non-opioid receptor NOP (nociceptin/orphanin FQ receptor), previously referred to as the opioid receptor-like 1 (ORL-1), and the mu (μ), kappa (κ), and delta (δ) opioid receptors (MORs, KORs, DORs) may be an appropriate target for depression treatment. Numerous research investigations have been published that examine The function of endogenous opioid receptors in depression treatment involves their activation across brain regions rich in these receptors, including the hippocampus, nucleus accumbens, prefrontal cortex, amygdala, thalamus, hypothalamus, claustrum, ventral tegmental area, and dorsal raphe nucleus. Endogenous opioid receptors elicit G protein-independent signaling pathways, such as those mediated by β-arrestins by their interaction with inhibitory heterotrimeric Gαi/o proteins. Buprenorphine acts at delta receptor (DOR) and nociceptin opioid peptide receptor (NOP) and is a partial agonist of ε and κ opioid receptors. Pre-clinical investigations indicate that buprenorphine's antidepressant effects are mediated through delta opioid receptors. In vivo, investigations and Nalmefene (NMF), a potent μ opioid receptor antagonist and partial κ opioid receptor agonist, have been shown through behavioural experiments to possess antidepressant qualities. Tianeptine is a MOR agonist that functions by stimulating different pathways of signaling from morphine. In preclinical studies, a selective blockage of NOP receptors was found to cause an antidepressant-like activity. BTRX-246040 (also known as LY-2940094), a NOP receptor antagonist, has antidepressant effects in animal models. The ε receptor, δ receptor, κ receptor, and NOP receptor have all had their high-resolution (HR) crystal structures solved, providing information about the molecular components necessary for binding to the ligand. (32)

3.1.4 NMDA receptor

Targeting ionotropic glutamate receptors—more especially, NMDA receptors—is one of the innovative ways to treat depression that has been highlighted by recent research.

These receptors are essential for the growth of synapses, synaptic plasticity, and cognitive processes. The pathophysiology of depression is highlighted by the dysregulation of NMDAR subunits, which is demonstrated by increased GluN1 and GluN2C and decreased GluN2A and GluN2B in the locus coeruleus of depressed people. Memantine and nitrous oxide (N2O), two NMDAR antagonists, present intriguing treatment options. Similar to ketamine, N2O increases neuronal firing rates and synaptic plasticity to quickly alleviate depressed symptoms. Memantine has promise as an SSRI/SNRI adjuvant without appreciable side effects, and it is especially beneficial in older individuals. These methods point to a move toward more focused and potent antidepressant therapies, which calls for more clinical research.(33)

3.1.5 Peroxisome Proliferator-activated Receptors

The unique strategy pertaining to peroxisome proliferator-activated receptors (PPARs) and depression centers on their function in neuroprotection, control of inflammation, and management of oxidative stress in different areas of the brain. PPARα, which is particularly important in the hippocampus, affects how depressed people behave and react to antidepressant medications. Pharmacological stimulation or overexpression of PPARα in the hippocampus has effects akin to those of an antidepressant, augmenting neuroplasticity and ameliorating damage caused by prolonged stress. Pioglitazone and rosiglitazone, two PPAR-γ agonists, have promise in preclinical models by lowering neuroinflammation and ameliorating depression symptoms. The combination of statins and conventional antidepressants with PPAR agonists improves treatment results and may be a useful supplementary therapy approach for people with depression who are not responding to treatment(34).

3.2 Antidepressants for Biological Processes

3.2.1 Hypothalamic, Pituitary, and Adrenal Axis

Hypothalamic corticotropin-releasing hormone (CRH), which works in concert with vasopressin, is the main factor responsible for the stimulation of the hypothalamic-pituitary-adrenocortical (HPA) axis. Several neuropeptides serve to increase the production of pituitary pro-opiomelanocortin (POMC)-derived peptides, such as corticotropin (ACTH) and endorphins. They are generated in identical neurons or in different neurons inside the paraventricular nucleus (PVN). While sympathetic innervation of the adrenal gland can influence the adrenal gland's adrenocortical response to ACTH, ACTH is the primary stimulant of adrenal glucocorticoid hormone production, which includes cortisol in humans and testosterone in rats (35). Adrenal secretions are regulated by a number of systems that synchronize them with periods of stress and rest. Most prominent of them is the suprachiasmatic nucleus' diurnal pattern of baseline activity (36). Afferent signals from several brain areas are involved in stress-induced HPA system responses. These include noradrenergic signals from the A1 and A2 cell groups in the brainstem, the pontine locus coeruleus (37), the amygdala (38,39), the cerebral cortex, and the hippocampus (40). In overall, the amygdala primarily supports HPA activity, whereas the septum and hippocampus generally restrict it. The inhibitory feedback imposed by adrenal hormones, which function through corticosteroid receptors found in different parts of the brain, is another component regulating HPA axis activity.

Through negative feedback mechanisms in the pituitary, hypothalamus, and brain structures such the hippocampus, amygdala, and septum, glucocorticoids attenuate the stress response.as shown in figure 2 Two different corticosteroid receptor types—type I, or mineralocorticoid receptor (MR), and type II, or glucocorticoid receptor (GR)—mediate this feedback. While the GR is frequently synthesized throughout the brain, especially in neuronal cells, the MR is mostly expressed either alone or in conjunction with the GR in hippocampal neurons (41).

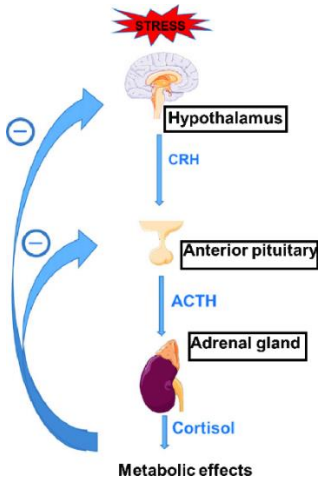

Figure 2: Negative Feed Mechanism Of HPA Axis

3.2.2 Gut microbiota

Recent research underscores the intricate interplay between the gut microbiota and the host's neurological system through the gut-brain axis, a dynamic biochemical network crucial for mood and cognitive function (42). Gut microbes influence this axis via neural, metabolic, hormonal, and immune pathways, producing neurotransmitters like serotonin and GABA, as well as key metabolites and proteins that regulate neuropeptide release and inflammation (43). Dysregulation in this axis, linked to anxiety and mood disorders, involves altered hypothalamic-pituitary-adrenal (HPA) axis function, increased glucocorticoids, and chronic inflammation (44, 45). Moreover, gut dysbiosis can exacerbate inflammation and affect cortisol levels, impacting mental health (42). Increased intestinal permeability due to stress-induced inflammation allows harmful bacteria to translocate, potentially triggering central nervous system inflammation and contributing to mental illnesses (46). Conditions like irritable bowel syndrome highlight the bidirectional relationship between gut health and mental well-being, underscoring the role of the gut microbiota in mood regulation and emotional processing (47). Metabolites from gut microbes directly influence neurotransmitter levels and CNS function, offering novel therapeutic avenues for managing depression (48, 49). Understanding and modulating the gut microbiota could thus provide innovative strategies for treating depression by targeting inflammation and restoring gut-brain axis balance (50).

IV. NOVEL NON-PHARMACOLOGICAL /ALTERNATIVE APPROACHES

Emerging non-pharmacological approaches for depression include psilocybin therapy utilizing psychedelic mushrooms, Cognitive Behavioral Therapy (CBT) for modifying thoughts and behaviors, and Electroconvulsive Therapy (ECT) and Transcranial Magnetic Stimulation (TMS) for brain stimulation. Lifestyle interventions such as exercise, diet adjustments, and mindfulness practices complement these treatments, highlighting a diverse approach to managing depression.

4.1 Psilocybin Therapy for Treatment-resistant Depression

Psilocybin is a naturally occurring substance that has been used medicinally for millennia and is present in several Psilocybe species mushrooms (51, 52). It functions as a serotonin 2A receptor agonist and is a prodrug of psilocin. In animal studies, it produces psychedelic effects that are associated with increased cortical neuronal plasticity, cognitive flexibility, and possible antidepressant benefits (53).

These results are corroborated by clinical neuroimaging investigations that show psilocybin-induced stabilization of hyperactivity in the depression-related medial prefrontal cortex (54). Comprehensive epidemiological study indicates that, in contrast to non-users of psychedelics, psychedelic use is linked to decreased rates of psychological distress and suicidality (55). More evidence of psilocybin's effectiveness in easing anxiety and depressive symptoms comes from recent clinical studies (56). The early nature of current research limits the practical applicability of psilocybin, despite its potential in treating disorders such as anxiety in terminal illness and obsessive-compulsive disorder (57). In order to minimize potential side effects and promote treatment outcomes, adequate psychological support and a supportive atmosphere are essential (58).

4.2 Cognitive Behavior Therapy

Cognitive behavioral therapy (CBT) is a systematic, instructional, and goal-oriented form of psychotherapy. This approach is direct and pragmatic, involving a collaborative effort between therapist and patient to alter maladaptive thought and behavior patterns, thereby promoting positive changes in mood and lifestyle. Treatment protocols are tailored to the patient's specific diagnosis and requirements, addressing various issues (59,60). Most CBT psychotherapists adjust their therapy to each patient's unique requirements. The first step is evaluating the patient and creating a customized conception. This cognitive behavioral therapy (CBT) framework is developed gradually, session by session, and presented to the patient at the right time. Early on in the therapeutic process, the therapeutic plan is created. The problems the patient wants to work through and the treatment objectives are decided upon together in the first or later sessions. Issues that are given priority are dealt with first.The framework of every session remains consistently the same: a quick update and a mood check. To maintain continuity, a bridge from the previous session is presented after this. The outline for the session is developed cooperatively, and the homework assigned to the patient between sessions is examined before to discussing any problems. A thorough discussion of the agenda topics is conducted, followed by analyses and suggestions. Extra homework assignments and a final summary are given before the program ends.

The American Psychological Association (2019) and the National Institute for Health and Care Excellence (2009) both suggest cognitive behavioral therapy (CBT) as the first-line psychological therapy for depression since it has been demonstrated to be effective in treating depression (61). But a lot of people experience relapses or prolonged symptoms.(62) Cognitive therapy with antidepressant medication is a more effective combo than either treatment alone for people with chronic depression.In order to overcome immobility in patients who have stopped engaging in activities that they find enjoyable in broad terms, CBT may initially concentrate on resuming behaviors that are beneficial. (63)

4.3 Electroconvulsive Therapy

When conventional therapies like medicine and psychotherapy fail to alleviate severe depression, patients may be referred for electroconvulsive

therapy (ECT) (64). In contrast to other approaches, ECT frequently shows notable improvement in individuals who were previously resistant (65-67). Its efficacy is vital since traditional therapies often prove ineffective (68,69). Developed more than 50 years ago, electrical stimulation causes widespread seizures in patients with significant depressive disorders and bipolar disorder, among other severe mental diseases. Technological developments like unilateral electrode implantation and anesthetic have made it more tolerable and effective despite possible adverse effects including headaches and muscular soreness (70). Clinical and animal research indicate the effectiveness of ECT in lowering depression symptoms with fewer side effects, as demonstrated by recent studies (64). In order to clarify ECT's mechanisms and offer useful information to patients and physicians contemplating this kind of treatment for depression, this review attempts to compile the most recent clinical and preclinical research on the drug.

4.4 Deep brain stimulation or Transcranial Magnetic Stimulation (TMS)

Advanced neurostimulation techniques, such as deep brain stimulation (DBS) and its derivative, deep transcranial magnetic stimulation (dTMS), are used to target subcortical brain areas either non-invasively or with surgical electrode insertion. DBS uses a subcutaneous pulse generator to provide continuous electrical stimulation while surgically implanting electrodes into predetermined brain areas. DBS can cause problems including infection and lead fractures, although being typically well tolerated (71).

DBS was first licensed for the treatment of movement disorders such as essential tremor and Parkinson's disease, but it is now being used in neuropsychiatric settings. By focusing on the anterior limb of the internal capsule, it has demonstrated effectiveness in treating severe obsessive-compulsive disorder (OCD) (72). Research indicates potential advantages for treating Gilles de la Tourette syndrome and severe addiction that is unresponsive to traditional therapy (73,74). After demonstrating safety and efficacy in people, DBS has showed promise in treating treatment-resistant depression (TRD), prompting more preclinical research. Research on animals has investigated how high-frequency stimulation of brain regions such as the nucleus accumbens (NAc) and ventromedial prefrontal cortex (vmPFC) can replicate the antidepressant effects shown in behavioral tests (75)

Animal optimization studies have improved DBS settings, demonstrating the impact of certain cortical targets, frequencies, and current intensities on treatment results (76). These results highlight the promise of DBS, supported by preclinical molecular insights as well as clinical data, in TRD and other neuropsychiatric diseases.

4.5 lifestyle changes (exercise and diet)

Evidence suggests that the development and severity of severe depression are influenced by a mix of lifestyle and bio-psycho-social variables. Healthy eating, exercise, and relaxation are important factors in the onset, course, and treatment of this illness.

Exercise: It has been demonstrated that engaging in physical activity and exercise causes notable changes in the brain. The hippocampus, amygdala, striatum, and frontal cortex are interrelated regions, and imaging investigations have revealed structural alterations in these areas associated with early-onset depression. A decrease in hippocampus volume has been the most consistently observed observation and has a substantial correlation with depression [222–224]. There is a positive correlation between decreased anxiety and higher hippocampal levels of brain-derived neurotrophic factor (BDNF). As mentioned before, research on imaging has shown that the hippocampus volume is lower in those who suffer from depression [222]. Exercise may also reduce depression symptoms by increasing cerebral neurogenesis, according to Ernst and colleagues [226] and research on antidepressant drugs [225]. They identified vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), serotonin, and beta-endorphins as the four molecular routes for enhanced neurogenesis. Exercise increases hippocampus neurogenesis, which is stimulated by all of these variables. The correlation between physical activity and increased levels of endocannabinoids, which are connected to analgesia, decreased anxiety, and an overwhelming feeling of well-being, is another theory for how exercise elevates mood [227]. Physical activity's mood-enhancing effects are also

thought to be influenced by alterations in the hypothalamic-pituitary-adrenal (HPA) axis, such as elevated adrenocorticotropic hormone (ACTH) and reduced cortisol production [228]. Lastly, exercise helps people with depressive disorders feel better about themselves, which may help them experience less depressed episodes [229].

Food - There is a complicated link between food, adiposity, anxiety, and mental health conditions linked to stress. In general, diets rich in omega-3 poly-unsaturated fats and low in saturated fat are linked to better medical results, a decreased risk of developing adiposity, metabolic syndrome, and mental illnesses brought on by anxiety. This encourages a diet similar to the European diet, which is strong in fruits, nuts, vegetables, and seafood. Particularly in fish oils, there are high concentrations of omega-3 fatty acids, which are known to have positive effects on mental and physical health. A false association may also be caused by other potentially confusing variables, such as improved health practices in those who follow specific diets. For the treatment or prevention of depressive symptoms in at-risk groups, the bulk of research has focused on dietary therapies such fish oils or polyunsaturated fats (PUFAs). Given the extensive use of food as an intervention, confirmation bias cannot be completely ruled out, and there is little evidence to support dietary treatments for populations of people who are at risk. (230)

CONCLUSION

The treatment landscape for depression encompasses a diverse array of therapies, reflecting the complexity of the condition. Conventional antidepressant medications, such as MAOIs, TCAs, SSRIs, and SNRIs, target various neurotransmitter systems to alleviate symptoms. Pharmaceutical advancements, like ketamine and esketamine, swiftly alleviate symptoms by modulating the NMDA receptor. Ongoing research explores GABA's potential as an innovative therapeutic target. Additionally, modifying Peroxisome Proliferator-Activated Receptors (PPARs) offers a novel approach to receptor-based therapy. In addition to receptor targeting, medications are investigating biological mechanisms such as the Hypothalamic-Pituitary-Adrenal (HPA) Axis and the gut microbiome, which significantly influence mood regulation and overall mental well-being. Non-pharmacological approaches are gaining popularity, with psilocybin therapy showing promise in cases resistant to traditional treatments. Established techniques like cognitive behavioral therapy (CBT), electroconvulsive therapy (ECT), and non-invasive brain stimulation methods such as Transcranial Magnetic Stimulation (TMS) provide alternative or adjunctive options. Furthermore, adopting a healthy lifestyle through regular physical activity and dietary modifications has demonstrated benefits in mood enhancement and overall mental health. Overall, the evolving landscape of depression treatment integrates pharmacological interventions targeting neurotransmitter systems and novel biological pathways, alongside non-pharmacological therapies that offer diverse approaches to managing this complex mental health condition.

REFERENCES

[1] World Health Organization. (2017). Depression and other common mental disorders: Global health estimates.

[2] Ritchie, H., & Roser, M. (2018). Mental health. Our World in Data.

[3] Brown, G. M., et al. Depressive disorders: Processes leading to neurodegeneration and potential novel treatments. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 80(Pt C), 189-204.

[4] Kessler, R. C.,et al. (2012). Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. International Journal of Methods in Psychiatric Research, 21(3), 169-184.

[5] Li, Z., et al. (2021). Major depressive disorder: Advances in neuroscience research and translational applications. Neuroscience Bulletin, 37(6), 863-880.

[6] Novick, D., et al. (2017). Recovery in patients with major depressive disorder (MDD): Results of a 6-month, multinational, observational study. *Patient Preference and Adherence, 11*, 1859–1868.

[7] Rush, A. J., et al. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *The American Journal of Psychiatry,* 163(11), 1905-1917.

[8] McAllister-Williams, R. H., et al. (2020). The identification, assessment and management of difficult-to-treat depression: An international consensus statement. *Journal of Affective Disorders*, 267, 264-282.

[9] Rush, A. J., et al. (2019). Difficult-to-treat depression: A clinical and research roadmap for when remission is elusive. *Australian & New Zealand Journal of Psychiatry, 53*, 109-118.

[10] Elias, E., et al. (2022). Novel pharmacological approaches to the treatment of depression. *Life (Basel, Switzerland), 12*(2), 196.

[11] Crane, G. E. (1957). Iproniazid (Marsilid) phosphate, a therapeutic agent for mental disorders and debilitating diseases. *Psychiatric Research Reports, 8*, 142-152.

[12] Dunlop, E., DeFelice, E. A., Bergen, J. R., et al. (1965). The relationship between MAO inhibition and improvement of depression: Preliminary results with intravenous modaline sulfate (W3207B). *Psychosomatics, VI*, 1-7.

[13] Amsterdam, J. D., & Chopra, M. (2001). Monoamine oxidase inhibitors revisited. *Psychiatric Annals, 31*, 361-370.

[14] Pare, C. M. B. (1985). The present status of monoamine oxidase inhibitors. *British Journal of Psychiatry, 146*, 576-584.

[15] Baker, G. B., Coutts, R. T., McKenna, K. F., et al. (1992). Insights into the mechanisms of action of the MAO inhibitors phenelzine and tranylcypromine: A review. *Journal of Psychiatric Neuroscience, 17*, 206-214.

[16] Cusack, B., Nelson, A., & Richelson, E. (1994). Binding of antidepressants to human brain receptors: Focus on newer generation compounds. *Psychopharmacology, 114*(4), 559-565.

[17] Aree, T. (2020). Supramolecular complexes of β-cyclodextrin with clomipramine and doxepin: Effect of the ring substituent and component of drugs on their inclusion topologies and structural flexibilities. *Pharmaceuticals, 13*, 278.

[18] Ansseau, M., et al. (1984). Double-blind clinical study comparing alprazolam and doxepin in primary unipolar depression. *Journal of Affective Disorders, 7*, 287-296.

[19] Hirschfeld, R. M. A. (2000). History and evolution of the monoamine hypothesis of depression. *Journal of Clinical Psychiatry*, 61(Suppl. 6), 4-6.

[20] Donoghue, J., Tylee, A., & Wildgust, H. (1996). Cross sectional database analysis of antidepressant prescribing in general practice in the United Kingdom, 1993–5. *BMJ, 313*, 861–862.

[21] National Collaborating Centre for Mental Health. (2010). *Depression: The treatment and management of depression in adults (Updated edition)*. Leicester, UK: British Psychological Society

[22] Malberg, J. E., Eisch, A. J., Nestler, E. J., & Duman, R. S. (2000). Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *Journal of Neuroscience, 20*(24), 9104–9110.

[23] Ji, O. S., Karalis, P. G., Daas, M., & Condon, J. (2019). Gynecomastia associated with citalopram. *Primary Care Companion to CNS Disorders, 21*, 27311

[24] Xu, D., et al. (2020). The antidepressant-like effects of fluvoxamine in mice involve the mTOR signaling in the hippocampus and prefrontal cortex. *Psychiatry Research, 285*, 112708.

[25] Papakostas, G. I. (2009). Serotonin norepinephrine reuptake inhibitors: Spectrum of efficacy in major depressive disorder. *Primary Psychiatry, 16*(5, Suppl. 4), 16–24.

[26] Fanelli, D., et al. (2021). New serotonin-norepinephrine reuptake inhibitors and their anesthetic and analgesic considerations. *Neurology International, 13*, 497–509.

[27] Lavender, E., Hirasawa-Fujita, M., & Domino, E. F. (2020). Ketamine's dose related multiple mechanisms of actions: dissociative anesthetic

to rapid antidepressant. *Behavioural Brain Research, 390,* 112631.

[28] MacDonald, J. F., Miljkovic, Z., & Pennefather, P. (1987). Use-dependent block of excitatory amino acid currents in cultured neurons by ketamine. *Journal of Neurophysiology, 58,* 251–266.

[29] Kim, J. W., Suzuki, K., Kavalali, E. T., & Monteggia, L. M. (2023). Bridging rapid and sustained antidepressant effects of ketamine. *Trends in Molecular Medicine, 29,* 364–375.

[30] Domino, E.F. (2020). Ketamine's dose related multiple mechanisms of actions: dissociative anesthetic to rapid antidepressant. *Behavioral Brain Research, 390*, 112631.

[31] Kim, J.W., Suzuki, K., Kavalali, E.T., & Monteggia, L.M. (2023). Bridging rapid and sustained antidepressant effects of ketamine. *Trends in Molecular Medicine, 29*, 364–375

[32] American Psychological Association. (2010). *Publication manual of the American Psychological Association* (6th ed.)

[33] N2O: Steinberg, A. The use of naloxone to counteract opioid-induced pruritus; Mayo Clinic Proceedings; 24(7)109

[34] Berger, J., & Moller, D. E. (2002). The mechanisms of action of PPARs. *Annual Review of Medicine, 53*(1), 409-435.

[35] Jasper, M. S., & Engeland, W. C. (1994). Splanchnic neural activity modulates ultradian and circadian rhythms in adrenocortical secretion in awake rats. *Neuroendocrinology, 59*(2), 97–109.

[36] Cascio, C. S., Shinsako, J., & Dallman, M. F. (1987). The suprachiasmatic nuclei stimulate evening ACTH secretion in the rat. *Brain Research, 423*(1-2), 173–179.

[37] Szafarczyk, A., Alonso, G., Ixart, G., Malaval, F., & Assenmacher, I. (1985). Diurnal-stimulated and stress-induced ACTH release in rats is mediated by ventral noradrenergic bundle. *American Journal of Physiology, 249*(2 Pt 1), E219–E226.

[38] Beaulieu, S., Pelletier, G., Vaudry, H., & Barden, N. (1989). Influence of the central nucleus of the amygdala on the content of corticotropin-releasing factor in the median eminence. *Neuroendocrinology, 49*(3), 255–261.

[39] Beaulieu, S., De Paolo, T., Côté, J., & Barden, N. (1987). Participation of the central amygdaloid nucleus in the response of adrenocorticotropin secretion to immobilization stress: Opposing roles of the noradrenergic and dopaminergic systems. *Neuroendocrinology, 45*(1), 37–46.

[40] Jacobson, L., & Sapolsky, R. (1991). The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocrine Reviews, 12*(2), 118–134. doi:10.1210/edrv-12-2-118

[41] Reul, J. M. H. M., & de Kloet, E. R. (1985). Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. *Endocrinology, 117*(6), 2505–2512. doi:10.1210/endo-117-6-2505

[42] Dinan, T. G., & Cryan, J. F. (2017). Gut instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration. *The Journal of Physiology, 595*(2), 489-503

[43] Bercik, P., Verdu, E. F., Foster, J. A., et al. (2010). Chronic gastrointestinal inflammation induces anxiety-like behavior and alters central nervous system biochemistry in mice. *Gastroenterology, 139*(6), 2102-2112.

[44] O'Sullivan, E., Barrett, E., Grenham, S., Fitzgerald, P., Stanton, C., Ross, R. P., ... Dinan, T. G. (2011). BDNF expression in the hippocampus of maternally separated rats: Does Bifidobacterium breve 6330 alter BDNF levels? *Beneficial Microbes, 2*(3), 199–207.

[45] Parada Venegas, D., De la Fuente, M. K., Landskron, G., González, M. J., Quera, R., et al. (2019). Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. *Frontiers in Immunology.*

[46] Foster, J. A., et al. (2017). Stress & the gut-brain axis: Regulation by the microbiome. *Neurobiology of Stress.*

[47] Sudo, N., et al. (2004). Postnatal microbial colonization programs the hypothalamic-

pituitary-adrenal system for stress response in mice. *Journal of Physiology, 558*(1), 263–275.

[48] Keller, J., et al. (2017). HPA axis in major depression: Cortisol, clinical symptomatology and genetic variation predict cognition. *Molecular Psychiatry, 22*(4), 527–536.

[49] Winter, G., et al. (2018). Gut microbiome and depression: What we know and what we need to know. *Reviews in the Neurosciences, 29*(6), 629–643.

[50] Kamada, N., et al. (2013). Role of the gut microbiota in immunity and inflammatory disease. *Nature Reviews Immunology, 13*(5), 321–335.

[51] Hofmann, A., Frey, A., Ott, H., Petr Zilka, T., & Troxler, F. (1958). Elucidation of the structure and the synthesis of psilocybin. *Experientia, 14*, 397–399.

[52] Hofmann, A., Heim, R., Brack, A., & Kobel, H. (1958). Psilocybin, a psychotropic substance from the Mexican mushroom Psilicybe mexicana Heim. *Experientia, 14*, 107–109.

[53] Buchborn, T., Schroder, H., Hollt, V., & Grecksch, G. (2014). Repeated lysergic acid diethylamide in an animal model of depression: normalisation of learning behaviour and hippocampal serotonin 5-HT2 signalling. *Journal of Psychopharmacology, 28*(6), 545–552.

[54] Carhart-Harris, R. L., Erritzoe, D., Williams, T., et al. (2012). Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proceedings of the National Academy of Sciences of the United States of America, 109*(6), 2138–2143.

[55] Hendricks, P. S., Thorne, C. B., Clark, C. B., Coombs, D. W., & Johnson, M. W. (2015). Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. *Journal of Psychopharmacology, 29*(3), 280–288.

[56] Gasser, P., Holstein, D., Michel, Y., et al. (2014). Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *Journal of Nervous and Mental Disease, 202*(7), 513–520.

[57] Ross, S., et al. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial. *Journal of Psychopharmacology, 30*(12), 1165–1180.

[58] Johnson, M. W., Richards, W. A., & Griffiths, R. R. (2008). Human hallucinogen research: Guidelines for safety. *Journal of Psychopharmacology, 22*(6), 603–620.

[59] O'Cleirigh, C., Safren, S. A., Taylor, S. W., Goshe, B. M., Bedoya, C. A., Marquez, S. M., Boroughs, M. S., & Shipherd, J. C. (2019). Cognitive Behavioral Therapy for Trauma and Self-Care (CBT-TSC) in Men Who have Sex with Men with a History of Childhood Sexual Abuse: A Randomized Controlled Trial. *AIDS Behavior, 23*(9), 2421-2431

[60] Sahranavard, S., Esmaeili, A., Salehiniya, H., & Behdani, S. (2019). The effectiveness of group training of cognitive behavioral therapy-based stress management on anxiety, hardiness and self-efficacy in female medical students. *Journal of Education and Health Promotion, 8*, 49

[61] Lopez, M. A., & Basco, M. A. (2015). Effectiveness of cognitive behavioral therapy in public mental health: Comparison to treatment as usual for treatment-resistant depression. *Administration and Policy in Mental Health, 42*(1), 87-98.

[62] Vittengl, J. R., Clark, L. A., Dunn, T. W., & Jarrett, R. B. (2007). Reducing relapse and recurrence in unipolar depression: A comparative meta-analysis of cognitive-behavioral therapy's effects. *Journal of Consulting and Clinical Psychology, 75*(3), 475-488.

[63] Rupke, S. J., Blecke, D., & Renfrow, M. (2006). Cognitive therapy for depression. *American Family Physician, 73*(1), 83-86.

[64] Li, M., et al. (2020). Effects of electroconvulsive therapy on depression and its potential mechanism. *Frontiers in Psychology, 11*, Article 80.

[65] Kellner, C. H., et al. (2016). Right unilateral ultrabrief pulse ECT in geriatric depression:

Phase 1 of the PRIDE study. *American Journal of Psychiatry, 173*(11), 1101–1109.

[66] Karayagmurlu, A., et al. (2019). Efficacy and safety of electroconvulsive therapy in adolescents: A retrospective chart review study from Turkey. *Journal of ECT.* Advance online publication.

[67] Husain, M. M., et al. (2004). Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): A Consortium for Research in ECT (CORE) report. *Journal of Clinical Psychiatry, 65*(4), 485–491.

[68] Spaans, H. P., et al. (2015). Speed of remission in elderly patients with depression: Electroconvulsive therapy v. medication. *The British Journal of Psychiatry, 206*(1), 67–71.

[69] Liang, C. S., et al. (2017). In-hospital mortality among electroconvulsive therapy recipients: A 17-year nationwide population-based retrospective study. *European Psychiatry, 42,* 29–35.

[70] Schoeyen, H. K., et al. (2015). Treatment-resistant bipolar depression: A randomized controlled trial of electroconvulsive therapy versus algorithm-based pharmacological treatment. *American Journal of Psychiatry, 172*(1), 41–51.

[71] FDA. (n.d.). *FDA-approved treatments for movement disorders.* Retrieved from

[72] Greenberg, B. D., et al. (2006). Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: Worldwide experience. *Molecular Psychiatry, 11*(6), 566–576.

[73] Ackermans, L., et al. (2011). Deep brain stimulation for Tourette's syndrome. *Stereotactic and Functional Neurosurgery, 89*(3), 149–156.

[74] Lujan, J. L., Chaturvedi, A., Malone, D. A., et al. (2013). Evolving use of neuromodulation for treatment of addiction disorders. *Neurosurgical Review, 36*(3), 537–546.

[75] Mayberg, H. S., et al. (2005). Deep brain stimulation for treatment-resistant depression. *Neuron, 45*(5), 651–660.

[76] Bewernick, B. H., et al. (2010). Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biological Psychiatry, 67*(2), 110–116.

[77] Gersner, R., et al. (2010). Site-specific antidepressant effects of repeated subconvulsive electrical stimulation: Potential role of brain-derived neurotrophic factor. *Biological Psychiatry, 67*, 125-132.

[78] Schmuckermair, C., et al. (2013). Behavioral and neurobiological effects of deep brain stimulation in a mouse model of high anxiety- and depression-like behavior. *Neuropsychopharmacology, 38*, 1234-1244.

[79] Sheline, Y. I., et al. (1996). Hippocampal atrophy in recurrent major depression. *Proceedings of the National Academy of Sciences USA, 93*, 3908-3913.

[80] Sheline, Y. I., et al. (1999). Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *Journal of Neuroscience, 19*, 5034-5043.

[81] Bremner, J. D., et al. (2000). Hippocampal volume reduction in major depression. *American Journal of Psychiatry, 157*, 115-118.

[82] Duman, R. S., et al. (2001). Regulation of adult neurogenesis by antidepressant treatment. *Neuropsychopharmacology, 25*, 836-844.

[83] Ernst, C., et al. (2006). Antidepressant effects of exercise: Evidence for an adult-neurogenesis hypothesis? *Journal of Psychiatry and Neuroscience, 31*, 84-92.

[84] De Moor, M. H. M., et al. (2006). Regular exercise, anxiety, depression and personality: A population-based study. *Preventive Medicine, 42*, 273-279.

[85] Wittert, G. A., et al. (1996). Adaptation of the hypothalamopituitary adrenal axis to chronic exercise stress in humans. *Medical Science and Sport Exercise, 28*, 1015-101